

**UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549**

FORM 10-K

Annual report pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934.

For the Fiscal Year Ended December 31, 2021

or
 Transition report pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934.

For the transition period from _____ to _____

Commission File No. 001-34079

Ocuphire Pharma, Inc.

(Exact name of registrant as specified in its charter)

Delaware
(State or other jurisdiction of incorporation or organization)

11-3516358
(I.R.S. Employer Identification No.)

37000 Grand River Avenue, Suite 120
Farmington Hills, MI
(Address of principal executive offices)

48335
(Zip Code)

Registrant's telephone number, including area code: (248) 681-9815

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol	Name of each exchange on which registered
Common Stock, \$0.0001 par value per share	OCUP	The Nasdaq Stock Market LLC

Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes No

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or 15(d) of the Act. Yes No

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days: Yes No

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes No

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company" and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer

Accelerated filer

Non-accelerated filer

Smaller reporting company
Emerging growth company

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act.

Indicate by check mark whether the registrant has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report. Yes No

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes No

The aggregate market value of the common equity held by non-affiliates of the registrant on June 30, 2021, based on the closing price on that date of \$5.28, was approximately \$83,840,460. As of March 23, 2022, there were 18,989,817 shares of the registrant's common stock outstanding.

Documents Incorporated by Reference

Portions of the registrant's Definitive Proxy Statement to be filed with the Commission pursuant to Regulation 14A in connection with the registrant's 2022 Annual Meeting of Stockholders, to be filed subsequent to the date hereof, are incorporated by reference into Part III of this report. Such Definitive Proxy Statement will be filed with the Securities and Exchange Commission not later than 120 days after the conclusion of the registrant's fiscal year ended December 31, 2021.

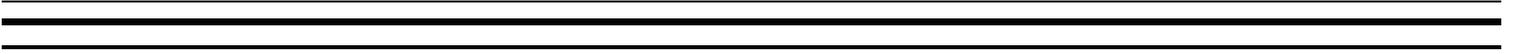


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In this Annual Report on Form 10-K, unless otherwise specified, references to “we,” “us,” “our,” “Ocuphire” or “the Company” mean Ocuphire Pharma, Inc., together with its former subsidiary OcuSub Inc. Our financial statements are prepared in accordance with accounting principles generally accepted in the United States (“U.S. GAAP”).

FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains forward-looking statements within the meaning of the safe harbor provisions of Section 27A of the Securities Act of 1933, as amended (the “Securities Act”), and Section 21E of the Securities Exchange Act of 1934, as amended (the “Exchange Act”). These forward-looking statements relate to us, our business prospects and our results of operations and are subject to certain risks and uncertainties posed by many factors and events that could cause our actual business, prospects and results of operations to differ materially from those anticipated by such forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, those described under the heading “Risk Factors” included in this Annual Report on Form 10-K. Readers are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date of this report. In some cases, you can identify forward-looking statements by the following words: “anticipate,” “believe,” “continue,” “could,” “estimate,” “expect,” “intend,” “may,” “ongoing,” “plan,” “potential,” “predict,” “project,” “should,” “will,” “would” or the negative of these terms or other comparable terminology, although not all forward-looking statements contain these words. We undertake no obligation to revise any forward-looking statements in order to reflect events or circumstances that might subsequently arise. Readers are urged to carefully review and consider the various disclosures made by us in this report and in our other reports filed with the U.S. Securities and Exchange Commission (the “SEC”) that advise interested parties of the risks and factors that may affect our business.

SUMMARY RISK FACTORS

Our business is subject to a number of risks, as fully described in “Item 1A. Risk Factors” in this Annual Report. The principal factors and uncertainties include, among others:

- Ocuphire currently depends entirely on the success of Nyxol and APX3330, its only product candidates. Ocuphire may never complete clinical development of, receive marketing approval for, or successfully commercialize, Nyxol alone or as adjunctive therapy with low dose pilocarpine (LDP), APX3330, or other product candidates it may pursue in the future for any indication.
- The results of previous clinical trials may not be predictive of future results, and the results of Ocuphire’s current and planned clinical trials may not satisfy the requirements of the FDA or non-U.S. regulatory authorities.
- Changes in regulatory requirements or FDA guidance, or unanticipated events during Ocuphire’s clinical trials, may result in changes to clinical trial protocols or additional clinical trial requirements, which could result in increased costs to Ocuphire or delays in its development timeline.
- Ocuphire has incurred only losses since inception. Ocuphire expects to incur losses for the foreseeable future and may never achieve or maintain profitability.
- Ocuphire’s recurring operating losses have raised substantial doubt regarding its ability to continue as a going concern.
- Raising additional capital may cause dilution to Ocuphire’s stockholders, restrict Ocuphire’s operations, or require Ocuphire to relinquish rights to its technologies or product candidates.
- Even if it receives marketing approval for its product candidates in the United States, Ocuphire may never receive regulatory approval to market such product candidates outside of the United States.

- Ocuphire employees or its representatives may engage in misconduct or other improper activities, including violating applicable regulatory standards and requirements or engaging in insider trading, which could significantly harm Ocuphire’s business.
- Ocuphire faces substantial competition, which may result in others discovering, developing, or commercializing products before or more successfully than it does.
- Ocuphire lacks experience in commercializing products, which may have an adverse effect on its business.
- If Ocuphire is unable to establish sales and marketing capabilities or enter into agreements with third parties to sell, market, and distribute its product candidates, if approved, it may not be successful in commercializing such product candidates if and when they are approved.
- Product liability lawsuits against Ocuphire, or its suppliers and manufacturers, could cause it to incur substantial liabilities and could limit commercialization of any product candidate that it may develop.
- Ocuphire is unable to control all aspects of its clinical trials due to its reliance on clinical research organizations (“CROs”), contract development and manufacturing organizations (“CDMOs”) and other third parties that assist Ocuphire in conducting clinical trials.
- Ocuphire is unable to control the supply, manufacture and testing of bulk drug substances and the formulation, testing and packaging of preclinical and clinical drug supplies of its product candidates, and will be unable to control these elements at the commercial stage, due to its reliance on third party manufacturers and analytical facilities.
- If Ocuphire is not able to establish new collaborations on commercially reasonable terms, it may have to alter its development, manufacturing, and commercialization plans.
- If Ocuphire is unable to obtain and maintain sufficient patent protection for its product candidates, its competitors could develop and commercialize products or technology similar or identical to those of Ocuphire, which would adversely affect Ocuphire’s ability to successfully commercialize any product candidates it may develop, its business, results of operations, financial condition and prospects.
- If Ocuphire does not obtain protection under the Hatch-Waxman Act and similar foreign legislation by extending the patent terms and obtaining data exclusivity for its product candidate, its business may be materially harmed.
- Ocuphire may not be able to protect or practice its intellectual property rights throughout the world.
- Obtaining and maintaining Ocuphire’s patent protection depends on compliance with various procedural, document submission, fee payment, and other requirements imposed by governmental agencies, and its patent protection could be reduced or eliminated for noncompliance with these requirements.
- Ocuphire depends on intellectual property sublicensed from Apexian Pharmaceuticals, Inc. (“Apexian”) for its APX3330 product candidate under development and its additional pipeline candidates, and the termination of, or reduction or loss of rights under, this sublicense would harm Ocuphire’s business.
- Ocuphire is dependent on its key personnel, and if it is not successful in attracting and retaining highly qualified personnel, it may not be able to successfully implement its business strategy.

- Ocuphire will need to develop and expand its company and may encounter difficulties in managing this development and expansion, which could disrupt its operations.
- The COVID-19 pandemic has and could continue to adversely impact Ocuphire’s business, including preclinical and clinical trials and regulatory approvals.
- Ocuphire’s insurance policies are expensive and protect only from some business risk, which leaves Ocuphire exposed to significant uninsured liabilities.
- If Ocuphire fails to comply with the continued listing standards of the Nasdaq Capital Market, Ocuphire common stock could be delisted. If it is delisted, Ocuphire common stock and the liquidity of its common stock would be impacted.
- The market price of Ocuphire common stock may fluctuate significantly.
- Ocuphire may be subject to securities litigation, which is expensive and could divert management attention.

INDUSTRY AND MARKET DATA

In this Annual Report, we reference information, statistics and estimates regarding the medical devices and healthcare industries. We have obtained this information from various third-party sources, including industry and general publications, reports by market research firms and other sources. This information involves a number of assumptions and limitations, and we have not independently verified the accuracy or completeness of this information. Some data and other information are also based on the good faith estimates of management, which are derived from our research, review of internal surveys, general information discussed in the industry, and third-party sources. We believe that these external sources and estimates are reliable but have not independently verified them. The industries in which we operate are subject to a high degree of uncertainty, change, and risk due to a variety of factors, including those described in “Item 1A. Risk Factors.” These and other factors could cause results to differ materially from those expressed in this Annual Report and other publications.

PART I

ITEM 1. BUSINESS

Overview

Ocuphire is a clinical-stage ophthalmic biopharmaceutical company focused on developing and commercializing therapies for the treatment of refractive and retinal eye disorders. Ocuphire's pipeline currently includes two small molecule product candidates targeting several of such indications.

Its lead product candidate, Nyxol[®] Eye Drops ("Nyxol"), is a once-daily eye drop formulation of phentolamine mesylate designed to reduce pupil diameter and improve visual acuity. As a result, Nyxol can potentially be used for the treatment of multiple indications such as reversal of pharmacologically-induced mydriasis ("RM") (dilation of the pupil), presbyopia (age-related blurry near vision) and dim light or night vision disturbances ("NVD") (halos and glares). Ocuphire's management believes these multiple indications potentially represent a significant market opportunity. Nyxol has been studied in a total of 9 clinical trials (3 Phase 1, 5 Phase 2 and 1 Phase 3) in a total of over 560 patients (with over 330 Nyxol-treated) and has demonstrated promising clinical data for use in the multiple ophthalmic indications mentioned above. Ocuphire reported positive top-line data from the first Phase 3 trial (MIRA-2) for RM, completed enrollment in a 2nd Phase 3 RM trial (MIRA-3) in February 2022, and completed enrollment on a pediatric safety study (MIRA-4) for RM in March 2022. Ocuphire also reported positive top-line data from a Phase 2 trial of Nyxol for treatment of presbyopia, both alone and with low-dose pilocarpine (pilocarpine hydrochloride 0.4% ophthalmic solution, "LDP") as adjunctive therapy. Ocuphire announced completion of enrollment of its NVD Phase 3 trial (LYNX-1) in January 2022. Ocuphire expects to report top-line results from the MIRA-3 RM Phase 3 study by end of the first quarter of 2022, followed by the LYNX-1 NVD Phase 3 study and the MIRA-4 RM pediatric study in the second quarter of 2022. Assuming successful and timely completion of the RM trials, Ocuphire anticipates submitting a new drug application ("NDA") to the U.S. Food and Drug Administration ("FDA") in late 2022 under the 505(b)(2) pathway for its drug led combination product. Ocuphire has started pre-commercialization planning and activities in anticipation of a successful RM approval.

Ocuphire's second product candidate, APX3330, is a twice-a-day oral tablet designed to target multiple pathways relevant to retinal and choroidal (the vascular layer of the eye) diseases such as diabetic retinopathy ("DR") and diabetic macular edema ("DME") which, if left untreated, can result in permanent visual acuity loss and eventual blindness. DR is a disease resulting from diabetes in which chronically elevated blood sugar levels cause progressive damage to blood vessels in the retina. DME is a severe form of DR which involves leakage of protein and fluid into the macula, the central portion of the retina, causing swelling and vascular damage. Prior to Ocuphire's in-licensing of the product candidate, APX3330 had been studied by other sponsors in a total of 11 clinical trials (6 Phase 1 and 5 Phase 2) in a total of over 420 healthy volunteers or patients (with over 340 APX3330-treated) for inflammatory and oncology indications, and had demonstrated evidence of tolerability, pharmacokinetics, durability, and target engagement. Ocuphire has also in-licensed APX2009 and APX2014, which are second-generation product candidates and analogs of APX3330. Ocuphire initiated a Phase 2 trial for APX3330 in April 2021 for the treatment of patients with DR, including moderately severe non-proliferative DR ("NPDR") and mild proliferative DR ("PDR"), as well as patients with DME without loss of central vision. In January 2022, Ocuphire reported masked safety data from the ongoing Phase 2 trial in DR/DME on 68 patients enrolled at the time. These safety data are consistent with safety data from the prior 11 clinical trials with total exposure experience of over 5000 subject days with 600 mg daily dose of APX3330. Ocuphire also reported enrollment completion of 103 patients in the ZETA-1 trial in March 2022, and expects to report top-line results from the ZETA-1 DR/DME Phase 2b study in the second half of 2022.

As part of its strategy, Ocuphire will continue to explore opportunities to acquire additional ophthalmic assets and seek strategic partners for late-stage development, regulatory preparation, and commercialization of drugs in key global markets.

Corporate History

On November 5, 2020, Ocuphire (formerly known as Rexahn Pharmaceuticals, Inc., and prior to the merger, referred to as “Rexahn”), completed its reverse merger with Ocuphire Pharma, Inc. (“Private Ocuphire”), in accordance with the terms of the Agreement and Plan of Merger, dated as of June 17, 2020, as amended, by and among Rexahn, Private Ocuphire, and Razor Merger Sub, Inc., a wholly-owned subsidiary of Rexahn (“Merger Sub”) (as amended, the “Merger Agreement”), pursuant to which Merger Sub merged with and into Private Ocuphire, with Private Ocuphire surviving as a wholly-owned subsidiary of Rexahn (the “Merger”).

In connection with, and immediately prior to the completion of, the Merger, Rexahn effected a reverse stock split of the common stock, at a ratio of 1-for-4 (the “Reverse Stock Split”). Under the terms of the Merger Agreement, after considering the Reverse Stock Split, Rexahn issued shares of its common stock to Private Ocuphire stockholders, based on a common stock exchange ratio of 1.0565 shares of common stock for each share of Private Ocuphire common stock. In connection with the Merger, Rexahn changed its name from “Rexahn Pharmaceuticals, Inc.” to “Ocuphire Pharma, Inc.,” Merger Sub changed its name from “Razor Merger Sub, Inc.” to “OcuSub Inc.,” and the business conducted by Rexahn became the business conducted by Private Ocuphire.

In December 2021, OcuSub Inc. was merged with and into the Company, with the Company remaining as the surviving entity.

Strategy

Ocuphire’s goal is to build a leading ophthalmic biopharmaceutical company that discovers, develops and commercializes best-in-class therapies for patients and provides attractive solutions for physicians and payers. The key elements of Ocuphire’s strategy to achieve its goal are the following:

- **Advance the clinical development of Nyxol and APX3330.** Ocuphire is currently conducting Phase 2 and Phase 3 registration trials of Nyxol and Phase 2b trials of APX3330 with the goal of filing a U.S. NDA in late 2022 for Nyxol for RM, and advancing APX3330 towards Phase 3 studies in the future.
- **Target Nyxol and APX3330 for large ophthalmic indications.** Ocuphire believes Nyxol has therapeutic potential to improve vision performance in RM, presbyopia and NVD. Ocuphire also believes APX3330 has potential to improve the health of the retina in patients with DR, DME, and wet age-related macular degeneration (wAMD), while reducing the burden of intravitreal injections.
- **Maintain and expand its intellectual property portfolio.** Ocuphire owns all global patent rights to Nyxol with respect to its formulation, combinations, and use in multiple indications. Ocuphire also owns an exclusive worldwide sublicense for the Ref-1 Inhibitor program, including its lead product candidate APX3330, for all its ophthalmic and diabetic indications, and compositions and methods of use for Ref-1 pipeline candidates, including APX2009 and APX2014. Ocuphire continues to explore additional opportunities to expand and extend this intellectual property protection, both in the U.S. and in other jurisdictions.
- **Maximize the global commercial value of Nyxol and APX3330.** Ocuphire plans to seek commercial partners both in and outside of the United States. Alternatively, Ocuphire believes it could independently commercialize Nyxol and/or APX3330 in the United States with a targeted sales force.
- **Evaluate in-licensing and acquisition opportunities.** Ocuphire’s team is well qualified to identify and in-license or acquire clinical-stage ophthalmological assets and is evaluating opportunities to expand and diversify its pipeline.

Ocuphire is developing Nyxol and APX3330 for multiple indications. Ocuphire believes the two programs present similar potential advantages: (1) promising clinical data to date; (2) both small-molecule clinical candidates; (3) convenient dosing route and schedule; (4) potential for first-line or adjunctive therapy; and (5) significant commercial potential. **TABLE 1** below summarizes Ocuphire’s current development pipeline of product candidates and their target indications and anticipated milestones for 2022:

TABLE 1. Ocuphire Pipeline: Product Candidates and Indications Pipeline

Indication	Product Candidate	Pre-clinical	Phase 1	Phase 2	Phase 3	Regulatory Approval	Anticipated Milestones
Reversal of Mydriasis (RM)	Nyxol® Eye Drop				MIRA-2 ✓ ★		<input type="checkbox"/> MIRA-3 Phase 3 data expected in end of Q1 2022 (n=330) <input type="checkbox"/> MIRA-4 Pediatric safety study data expected in 2Q 2022 (n=20)
Presbyopia (P)	Nyxol® Eye Drop			VEGA-1 ✓			<input type="checkbox"/> VEGA Phase 3 program planned to initiate in mid 2022
	Nyxol® + Low-Dose (0.4%) Pilocarpine Eye Drops						
Dim Light or Night Vision Disturbances (NVD)	Nyxol® Eye Drop				★		<input type="checkbox"/> LYNX-1 Phase 3 data expected in 2Q 2022 (n=140)
Diabetic Retinopathy (DR)/ Macular Edema (DME)	APX3330 Oral Pill			★			<input type="checkbox"/> ZETA-1 Phase 2b data expected in 2H22 (n=90-100)
DME or Wet Age-Related Macular Degeneration (wAMD)	APX2009 (Intravitreal or Local Delivery)				✓ Positive trial data ★ Ongoing trial		<input type="checkbox"/> Seeking partner funding for IND enabling studies and further development

Note: 0.75% POS (Phentolamine Ophthalmic Solution) is the same as 1% PMOS (Phentolamine Mesylate Ophthalmic Solution). References to Nyxol with both designations appear throughout this document, there is no difference in formulation between the two designations.

Based on the safety and efficacy data generated to date, as well as data expected from the MIRA-3 and MIRA-4 trials, Ocuphire anticipates submitting its first NDA to the FDA for Nyxol for RM in late 2022 utilizing the 505(b)(2) pathway of the U.S. Federal Food, Drug, and Cosmetic Act (“FDCA”), which the FDA indicated would be acceptable for the Nyxol application. In addition, Ocuphire anticipates filing NDAs for presbyopia and NVD and advancing APX3330 towards an NDA in the future. Ocuphire further anticipates that in the longer term, it will also submit marketing applications with regulators in other global markets, initially considering the European Medicines Agency (“EMA”) and Japan’s Pharmaceuticals and Medical Devices Agency, and potentially other markets such as China.

In February 2018, Ocuphire was founded by Mina Sooch and subsequently merged in April 2018 with Ocularis Pharma, LLC, founded by Gerald Horn MD (the original innovator of phentolamine mesylate ophthalmic solution to treat NVD), Alan R. Meyer, William Pitlick PhD, and Keith Terry. Many of Ocuphire’s employees, directors, advisors and consultants have been involved in the development of Nyxol and other ophthalmic drugs including approved products such as LUMIFY®, Zigan®, Durezol®, Upneeq®, Rhopressa®, Roclatan®, Vyzulta®, Xiidra®, Cequa®, and Dextenza®. The management team, led by CEO Mina Sooch, collectively has significant experience in operating pharmaceutical companies and discovering, developing, and commercializing treatments in multiple therapeutic areas. Ocuphire also has a world-class medical advisory board of over 15 key opinion leaders including retina specialists, refractive surgeons, and optometrists.

Overview of Eye Disease Market

Anterior (Front of the Eye) Segment Disease Market

There are approximately 100 million dilations in the United States and this number is expected to go up with the increasing aging and diabetic population that requires more frequent eye exams and procedures. Millions of Americans also suffer from various refractive errors. Presbyopia, one such refractive error, is common in patients over the age of 40 years which results in decreased ability to see objects at a near distance. This condition affects over 120 million Americans and usually requires reading glasses and/or contact lenses for focusing on near objects. Further according to GlobalData, approximately 38 million patients in the U.S suffer from dim light or night vision disturbances caused by LASIK, night myopia, keratoconus, eye surgery, or natural aging process. There is also a global trend in vision disturbances in younger individuals due to the overuse of smartphones. Ocuphire's lead product candidate, Nyxol, is currently in late-stage clinical development for reversal of mydriasis (dilation), presbyopia and night vision disturbances, and has the potential to address an unmet need for millions of patients in the US.

Retinal (Back of the Eye) Disease Market

Retinal damage is one of the leading causes of blindness and continues to grow with aging and larger diabetic populations around the world. Diabetes is the leading cause of blindness among adults aged 20 – 74. According to the National Eye Institute, in the United States alone, over 7 million patients suffer from diabetic retinopathy (DR), a complication of diabetes in which chronically elevated blood sugar levels cause damage to blood vessels in the retina. An additional 750,000 patients suffer from diabetic macular edema (DME), one of the most common complications of diabetic retinopathy where the macula swells from fluid leaked from damaged blood vessels. The disease progression of both DR and DME involves abnormal vessel proliferation via VEGF signaling and inflammation. Ocuphire's APX3330 oral tablet is currently in a Phase 2 clinical trial for DR and has the potential to address this large DR and DME market with a novel, dual mechanism of action of inhibiting VEGF and inflammation. In addition, over 1 million patients in the United States suffer from wAMD. These retinal and choroidal vascular diseases, which cause damage to the macula, are leading causes of severe, permanent vision loss. Currently, there are several drugs on the market indicated for anti-VEGF therapy, including Lucentis® (ranibizumab), a monoclonal antibody marketed by Genentech, and EYLEA® (aflibercept), a recombinant fusion protein marketed by Regeneron Pharmaceuticals, Inc., that have become the standard of care for treating severe forms of DME and wAMD amongst other retinal conditions. Avastin® (bevacizumab), a monoclonal antibody marketed by Genentech, is also used off-label to treat these same indications as it is more cost-effective than the other branded drugs. These three injectable drugs are biologics with treatment administered in an ophthalmologist's office. Annual worldwide sales of Lucentis and EYLEA for all indications totaled over \$13 billion in 2020 (\$3.5 billion for Lucentis and over \$10 billion for EYLEA).

Summary of Ocuphire's Product Candidates

Nyxol (phentolamine 0.75% ophthalmic solution)

Nyxol is a once-daily, sterile, preservative-free eye drop formulation containing phentolamine mesylate, a reversible, non-selective alpha-1 and alpha-2 adrenergic antagonist that acts on the adrenergic nervous system and inhibits contraction of smooth muscle. Phentolamine mesylate, the drug substance and active component of Nyxol, is the active pharmaceutical ingredient (API) in two FDA-approved drugs, Regitine® and OraVerse®. Regitine, an injectable approved in 1952, is used mainly to treat pre- or intra-operative hypertensive episodes in patients with pheochromocytoma. OraVerse, approved in 2007, is an intraoral submucosal injection used to reverse anesthesia after oral surgery. The FDA has stated that it would be acceptable for the Nyxol application to reference the FDA's previous review of safety and efficacy for Regitine® (Phentolamine Mesylate Injection, NDA 008278) and OraVerse® (Phentolamine Mesylate Injection, NDA 22159), pursuant to section 505(b)(2) of the U.S. Federal Food, Drug, and Cosmetic Act ("FDCA"). In multiple clinical trials, Nyxol has shown to reduce pupil size, improve near and distance visual acuity in light and dark conditions, and improve low contrast visual acuity. Ocuphire is pursuing multiple indications for Nyxol, including RM, presbyopia, and NVD. For treatment of presbyopia, Ocuphire is evaluating the efficacy of Nyxol both as a single-agent eye drop and as a combination with LDP.

Key attributes of Ocuphire's product candidate Nyxol include the following:

- **Reduction in pupil diameter with durable effects.** In multiple Phase 2 and Phase 3 trials Nyxol reduced pupil diameter by approximately ~1 – 1.5 mm in both mesopic (dim) and photopic (bright) conditions, with such reductions sustained over 24 hours. Nyxol with LDP as adjunctive eye drop provides an optimal pupil size of 2 mm – 3 mm.

- **Improvement in distance corrected near visual acuity.** When studied in patients with presbyopia in Phase 2 trials, Nyxol alone and in combination with LDP showed statistically significant improvement in distance-corrected near visual acuity with ≥ 3 lines gain from baseline.
- **Improvement in low contrast visual acuity.** When studied in patients with NVD in multiple Phase 2 trials, Nyxol showed statistically significant improvement in low contrast mesopic best-corrected distance visual acuity at ≥ 1 and ≥ 2 lines, with a trend at ≥ 3 lines on a standard visual chart.
- **Favorable tolerability profile.** To date, Nyxol has been observed to be well-tolerated, with unchanged or decreased intraocular pressure in the nine completed Phase 1, Phase 2 and Phase 3 clinical trials conducted. Nyxol produces a transient, mild hyperemia effect that disappears within several hours or immediately upon application of anti-redness eye drops. Nyxol is also observed to have no systemic effects such as changes in blood pressure or heart rate.
- **Designed to be a convenient, once-daily eye drop or tunable combination option.** Nyxol is being evaluated for chronic use as a once-daily administration before bedtime. Nyxol has been shown in multiple Phase 2 trials and a Phase 3 trial to have a durable effect of over 24 hours, which could encourage patient compliance. Use of LDP eye drops as an adjunct to Nyxol may offer the benefit of tunability to presbyopia patients based on their vision and lifestyle needs.
- **Stable, cost-effective ophthalmic formulation.** Nyxol is a single-use, preservative-free, proprietary eye drop formulation with stability suitable to support potential commercialization. Its active pharmaceutical ingredient, phenolamine mesylate USP grade, is a small molecule with advantages of standardized, scalable, and lower-cost manufacturing processes.

Ocuphire is initially pursuing Nyxol for the following three indications as a first-line therapy (in the case of presbyopia, both as a single agent and with low-dose pilocarpine as an adjunctive drop):

- **RM**, the reversal of pharmacologically induced dilation of the pupils, where dilation leads to increased sensitivity to light and an inability to focus, making it difficult to read, work, and drive. RM is a single-use indication for which no approved therapy is commercially available at present.
- **Presbyopia**, a condition in which the eye's lens loses elasticity, affecting its ability to focus on near objects. Presbyopia typically occurs after age 40 and most patients use reading glasses in order to read or see objects close to them. VuityTM, approved in October 2021 and launched in December 2021, is the only eye drop currently marketed for the treatment of presbyopia.
- **NVD**, a condition in which peripheral imperfections (aberrations) of the cornea scatter light when the pupil opens wide in dim light. Patients with NVD experience glare, halos, starbursts, and decreased contrast sensitivity. NVD is a new indication with no approved therapies.

APX3330

APX3330 (E3330), originally developed by Eisai Co., Ltd. and Apexian Pharmaceuticals, Inc., is a small molecule that specifically targets Apurinic/Apyrimidinic Endonuclease 1/Redox Factor-1 (APE-1/Ref-1, referred to as Ref-1), a dual function protein involved in the regulation of transcription factors critical to cell signaling. Ref-1 regulates inflammation, angiogenesis (blood vessel formation), and reduction-oxidation (redox) signaling, as well as DNA repair that is critical to normal function of neurons. By inhibiting redox activity and not DNA repair, APX3330 has been shown in preclinical studies to reduce angiogenesis and inflammation via modulation of several important proangiogenic and proinflammatory transcription factors such as NF- κ B and HIF-1 α and its downstream target, VEGF (Vascular Endothelial Growth Factor). These transcription factors are implicated in multiple pathways relevant to the pathophysiology of retinal and choroidal vascular diseases, including diabetic retinopathy (DR), diabetic macular edema (DME), and wet age-related macular degeneration (wAMD). Moreover, data from these preclinical studies suggest that APX3330 is a promising candidate for clinical evaluation of the efficacy and safety of an oral systemic therapy to treat these important diseases.

Key attributes of OcuPhire's product candidate APX3330 include the following:

- **Potential to be the first oral therapy.** Compared to frequent intravitreal anti-VEGF injections, associated with ocular complications, once or twice a day oral administration of APX3330 could be a convenient alternative treatment for retinal disease, if approved.
- **Upstream target implicated in two validated pathways.** APX3330 is designed to lead to inhibition of two validated cell signaling pathways (angiogenesis and inflammation) known to cause various retinal diseases. Moreover, the APX3330 mechanism of action is distinct in working upstream of the current anti-VEGF therapies, suggesting that it could complement anti-VEGF therapies and potentially reduce frequency of doctor visits and intravitreal injections.
- **Favorable tolerability profile.** In 11 completed Phase 1 and Phase 2 clinical trials, APX3330 was well-tolerated with no significant acute neurologic, cardiovascular, hepatic, or pulmonary events.
- **Potential benefit of systemic administration.** As a systemic agent, APX3330 can be expected to treat bilateral (both eyes) retinal vascular disease.
- **Stable, cost-effective oral tablet.** APX3330 is formulated as an oral tablet with favorable stability characteristics, and its active pharmaceutical ingredient is a small molecule with the advantages of standardized, scalable, and lower-cost manufacturing processes.

OcuPhire is initially pursuing APX3330 for the following indications as a first-line or adjunctive therapy:

- **DR**, the leading cause of vision loss in adults aged 20–74 years, which results from chronic elevations of glucose in the blood that leads to cell damage in the retina.
- **DME**, one of the most common complications of DR, in which vascular leakage causes swelling of the retinal macula and a loss of visual acuity.
- **wAMD**, a chronic eye disorder that causes visual distortions in the central part of one's vision, in which abnormal blood vessels leak fluid or blood into the macula, the part of the eye that is critical for central and color vision.

OcuPhire's Target Indications

RM (Nyxol)

Mydriasis Overview

Every year in the U.S., over 100 million eye exams or procedures are performed that require dilation of the pupil (mydriasis) to examine the back of the eye either for routine check-ups, disease monitoring or surgical procedures. The mydriasis is achieved either by stimulating the iris dilator muscle with the use of alpha agonists (e.g., phenylephrine), or by blocking the iris sphincter muscle with the use of muscarinic antagonists (e.g., tropicamide) or a combination of both mydriatic agents. Typically, pharmacologically induced mydriasis dilates the pupil to 7 mm to 8 mm, a size suitable for ophthalmic examination of the retina and other structures of the interior of the eye. Such pharmacologically induced mydriasis can last from a few hours (typically 6 hours) up to 24 hours, depending on the pigmentation of the iris, one's age, and other factors. Side effects of mydriasis include sensitivity to light and blurred vision, which make it difficult to read, work, or drive. Many dilating drops also cause cycloplegia, the temporary paralysis of the muscle which allows the eye to focus on near objects. For this reason, many patients may request to avoid dilation, thus limiting the eye care provider's ability to conduct a comprehensive annual eye exam.

Limitations of Existing Treatments for Reversal of Mydriasis

There is no approved product presently on the market for reversal of mydriasis and Ocuphire is not aware of any others in development. In 1990, the FDA approved the selective alpha-1 antagonist dapiprazole, marketed as Rev-Eyes[®], to reverse mydriasis induced by adrenergic or anticholinergic agents. Rev-Eyes was eventually withdrawn from the market for reasons unrelated to safety or efficacy, according to the FDA.

Nyxol Opportunity in RM

Nyxol has been shown in clinical studies to expedite the reversal of mydriasis compared to the eye's natural process. According to GlobalData market research, over 65% of patients report a moderate to severe negative impact of a dilated exam, underscoring the potential value of Nyxol's role in improving comfort and daily function after pupil dilation. Additionally, an estimated 45% of patients responded that they would be very likely to request a dilation reversal drop, and more than 40% of eye care providers would be likely to use a reversal drop if such a treatment were commercially available. Ocuphire believes that many people who undergo pupil dilation would benefit from a reversal treatment that has the potential to get patients back to their normal routines faster and avoid the subjective discomfort of dilation. Ocuphire also believes that if providers can offer a reversal drop there could potentially be more compliance with annual dilated eye exams.

Presbyopia (Nyxol)

Presbyopia Overview

Presbyopia is an age-related condition with onset most common in people over 40 years old. As the eye ages, the lens becomes stiffer, which limits the eye's ability to adjust its focus for reading or for other tasks that require clear vision at near distances. Presbyopia patients experience blurred near vision, difficulty seeing in dim light, and eye strain. In young healthy eyes, lenses are able to focus light from objects at different distances by a process called accommodation. During accommodation, muscles surrounding the lens contract, causing the lens to change shape and increasing the focusing power of the eye. This allows dynamic, clear vision at both near and far distances. With increasing age, the lens becomes stiffer as the structural crystallin proteins become misfolded. This increased lens stiffness limits the eye's ability to adjust its focus for reading or for other tasks that require clear vision at near distances. Because of the ubiquity of the condition, presbyopia represents a large market both in the United States and abroad totaling over 2 billion presbyopia patients. It is estimated that 120 million Americans have presbyopia, and this number is expected to grow as the population above the age of 45 increases.

Existing Treatments for Presbyopia

The U.S FDA approved Vuity[™] (1.25% pilocarpine) eye drop for the treatment of presbyopia in October 2021. Vuity was launched in December 2021 and is marketed by Allergan, an AbbVie company. Additional available treatments for presbyopia include reading glasses, bifocals, gradients, bifocal contact lenses, and multifocal intraocular lenses. Reading glasses can be inconvenient and must be taken off and put on frequently throughout the day to see objects at far and near distances, respectively. Many patients express frustration with losing or forgetting their glasses. Additionally, some patients find glasses unflattering. Contact lenses for presbyopia also have drawbacks. They can only be used monocularly, where one eye is fitted with a presbyopic lens while the other is used for distance vision, which often leads to eye strain and other negative side effects.

A small portion of patients elect surgical intervention, including laser treatment to achieve monovision and insertion of KAMRA Inlays, a plastic implant into the cornea of the non-dominant eye to increase its depth of field. The risks of such interventions are those associated with all ocular surgeries, such as a potential decrease in contrast sensitivity and the creation or worsening of NVD.

Nyxol Opportunity in Presbyopia

Pupil diameter management is a promising strategy for the pharmacological treatment of presbyopia. Recent research suggests that an optimal pupil size of 2 mm to 3 mm diameter will lead to significant improvement in presbyopia symptoms by increasing depth of focus without compromising distance vision in photopic or mesopic lighting conditions. Ocuphire is evaluating Nyxol as both a single-agent eye drop and with LDP as an adjunctive eye drop to achieve optimal pupil size and improve near vision. Nyxol has shown in several Phase 2 trials the ability to reduce pupil diameter size by 1-1.5 mm alone and by 2-2.5 mm when Nyxol is used with LDP. Nyxol alone provides durable near vision efficacy gain of up to 18 hours, and the Nyxol + LDP combination allows additional efficacy gains of up to at least 6 hours.

With respect to the treatment of presbyopia, Ocuphire believes that tolerability, convenience, and preservation of distance vision quality are of the utmost importance. Presbyopia is considered a “benign” condition, in that there is no risk of death or complete vision loss. Thus, any therapies without robust tolerability will not be suitable alternatives to reading glasses or contact lenses. Nyxol is being developed to be applied once daily before bed, with potential resolution of any mild transient hyperemia by morning. According to GlobalData market research, 69% of patients would consider an eye drop alternative. Ocuphire believes that many presbyopes who are unsatisfied with their reading glasses or monocular contact lenses, and who would prefer a less invasive alternative than surgical intervention, would find Nyxol single-agent eye drop or the Nyxol + LDP drops a promising option, if approved.

NVD (Nyxol)

NVD Overview

Vision at night or in dim light conditions is different from daytime vision in several important ways. Most notably, at night, the pupils dilate to allow more light into the eye. Diminished night vision is a natural part of aging as well as a common side effect of several conditions and procedures. NVD is caused by peripheral imperfections (aberrations) of the cornea which scatter light when the pupil dilates in dim light conditions. These imperfections can be naturally occurring, especially with age, or surgically induced from refractive procedures such as LASIK. As the pupil dilates in response to mesopic conditions, light passes through the periphery of the cornea and lens, unlike during photopic conditions. Any imperfections or aberrations present on the periphery cause light to reach the retina in a non-focused and scattered way, creating glare, halos, starbursts, ghosting, and a loss of contrast sensitivity (“CS”). These visual disturbances can be debilitating to a variety of everyday activities, especially driving. The light emitted by traffic lights and other cars scatters and obscures most of the visual field, making driving in dim light conditions hazardous. Glare, in particular, can be dangerous while driving. In one study of 297 drivers given vision tests that correlate with accidents, 45% of the drivers who reported difficulty driving at night were unable to perform any of the tests with glare.

The effects of NVD can be reduced or eliminated by reducing the pupil size to a smaller diameter that prevents the scattering effect without impeding the ability to see at night. NVD can occur naturally (night myopia) and is commonly caused by ocular surgery (“LASIK”). One significant cause of night myopia is keratoconus, an orphan disease that starts at a young age with progressive thinning of the cornea usually due to genetic and environmental causes. Ocuphire estimates there are about 38 million individuals in the US that suffer from NVD, with an estimated 16 million having moderate-to-severe NVD that may be directly addressable with a pupil management approach. Market research conducted by GlobalData of patients who self-report NVD showed 25% completely avoid driving at night. Furthermore, 67% who report moderate or severe NVD would be willing to try an eye drop treatment option. These patients can be segmented by the origins of their vision disturbance. Approximately 44% of NVD are the result of night myopia, followed by approximately 30% from cortical cataracts, 15% from post-intraocular lens (“IOL”) implants, and 10% following LASIK surgery. These conditions span an age range of late teenagers to those 80 years and older.

Limitations of Existing Treatments for NVD

The biggest challenge for the treatment of NVD is the lack of safe, tolerable, convenient, and effective treatments. Despite a large number of addressable patients with moderate-to-severe NVD, there is no FDA-approved treatment on the market for NVD. Some commonly used tools such as tinted glasses are not effective, and in fact, may worsen patients’ vision at night. Off-label use of approved miotic agents, such as regular-strength pilocarpine, are unsuitable for the treatment of NVD because they reduce pupil size to a degree that may impede safe night vision and may cause loss of accommodation.

Nyxol Opportunity in NVD

Ocuphire believes it may have a new NVD treatment option that could improve patients' ability to see in dim lighting and significantly improve their quality of life. Nyxol is currently the only product candidate in development for NVD and could become the first pharmacological treatment option if approved. In addition to a potential first-mover advantage, Nyxol is being developed to be administered via convenient, once-daily dosing before bedtime and has been shown in multiple Phase 2 clinical trials to improve low contrast visual acuity in mesopic (dim) conditions on the standard visual chart. Nyxol has also been shown to be well-tolerated in these trials.

Diabetic Retinopathy (APX3330)

Diabetic Retinopathy Overview

Diabetic Retinopathy ("DR") is an eye disease resulting from diabetes, affecting over 7 million patients in the U.S., in which chronically elevated blood sugar levels cause damage to blood vessels in the retina. It is the leading cause of vision loss in adults aged 20–74 years. There are two major types of DR:

- *Non-proliferative DR, or NPDR.* NPDR is an earlier, more typical stage of DR and can progress into more severe forms of DR over time if untreated and if exposure to elevated blood sugar levels persists.
- *Proliferative DR, or PDR.* PDR is a more advanced stage of DR than NPDR. It is characterized by retinal neovascularization and, if left untreated, leads to permanent damage and blindness.

Therapies for NPDR and PDR are distinct. For NPDR, treatment is usually directed at observation, lifestyle changes, and control of elevated blood sugars that led to progression of NPDR in the first place. On the other hand, PDR has historically been treated with laser therapy but, more recently, use of anti-VEGF therapies has emerged as a complementary first-line treatment for PDR. In the Protocol S trial by the Diabetic Retinopathy Clinical Research Network, Lucentis was found to be noninferior to laser therapy in patients with PDR. Moreover, in 2018, from Regeneron's PANORAMA trial, EYLEA[®] reversed disease progression in patients with moderately severe to severe NPDR.

Diabetic Macular Edema (APX3330)

Diabetic Macular Edema Overview

Diabetic Macular Edema ("DME") is a common complication of DR where the macula swells with fluid leaked from damaged blood vessels as a result of worsening diabetic retinopathy. It is one of the most common reasons for blindness in diabetics, affecting approximately 750,000 patients. DME may cause blurriness in the center of vision, the appearance of straight lines as wavy, colors that look dull or washed out, or blind spots. The pathogenesis of DME involves vascular leakage, retinal ischemia, and release of vaso-proliferative growth factors and inflammatory mediators.

In DME, corticosteroids and anti-VEGF agents are used to treat vascular leakage, inflammation and hypoxia/angiogenesis. In patients whose disease has progressed to DR with DME, anti-VEGF agents are first line therapy followed by corticosteroids. Lucentis was approved for treatment of DME with a dosing regimen of a 0.3 mg injection approximately every four weeks. Similarly, EYLEA[®] was approved with a dosing regimen of a 2.0 mg injection approximately every four weeks.

Limitations of Existing Treatments for DR and DME

In DR (especially NPDR), despite the approvals of anti-VEGF therapeutics in recent years, the use of injectables is not adopted in practice as preferred treatment as the disease is asymptomatic and patients are reluctant to undergo injections or laser therapy.

In DME and late-stage DR, intravitreal VEGF inhibitors are approved globally, however these therapies rarely provide a complete solution to the underlying vascular problem associated with DR and DME. Although these therapeutic agents have been successful for some patients, significant proportions of patients are resistant and refractory. Moreover, serious side effects including hemorrhage and intraocular infections are possible with intravitreal injections. Both Lucentis and EYLEA are also associated with increased risks of blood clots in the arteries. In addition, intravitreal injections require frequent visits to the ophthalmologist, usually on the order of every 4 weeks with a few anti-VEGF therapies in development that are working on increasing the time between injections (8 – 12 weeks).

APX3330 Opportunity in DR and DME

Anti-VEGF therapies block the activity of VEGF, but in chronic diseases such as DR and DME, an agent that prevents the production of VEGF poses a large opportunity to improve patient outcomes. Moreover, recent reports in scientific literature demonstrate that diabetic eye disease has an inflammatory component, unrelated to VEGF's actions. Because inflammation and hypoxic signaling (VEGF production) play crucial roles in both vascular leakage and neovascularization of DR and DME, treatments that impinge upon both pro-inflammatory and hypoxic signaling offer a promising therapeutic strategy. APX3330's target of Ref-1 may leverage this dual mechanism to reduce the production and hence the quantity of VEGF and prevent inflammatory damage. This potentially allows for improved response to treatment and may extend the duration between invasive treatments for late-stage retinal diseases (DME, wAMD). Moreover, as a potential first-in-class, orally administered product candidate twice a day, it has the potential to be a more convenient option at an earlier stage of disease especially for DR than intravitreal anti-VEGF injections, which are burdensome to patients and have a significant side effect profile including cataract formation, increased intraocular pressure, intraocular infections, and retinal detachments. APX3330 was well-tolerated and demonstrated a favorable safety profile in completed clinical trials of healthy volunteers and patients with hepatitis or cancer. The safety data from the ongoing masked ZETA-1 trial in diabetic patients is consistent with data from the prior eleven clinical trials.

Other Indications: wAMD (APX3330)

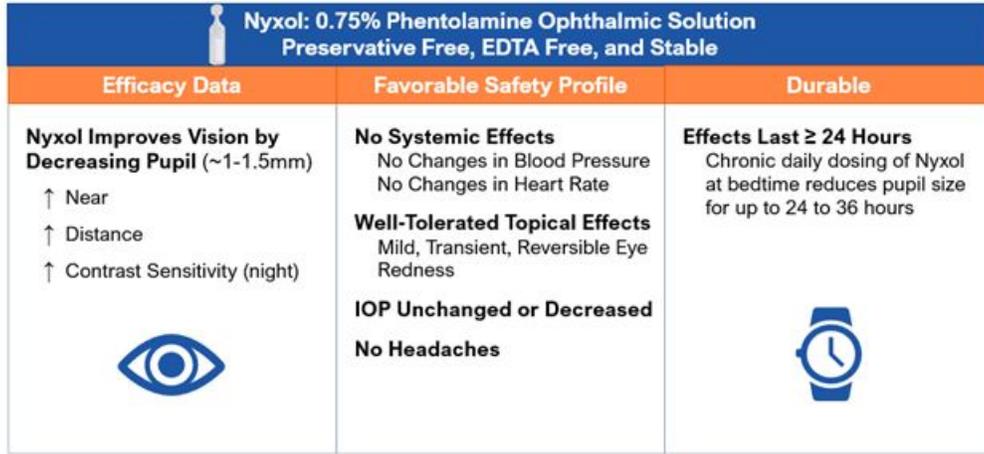
Age-Related Macular Degeneration ("AMD") is a common eye condition affecting 11 million individuals in the U.S. and 196 million globally, mostly over the age of 55 years. It is a progressive disease affecting the central portion of the retina, known as the macula, which is the region of the eye responsible for sharpness, central vision and color perception. wAMD is an advanced form of AMD characterized by neovascularization and fluid leakage under the retina. It is the leading cause of severe vision loss in patients over the age of 50 in the United States and EU. While wAMD represents only 10% of the number of cases of AMD overall, it is responsible for 90% of AMD-related severe vision loss. Untreated or undertreated wAMD results in further blood vessel leakage, fluid in the macula, and ultimately scar tissue formation, which can lead to permanent vision loss or even blindness as a result of the scarring and retinal deformation that occur during periods of non-treatment or undertreatment. Similar to severe DR and DME, current therapy for wAMD consists of intravitreal injections, mainly of Lucentis and EYLEA. The limitations of these therapies are described in the section above titled, "Limitations of Existing Treatment for DR and DME". Based on APX3330 targeting Ref-1 and reduction of VEGF production, it has potential use in wAMD. Further, to enter the wAMD injectable market, Ocuphire is considering the utility of an intravitreal formulation of APX2009, a second-generation product candidate analog of APX3330. APX2009 data suggest improved efficacy against the Ref-1 target compared to APX3330 (as published in the Journal of Pharmacology and Experimental Therapeutics).

Ocuphire’s Product Candidates

Nyxol Mechanism of Action

Ocuphire’s lead product candidate, Nyxol, is a once-daily sterile eye drop formulation of phentolamine mesylate designed to reduce pupil diameter and improve visual acuity. The active pharmaceutical ingredient of Nyxol, phentolamine mesylate, is a non-selective alpha-1 and alpha-2 adrenergic antagonist that inhibits activation of the smooth muscle of the iris, reducing pupil diameter. Nyxol shares many of the attributes of existing ophthalmic eye drops, including a convenient route of administration and cost-effective manufacturing process, with the potential advantage of once-daily dosing (**FIGURE 1**).

FIGURE 1. Nyxol Product Candidate Profile



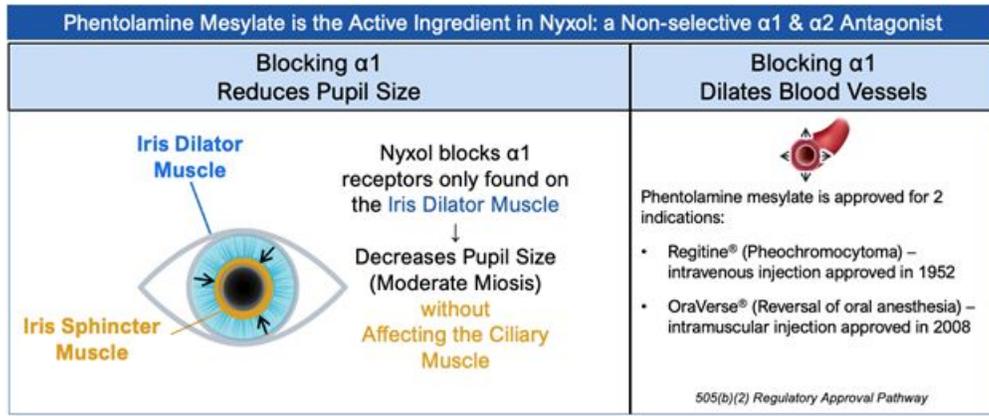
Phentolamine is a nonselective alpha-1 & alpha-2 adrenergic antagonist. Dilation of the pupil is controlled by the radial iris dilator muscles surrounding the pupil which are activated by the alpha-1 receptors of the adrenergic nervous system. Alpha-1 antagonists bind to the receptors to inhibit the pupillary response and reduce dilation (**FIGURE 2**). Phentolamine mesylate is the active ingredient in two injectable FDA-approved drugs, Regitine and OraVerse, as described previously.

For the RM indication, pharmacologically induced mydriasis is achieved either by stimulating the iris dilator muscle with the use of alpha agonists (e.g., phenylephrine), or by blocking the iris sphincter muscle with the use of muscarinic antagonists (e.g., tropicamide). Nyxol, either by directly antagonizing the alpha-1 agonist or by indirectly antagonizing the pupil dilation effect of muscarinic blocking, may expedite the reversal of mydriasis prior to natural reversal.

For presbyopic patients, to overcome the lens’ inability to change shape (accommodation) and focus light from near objects, pupil diameter reduction to a small size will allow light to come in the eye only in a near straight direction and increase the depth of focus (the “pinhole effect”). Ocuphire believes that it is possible to reach a target 2 mm to 3 mm optimal pupil diameter by relaxing the dilator iris muscle with Nyxol and contracting the iris sphincter muscle with a muscarinic agonist such as a low dose pilocarpine. This could result in an optimal depth of focus and near vision clarity without the assistance of lenticular accommodation.

Lastly, for the NVD indication, it is proposed that a moderate miotic effect by application of Nyxol might mitigate night vision difficulties, a large portion of which are caused by imperfections or aberrations present on the periphery of the cornea. Therefore, the effects of these imperfections can be reduced or eliminated by reducing the pupil size to a smaller diameter, knowing that a smaller pupil blocks what would be unfocused, aberrant rays of light on the retina.

FIGURE 2. Nyxol's Mechanism of Action



Nyxol Clinical Experience Summary

Nyxol has been assessed in nine investigator-initiated and sponsored Phase 1, Phase 2 and Phase 3 clinical trials. Across all trials, over 330 adult patients have been exposed to at least one dose of phentolamine ophthalmic solution. All Phase 2 and Phase 3 trials have been accepted for poster or oral presentation at the annual American Academy of Ophthalmology (AAO), Association for Research in Vision and Ophthalmology (ARVO), or American Society of Cataract and Refractive Surgery (ASCRS) meetings.

Ocuphire believes that results from Nyxol's Phase 1, Phase 2 and Phase 3 trials support its current development plan focused on RM, presbyopia and NVD patients. Specifically, patients treated with Nyxol were observed to have statistically significant decreases in pupil diameter and improved visual acuity. Nyxol has shown consistent ability to decrease pupil diameter at the selected dose of 0.75% POS by approximately 20-25% (~1 – 1.5 mm) in both mesopic and photopic conditions.

A summary of Ocuphire's completed clinical trials is shown below (TABLE 2). Note that Nyxol in its current proprietary formulation of phentolamine mesylate ophthalmic solution was first introduced in the NYX-01a2 trial, and prior to that, a formulation of phentolamine mesylate in artificial tears solution was used.

TABLE 2. Summary of Completed and Ongoing Clinical Trials with Nyxol

Trial Name (IND Number)	Patient / Indication	Phase	Trial Objectives	Doses	Number of Patients [^]	Dosing	Key Endpoints
NYX-001 (67-288)	Healthy Volunteers	1	Double-masked, randomized, single dose, 3-arm controlled, parallel trial to determine the efficacy and safety of phentolamine mesylate	0.2% PMOS	Nyxol [*] =15, Visine=15, Visine + Nyxol [*] =15 Total = 45	Single-dose	Safety and Efficacy (PD)
NYX-002 [^] (67-288)	Healthy Volunteers	1	Double-masked, randomized, placebo-controlled, single-dose, incomplete block, 3-period crossover, dose escalation trial evaluating the tolerability and efficacy of phentolamine mesylate	0.2%, 0.4%, 0.8% PMOS	Nyxol [*] =16 Placebo=12 Total = 16	Single-dose	Safety and Efficacy (PD, VA)

OP-NYX-004 [^] (73-987)	Night Vision Disturbances Patients	1 / 2	Double-masked, randomized, placebo-controlled, single-dose, incomplete block 3-period crossover, dose escalation trial to determine the efficacy and safety of phentolamine mesylate	0.2%, 0.4%, 0.8% PMOS	Nyxo ^l *=16 Placebo=12 Total = 16	Single-dose	Safety and Efficacy
OP-NYX-SNV (70-736)	Severe Night Vision Disturbances Patients	2	Double-masked, randomized, placebo-controlled, single-dose trial to assess the efficacy and safety of phentolamine mesylate ophthalmic solution	1.0% PMOS	Nyxo ^l *=16, Placebo=8 Total = 24	Single-dose	Safety and Efficacy (PD, LCVA, CS, WA)
OP-NYX-01a2 (70-499)	Severe Night Vision Disturbances Patients	2	Double-masked, randomized, placebo-controlled, single-dose, 3-arm trial to assess the efficacy and safety of Nyxo ^l	0.5%, 1.0% PMOS	Nyxo ^l =40 Placebo=20 Total = 60	Multiple doses (15-28 days)	Safety and Efficacy (PD, LCVA, CS)
OPI-NYXG-201 (ORION-1) (70-499)	Glaucoma and Ocular Hypertension, Elderly Patients	2b	Double-masked, randomized, placebo-controlled, multiple-dose, multi-center trial to assess the efficacy and safety of Nyxo ^l	1.0% PMOS	Nyxo ^l =19 Placebo=20 Total = 39	Multiple doses (14 days)	Safety and Efficacy (IOP, PD, near VA, VA)
OPI-NYXRM-201 (MIRA-1) (70-499)	Healthy Patients/ Reversal of Mydriasis	2b	Double-masked, randomized, placebo-controlled, crossover, single-dose, multi-center trial to assess the efficacy and safety of Nyxo ^l in reducing pharmacologically induced mydriasis	1.0% PMOS	Nyxo ^l =31 Placebo=32 Total = 32	Single-dose	Safety and Efficacy (PD, Accommodation, VA)
OPI-NYXRM-301 (MIRA-2) (70-499)	Healthy Patients/ Reversal of Mydriasis (including 12-17 years-old)	3	Double-masked, randomized, placebo-controlled, single-dose, multi-center trial to assess the efficacy and safety of Nyxo ^l in reducing pharmacologically induced mydriasis	0.75% POS	Nyxo ^l =94 Placebo=91 Total = 185	Single-dose	Safety and Efficacy (PD, Accommodation, VA)
OPI-NYXRM-302 (MIRA-3) (70-499)	Healthy Patients/ Reversal of Mydriasis (including 12-17 years old)		Double-masked, randomized, placebo-controlled, single-dose, multi-center trial to assess the efficacy and safety of Nyxo ^l in reducing pharmacologically induced mydriasis	0.75% POS	Pending data Total = 368	Single-dose	Safety and Efficacy (PD, Accommodation, VA)

OPI-NYXRMP-303 (MIRA-4) (70-499)	Healthy Patients/ Reversal of Mydriasis (between ages of 3-and 11)		Randomized, Parallel-Arm, Double-Masked, Placebo-Controlled Study of the Safety and Efficacy of Nyxol (0.75% Phentolamine Ophthalmic Solution) to Reverse Pharmacologically Induced Mydriasis in Healthy Pediatric Subjects	0.75% POS	Pending data Total = 23	Single-dose	Safety and Efficacy (PD)
OPI-NYXP-201 (VEGA-1) (70-499)	Presbyopia patients (ages of 40 and 64)	2	Randomized, Placebo-Controlled, Double-Masked Study of the Safety and Efficacy of Nyxol (0.75% Phentolamine Ophthalmic Solution) with Low-Dose (0.4%) Pilocarpine Eye Drops in Subjects with Presbyopia	0.75% POS	Nyxol +LDP = 44 Placebo alone = 45 Nyxol alone = 30 Placebo +LDP = 31	Multiple doses (up to 4 days), Single dose of LDP	Safety and Efficacy (DCNVA, VA, PD)
OPI-NYXDLLD-301 (LYNX-1) (70-499)	Night Vision Disturbances in adults		Randomized, Placebo-Controlled, Double-Masked Study of the Safety and Efficacy of Nyxol (0.75% Phentolamine Ophthalmic Solution) in Subjects with Dim Light Vision Disturbances	0.75% POS	Pending data Total =145	Multiple doses (14 days)	Safety and Efficacy (mLCVA, VA, PD)

Note: Nyxol = phentolamine mesylate in proprietary formulation, Nyxol* = phentolamine mesylate in commercial artificial tears solution. ^ Total patient numbers will not equal to the sum of the subgroups in crossover studies (NYX-002, NYX-004, and NYXRM-201). 0.75% POS (Phentolamine Ophthalmic Solution) is the same as 1% PMOS (Phentolamine Mesylate Ophthalmic Solution). References to Nyxol with both designations appear throughout this document, there is no difference in formulation between the two designations.

MIRA PROGRAM – Reversal of Mydriasis Indication for Nyxol

Nyxol RM: MIRA-3 Second Phase 3 Trial (Ongoing)

Ocuphire completed enrollment of MIRA-3, a Phase 3, double-masked, randomized, placebo-controlled, multi-center trial in healthy patients, in February 2022. The MIRA-3 trial evaluates the safety and effect of Nyxol to reverse pharmacologically induced mydriasis. The trial expected to enroll approximately 330 healthy patients, and ultimately enrolled 368 (including 12–17-year-old patients). Eligible patients are administered a mydriatic (phenylephrine, tropicamide, and a combination thereof) and then given 2 drops of Nyxol approximately 1 hour later after maximum pupil diameter, and then measured at multiple time points from 30 min to 6 hours and 24 hours. The primary endpoint is a statistically significant improvement in the percent of patients who return to within 0.2 mm of their pupil diameter baseline at 90 minutes, with 60 minutes also being evaluated. Key secondary endpoints are pupil diameter at all other timepoints, accommodation, glare, and time savings (to return normal baseline). Patient safety is assessed by AE monitoring, conjunctival redness monitoring, visual acuity, IOP, and vital sign assessments (heart rate and blood pressure). In addition, sparse pharmacokinetics (PK) sampling was performed in this trial. Acute safety exposure for 300 healthy patients followed for 24 hours was also evaluated across the MIRA-2 and MIRA-3 trials. Ocuphire expects to report top-line data for this acute indication Phase 3 registration trial around the end of first quarter of 2022.

Nyxol RM: MIRA-4 Pediatric Trial (Ongoing)

Ocuphire completed enrollment of MIRA-4, a Phase 3, double-masked, randomized, placebo-controlled trial in healthy pediatric patients (ages 3-11) in March 2022. The MIRA-4 trial evaluated the safety and effect of Nyxol to reverse pharmacologically induced mydriasis in healthy pediatric patients. The trial was expected to enroll approximately 20 healthy pediatric patients in 2 age groups (3 to 5 years old and 6 to 11 years old), and ultimately enrolled 23 healthy pediatric patients (eleven 3 to 5 years old and twelve 6 to 11 years old). Eligible pediatric patients were administered a mydriatic agent (phenylephrine, tropicamide, or Paremyd, a combination thereof) and then given 1 drop of Nyxol approximately 1 hour later after maximum pupil diameter, and then measured at multiple time points from 90 minutes to 3 hours and 24 hours. The primary endpoint is safety and key secondary endpoints are pupil diameter, accommodation, and time savings. Patient safety is assessed by AE monitoring, conjunctival redness monitoring, visual acuity, IOP, and vital sign assessments (heart rate and blood pressure). Ocuphire expects to report top-line data for this acute indication Phase 3 registration trial in the second quarter of 2022.

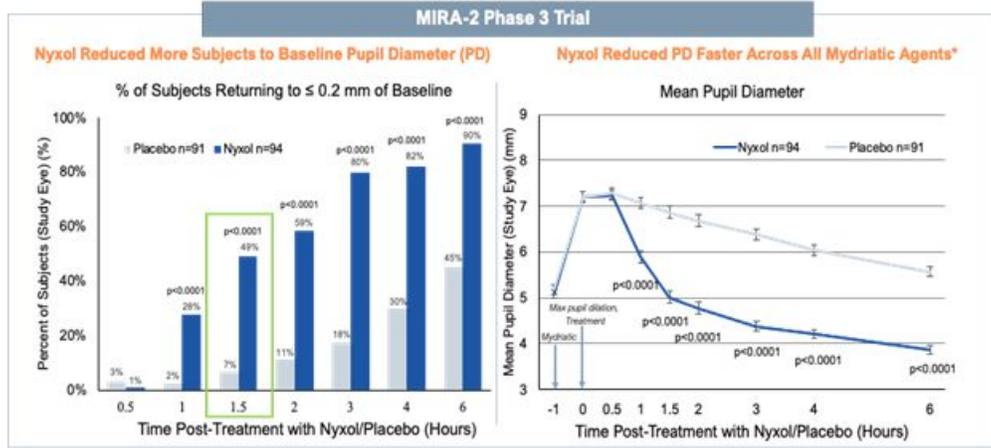
Nyxol RM: MIRA-2 First Phase 3 Trial (Completed)

In MIRA-2 (OPI-NYXRM-301), the first of two Phase 3 studies for the reversal of pharmacologically induced mydriasis, 185 patients, including 14 pediatric patients aged 12 to 17 years, were randomized to receive either Nyxol or placebo 1 hour after receiving one of 3 mydriatic agents (phenylephrine, tropicamide or Paremyd randomized 3:1:1, respectively). Pediatric patients received 1 drop of study drug in each eye, and adult patients received 2 drops of study drug in study eye and the fellow eye received a single drop of study drug. The primary endpoint was an increase in the percent of study eyes returning to within 0.2 mm of baseline PD at 90 min after Nyxol dosing compared to placebo dosing in patients who were pharmacologically dilated. The data from this study were presented at ASCRS 2021 by Dr. Jay Pepose MD, PhD in July 2021, and the presentation was given the Best Paper of the Session award.

The primary endpoint was met in this Phase 3 study. For patients in the mITT Population treated with Nyxol, 49% had PD returned to within 0.2 mm of baseline PD at 90 min compared to only 7% of patients treated with placebo ($p < 0.0001$). This benefit was seen as early as 60 min post dose (28% vs 2%; $p < 0.0001$). Further, Nyxol returned more patients to baseline PD than placebo at all time points from 1-6 hours ($p < 0.0001$ for each timepoint). Similarly, significant differences in PD between Nyxol and placebo were seen at all time points from 1-6 hours ($p < 0.0001$ for each).

The mean time to return to baseline PD 2 hours in Nyxol-treated study eyes and 6 hours in placebo-treated study eyes. Examination of mean PD by treatment group further support the results of the categorical responder analysis. Significant benefit of Nyxol was also observed in fellow eyes that received a single drop of Nyxol. For the mITT Population, the reduction in mean PD from the maximum PD observed at 1 hour post-mydriatic dosing was 1.15 mm at 60 min after Nyxol administration and increased to a mean reduction of 1.95 mm at 90 min. Both of these reductions from the maximum PD were statistically significant ($p < 0.0001$). See **FIGURE 3**. Nyxol treatment was efficacious for all 3 mydriatic agents and for patients with either light or dark irides.

FIGURE 3. Study OPI-NYXRM-301 (MIRA-2): Percent of patients returning to ≤ 0.2 mm of baseline pupil diameter (left panel) and mean pupil diameter (right panel)



NyxoL was well-tolerated with a favorable safety profile. Instillation site discomfort and conjunctival hyperemia were the only adverse events (AEs) that occurred in $\geq 5\%$ patients treated with NyxoL, and 95% of the AEs were mild. Visual acuity was not adversely affected. There were no deaths, no systemic AEs, no serious AEs or withdrawals due to AEs.

NyxoL RM: MIRA-1 Phase 2b Trial (Completed)

MIRA-1 (NYXRM-201) was a double-masked, randomized, placebo-controlled, multicenter, cross-over trial of NyxoL compared with vehicle (placebo) ophthalmic solution in normal healthy patients with eyes dilated using a mydriatic agent (phenylephrine or tropicamide). Thirty-two patients (median age of 27) were randomized in a 1:1 ratio to placebo at Visit 1 followed by NyxoL at Visit 2 or NyxoL at Visit 1 followed by placebo at Visit 2. The study medication was administered 1 hour after dilation and measurements were taken between 0 and 6 hours. The primary efficacy endpoint was a change in mean pupil diameter (PD) at 2 hours post-treatment. Highlights of this trial were presented at the 2020 annual meeting of the Association for Research in Vision and Ophthalmology (ARVO) by Dr. Paul Karpecki and were also published in February 2021 in *Optometry and Visual Science*, the international, peer-reviewed journal of the American Academy of Optometry.

The primary efficacy endpoint for this trial, the change in mean pupil diameter at 2 hours post-treatment, was met with a statistically significant result (-1.69 mm vs -0.69 mm, $p < 0.0001$, primary efficacy endpoint). A statistically significant difference favoring NyxoL treatment was also observed at all time points tested from 1 hour through 6 hours in the study eye and non-study eye. This was true for participants dilated with both 2.5% phenylephrine and 1% tropicamide. A greater percentage of patients receiving NyxoL treatment compared with placebo had study eyes that showed reversal of mydriasis (returning to within 0.2mm of baseline diameter) at 2 hours and 4 hours, with a trend towards significance at 1 hour. This confirmed the FDA approvable endpoint for the timepoints measured in MIRA-1, which helped inform the Phase 3 trial design for the RM indication. NyxoL also improved accommodation in patients treated with tropicamide.

When treated with NyxoL, 36% of patients experienced eye disorder TEAEs (all mild cases of conjunctival hyperemia), with no serious TEAEs or TEAEs leading to withdrawal or study medication discontinuation. No other TEAEs were observed with NyxoL treatment.

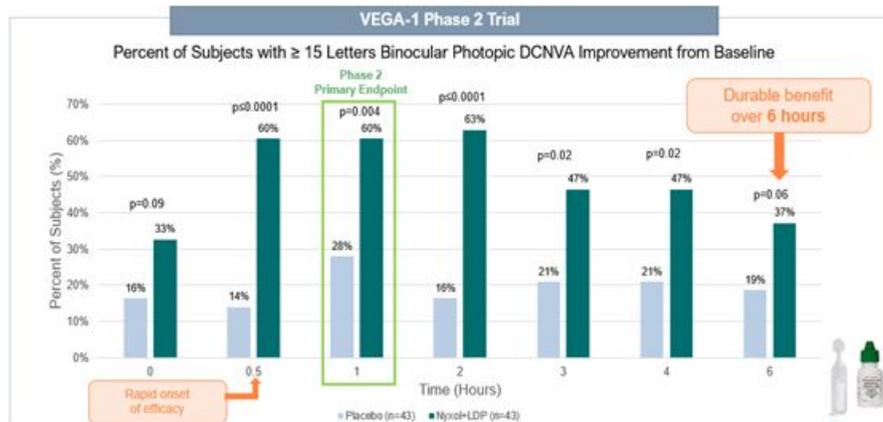
VEGA PROGRAM – Presbyopia Indication for Nyxol and Nyxol+LDP

Nyxol Presbyopia: Phase 2 VEGA-1 Trial (Completed)

VEGA-1 (NYXP-201) was a double-masked, randomized, placebo-controlled, multi-center trial of Nyxol and LDP compared with vehicle (placebo) ophthalmic solution in presbyopic patients. A total of 150 patients were randomized 3:2:2:3 to receive Nyxol + LDP, Nyxol alone, LDP alone, or placebo, respectively. Nyxol or placebo was dosed for 3 or 4 consecutive evenings prior to binocular and monocular testing under photopic and mesopic lighting conditions. Measurements were made between 0 and 6 hours following administration of Treatment 2 (LDP or No Treatment). The primary efficacy endpoint for this study was the percent of patients who improved by ≥ 15 letters in DCNVA at 90 minutes post-treatment. The data from this study were presented at ASCRS 2021 by Dr. Jay Pepose, MD, PhD in July 2021.

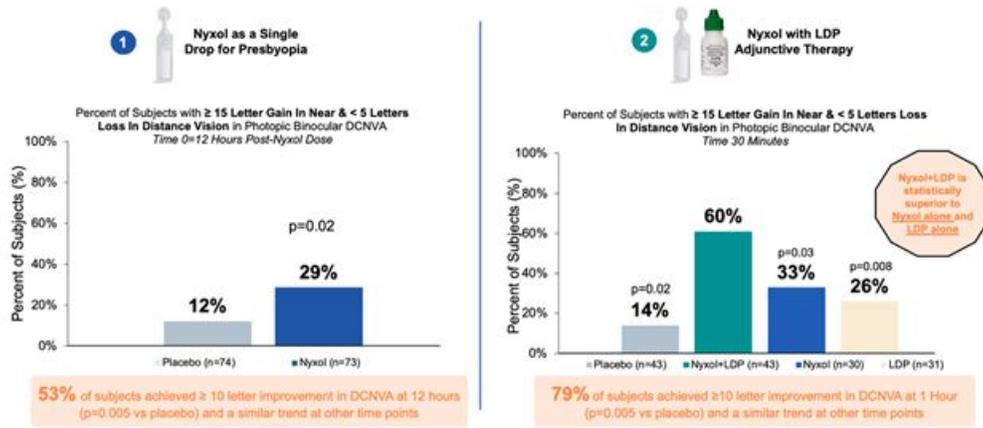
The primary endpoint of an increase in the percent of patients gaining ≥ 15 letters binocular photopic DCNVA at 1 hour in patients treated with Nyxol + LDP compared to placebo was met. In addition, key prespecified secondary endpoints were met, including the effect of Nyxol monotherapy on DCNVA and PD 12 hours after dosing, near vision gains at multiple time points and PD change. No clinically relevant loss of BCDVA was observed. Sixty percent of patients treated with Nyxol + LDP gained ≥ 15 letters at 1 hour compared to 28% of placebo-treated ($p = 0.003$; primary endpoint). By this 1-hour time point, 84% of patients had DCNVA of 20/40 or better. The difference between Nyxol + LDP and placebo was statistically significant beginning at 30 minutes, with durability over the 6 hours of measurement (**FIGURE 4**). Nyxol + LDP was numerically superior to each component alone at all time points post-LDP dosing. Treatment was effective in improving DCNVA in patients with both light and dark irides. Key prespecified secondary endpoints were met, including the effect of Nyxol monotherapy on DCNVA and PD 12 hours after dosing, near vision gains at multiple time points and PD change.

FIGURE 4. Study OPI-NYXP-201 (VEGA-1): Percent of Patients Gaining ≥ 15 Letters in Binocular Photopic DCNVA by Treatment Arm and Timepoints (PP Population)



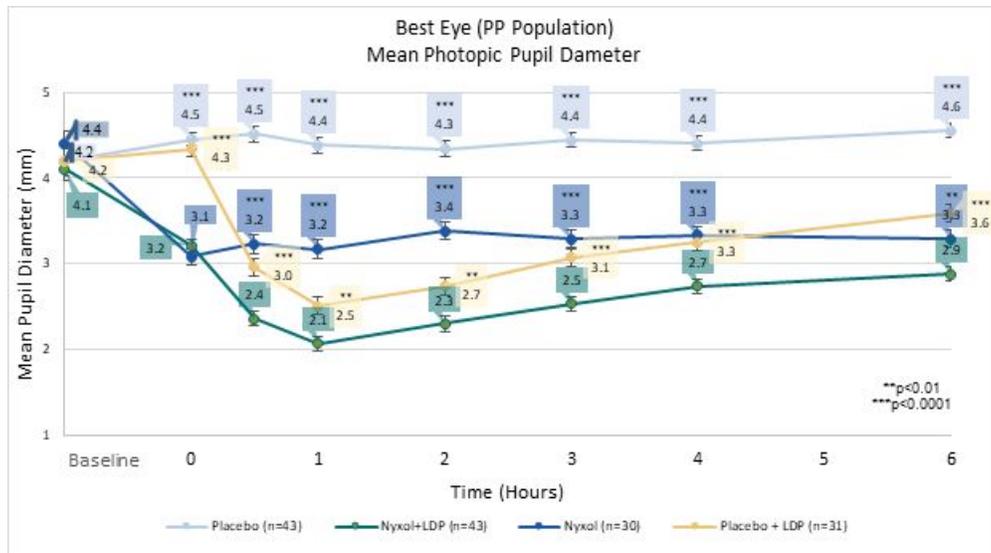
The effect of Nyxol alone on presbyopia was assessed in a prespecified secondary analysis 12 hours after the last dose following 3-4 days of Nyxol or placebo evening dosing prior to randomization and treatment with LDP. In the Nyxol-treated group ($n=73$), a significantly greater percent of patients ($n=73$) had ≥ 15 letters improvement and < 5 letters loss in distance vision in photopic binocular DCNVA compared with placebo-treated patients ($n=74$) at 0 min (29% vs 12%, respectively; $p = 0.02$) (**FIGURE 5**). After treatment with LDP, the Nyxol+LDP combination led to a greater percentage of patients achieving a ≥ 15 letters improvement in DCNVA and < 5 letters loss in distance vision in photopic binocular DCNVA than Placebo, Nyxol alone, or LDP alone (60% vs 14% vs 33% vs 26%, respectively; $p<0.05$ for each). After treatment with Nyxol alone and Nyxol with LDP, the Nyxol+LDP combination led to a greater percentage of patients achieving a ≥ 10 letters improvement in DCNVA (53% in Nyxol; $p=0.005$ and 79% in Nyxol+LDP; $p= 0.005$).

FIGURE 5. Nyxol as Single Agent and Nyxol+LDP Achieved Statistically Significant Near Vision Improvement



Nyxol and Nyxol+LDP provided durable optimal pupil diameter of ~ 2 mm to 3 mm, offering improvement in near vision without the loss of distance vision (FIGURE 6). Nyxol and Nyxol+LDP maintained a dynamic pupillary response when transitioning between photopic and mesopic lighting conditions.

FIGURE 6. Study OPI-NYXP-201 (VEGA-1): Mean pupil diameter



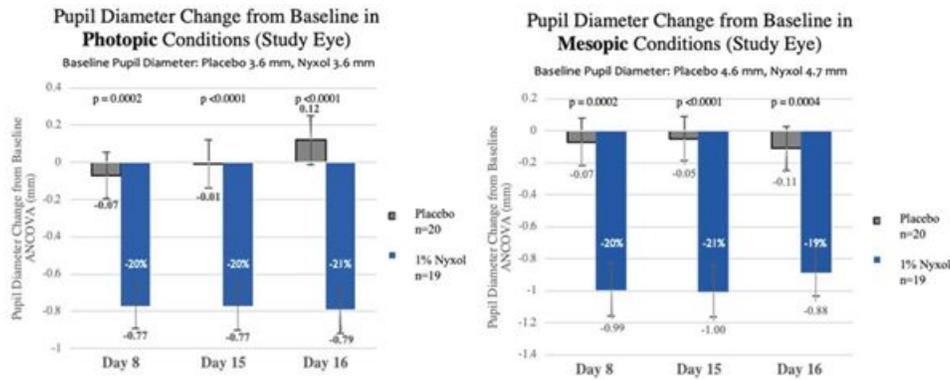
Nyxol alone as well as Nyxol +LDP were both well-tolerated with a favorable safety profile. Instillation site discomfort and conjunctival hyperemia were the only adverse events (AEs) that occurred in ~5% patients, and 95% of the AEs were mild and none were severe. Visual acuity was not adversely affected. There were no deaths, no systemic AEs, no serious AEs or withdrawals due to AEs in patients receiving Nyxol only. No headaches, brow aches or blurry vision AEs were observed.

Nyxtol Presbyopia: Phase 2b ORION-1 Trial (Completed)

ORION-1 (NYXG-201) was a double-masked, randomized, placebo-controlled, multi-center Phase 2b trial of Nyxtol compared with placebo ophthalmic solution for 14 days in patients with open angle glaucoma or ocular hypertension, many of whom were also presbyopic. A total of 39 elderly patients with elevated intraocular pressure (median age of 63; no prior use of IOP lowering medications in ≥ 30 days) were randomized to Nyxtol (n = 19) or placebo (n = 20) nightly for 14 days. The primary efficacy endpoint was the change from baseline in mean diurnal IOP (mean of the IOP measurements at 8AM, 10AM, and 4PM) at Day 15. Secondary efficacy endpoints included change in pupil diameter (PD), change in distance-corrected near visual acuity (DCNVA), and change in best-corrected distance visual acuity (BCDVA), as well as additional IOP analyses. Highlights of this trial were presented at the 2020 annual meeting of the Association for Research in Vision and Ophthalmology (ARVO) by Dr. Jay Pepose, and published in January 2021 in *Clinical Ophthalmology*, an international, peer-reviewed, open access journal.

In the ORION-1 trial, patients treated with Nyxtol showed statistically significant reduction in PD and improvement in near visual acuity relative to placebo with evening bedtime daily dosing regimen. The primary endpoint for change in diurnal IOP was not met with statistical significance although in a post-hoc analyses there was a trend for IOP lowering in the Nyxtol arm with patients at lower IOP baselines. More importantly in the ORION-1 trial, key prespecified secondary endpoints for other indications such as NVD and Presbyopia were successfully met with evening daily dosing of Nyxtol eye drops, including PD reduction and visual acuity performance. Statistically significant mean $\sim 20\%$ (~ 1 mm) PD reduction from baseline in the Nyxtol arm as compared to the placebo arm was observed at all timepoints tested for study eye in both photopic and mesopic conditions that was sustained over 24 hours with bedtime daily dosing ($p \leq 0.0003$), as measured for a prespecified secondary endpoint. Under photopic conditions, change from baseline was statistically significant favoring the Nyxtol arm vs placebo at every time point, for example on Day 15 (-0.77 mm vs -0.01 mm, $p < 0.0001$) (FIGURE 7A). Similarly, under mesopic conditions, change from baseline was statistically significant favoring the Nyxtol arm vs placebo at every time point, for example at Day 15 (-1.00mm vs -0.05 mm, $p < 0.0001$) (FIGURE 7B). A statistically significant percent of patients, favoring the Nyxtol arm compared with the placebo arm in the study eye under photopic and mesopic conditions, achieved ≥ 1 line of DCNVA improvement at one or more timepoints (photopic Day 15: 63% vs 20%, $p = 0.026$; mesopic Day 15: 58% vs 15%, $p = 0.014$), as measured for a prespecified secondary endpoint. Nyxtol was well tolerated and there were no major ocular or systemic safety issues.

FIGURE 7A and 7B: Pupil Diameter Change from Baseline by Visit in Photopic (A) and Mesopic (B) Conditions (ORION-1)



LYNX PROGRAM – Night Vision Disturbance Indication for Nyxol

Nyxol NVD: Phase 3 LYNX-1 Trial (Ongoing)

Ocuphire initiated LYNX-1, a Phase 3 double-masked, randomized, placebo-controlled, multi-center, multi-dose trial in patients with severe NVD in the fourth quarter of 2020 in the United States. The LYNX-1 trial for the treatment of NVD completed enrollment in January 2022 with 145 patients. The trial enrolled moderate-to-severe self-reported NVD and among other criteria include patients showing improvement potential in mesopic LCVA during illumination of the contralateral eye with a brightness acuity tester (BAT). Eligible participants are expected to receive a single drop of Nyxol or placebo in each eye daily before bedtime for 14 days. The primary endpoint is a statistically significant improvement of 3 lines or greater in mesopic low contrast best-corrected distance visual acuity at 7 days. Key secondary endpoints are pupil diameter, wavefront aberrometry (measured on OPD-Scan III analyzer at a sub-set of study sites), distance and near high contrast visual acuity, and psychometric questionnaire. Patient safety is assessed by AE monitoring, conjunctival redness monitoring, IOP monitoring, and assessments of heart rate and blood pressure. Ocuphire expects to report top-line data for this chronic indication Phase 3 registration trial in the second quarter of 2022. Dim light performance data of Nyxol from LYNX-1 may support the Nyxol single agent Presbyopia VEGA program.

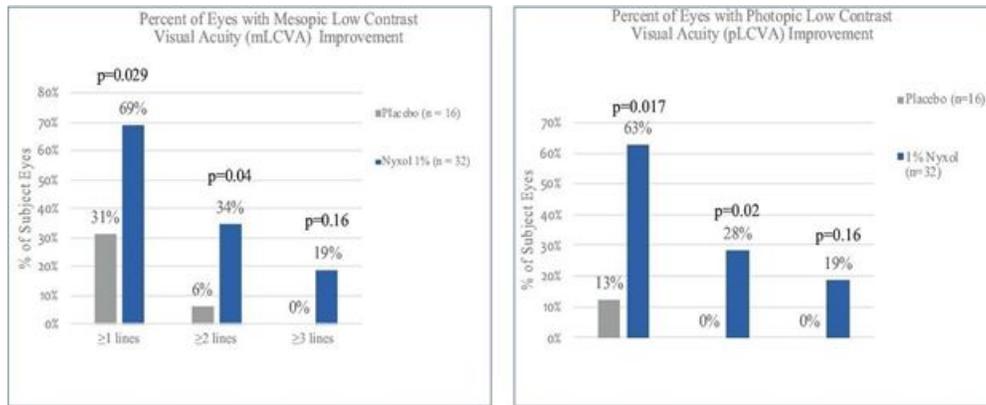
Nyxol NVD: Phase 2 Trial NYX-SNV (Completed)

NYX-SNV was a double-masked, randomized, placebo-controlled, single-dose, 1-day trial assessing the tolerability and effect of a single topical drop of 1.0% solution of phentolamine mesylate in Tears Naturale II in each eye or Tears Naturale II (placebo) on pupil diameter (PD), CS, visual acuity (VA), and wavefront aberrometry (WA). A total of 24 patients (median age of 39) with severe night vision complaints were randomly assigned 2:1 to treatment groups (active treatment n = 16; placebo control n = 8). Highlights of this trial were presented at the American Academy of Ophthalmology (McDonald et al., 2010) and the American Society of Cataract and Refractive Surgery (McDonald et al., 2011).

In NYX-SNV trial, patients treated with Nyxol exhibited greater reductions in pupil diameter and greater improvements in low contrast visual acuity compared to those on placebo. The primary endpoint of the mean change in contrast sensitivity under mesopic conditions at each of five spatial frequencies (continuous analysis) was not met, but mean change was statistically significant at three out of five CS frequencies. Statistically significant changes were also found in key secondary endpoints including LCVA (mesopic and photopic), change in PD, reduction in aberration errors (errors that affect light transmission in specific pupil diameter sizes), and percent of patients with an improvement in CS in three out of five frequencies.

For NVD, the planned FDA primary endpoint is percent of patients with 3 lines of improvement in mesopic low contrast best-corrected distance visual acuity (mLCVA) at a single timepoint. In this trial, even with small sample size, there was a positive trend of 3-line (15-letter or greater) improvement in mLCVA (19% Nyxol versus 0% for placebo, p = 0.16) and photopic low contrast distance visual acuity (PLCVA) (19% Nyxol versus 0% for placebo, p = 0.16). Additionally, greater fractions of Nyxol-treated eyes registered a 1-line (5-letter or greater) improvement in MLCVA (69% versus 31% for placebo, p = 0.029) and PLCVA (63% versus 13% for placebo, p = 0.017), as well as a 2-line (10-letter or greater) improvement in mLCVA (34% versus 6% for placebo, p < 0.03) and PLCVA (28% versus 0% for placebo, p < 0.02); **(FIGURE 8)**. There were statistically significant improvements with Nyxol from pre-treatment across all mean VA measurements (p < 0.0001). Further, mean MLCVA showed statistically significant improvement for both treatment groups 2–3 hours post treatment, with the mean magnitude of improvement for phentolamine mesylate patients being over twice that of placebo patients (8.0 versus 3.1 letters, respectively; p = 0.035).

FIGURE 8. Percent of Eyes with 1, 2, and 3 or More Lines of Improvement in Mesopic Low Contrast Visual Acuity (left) and Photopic Low Contrast Visual Acuity (right) (NYX-SNV)



Mean PD decreased at a statistically significant amount of an average of 1.3 mm ($p < 0.0001$), or ~20%, for phentolamine mesylate treated patients, whereas mean PD of placebo patients did not significantly change between pre-treatment and post-treatment. The difference in mean change between treatment groups was also statistically significant (1.1 mm, $p < 0.0001$) In a post-hoc analysis that helped inform the Phase 3 trial design, there was an average of ~1.5 mm pupil diameter reduction in patients with baselines above 6mm, compared to ~1 mm reduction in patients with baselines below 6 mm. Measurements were taken 2–3 hours after dosing.

No serious adverse events or other adverse events were reported during the trial. Overall, study treatment appeared to be well-tolerated. The most common mild AE was conjunctival hyperemia. No meaningful differences in mean HR or mean systolic and diastolic BP between treatment groups were observed. The mean change in IOP of phentolamine mesylate treated eyes from screening to 2–3 hours post-treatment (-1.8 mmHg) was statistically significant ($p < 0.0004$).

Nyxol NVD: Phase 2 NYX-01a2 Trial (Completed)

NYX-01a2 was a 15-day, double-masked, randomized, placebo-controlled, multiple-dose Phase 2 trial in patients with severe NVD. Following the 15-day double masked period (Study Period 1), all patients were given 6 additional doses Nyxol to be taken as needed, with a follow-up study visit on Day 32 (Study Period 2). Sixty people (median age of 35.5) with subjective complaints of severe NVD were randomized 1:1:1 into 3 groups of 20 patients who each received placebo (vehicle control), 0.5% PMOS, or 1% PMOS one drop in each eye, once daily.

In NYX-01a2, improvements in contrast sensitivity frequencies and VA, as well as reductions in intraocular pressure (IOP) and pupil diameter were observed. The NYX-01a2 trial did not meet the contrast sensitivity primary endpoint at Day 15. However, statistically significant results for contrast sensitivity (CS) improvements in 6-12-18 cpd were observed at Day 8. The trial did demonstrate a dose response favoring 1% PMOS. Further, statistically significant reductions in pupil diameter were demonstrated. Durability of effect on PD was observed 24 hours later for Nyxol with daily morning doses. Trends in improvement in the planned Phase 3 endpoint for NVD (low contrast distance visual acuity in dim lighting conditions as well as bright light) were shown. In a post-hoc analysis, a statistically significant gradual improvement was seen in mesopic LCVA in all treated eyes with 65% of eyes receiving Nyxol showing at least 1 line of improvement compared to 35% of eyes receiving Placebo on Day 15 ($p = 0.02$).

Regarding safety, multiple doses of up to 1% PMOS over 14-days and one month appeared well tolerated in patients with severe night vision complaints, with no clinically meaningful changes in vital signs, no deaths, and no SAEs. Both the mean absolute IOP and mean change in IOP post treatment showed a statistically significant decrease (2.5 mmHg placebo-adjusted) with 1% PMOS in one or both eyes with IOP in the normal range (12-22 mmHg).

Nyxol Non-Drug Trials: NVD Epidemiology (OP-EPI-001)

To gain further insight into NVD, Ocuphire conducted an epidemiological trial, OP-EPI-001, to describe the signs and symptoms of NVD and the effect of pupil constriction driven by contralateral illumination on low and high contrast visual acuity. A total of 102 patients completed all study measurements, including post-surgery (n = 22), high myopia/astigmatism (n = 21), contact lenses (n = 21), night myopia (n = 20), and cataract (n = 18) patients. The study identified 2 population subgroups (post refractive surgery patients and patients with night myopia) that can benefit the most by a reduction in pupil size in mesopic conditions.

Nyxol Phase 1 Clinical Trials

Ocuphire evaluated efficacy and safety of Nyxol in 3 double-masked, randomized Phase 1 trials (NYX-001, 002, and 004) in a total of 77 healthy volunteers. Efficacy was observed in only 2 of these 3 trials given the lack of exclusion of patients that wear contact lenses in NYX-004. In the 2 trials that reported efficacy, Nyxol demonstrated statistically significant decreases in pupil diameter compared to placebo at various doses (0.2%, 0.4%, 0.8% phentolamine mesylate). From a safety perspective, no serious adverse events occurred in any of the 3 trials. There were no effects on heart rate, systolic BP, or diastolic BP that could be attributed to treatment, and these values were not clinically meaningful since all measures remained within normal range at all assessments. There was mild transient redness in the patients treated with Nyxol compared to placebo.

Nyxol Nonclinical Toxicology Studies

As part of a comprehensive nonclinical toxicity program, Ocuphire conducted 3 exploratory and 2 GLP single and repeated-dose toxicity studies of phentolamine mesylate drug substance in rabbits and beagle dogs. There were no Nyxol-related histopathologic ocular pathology findings.

Nonclinical information (pharmacological properties and general toxicology) for phentolamine mesylate is described in the literature in connection with other approved phentolamine drug products or formulations, and was reviewed by the FDA in the approval process of Oraverse and Regitine.

For chronic administration of Nyxol, a 6-month repeated-dose toxicity study with Nyxol in Dutch belted rabbits has completed the in-life portion. This 6-month toxicology study would support a long-term safety exposure trial. With completion of this study, Ocuphire believes it will meet the nonclinical toxicology obligations for an NDA filing in any chronic indication for Nyxol. Ocuphire is also initiating a 90-day nonclinical toxicology study with Nyxol and LDP doses in Dutch belted rabbits to support any future chronic indication for such combination.

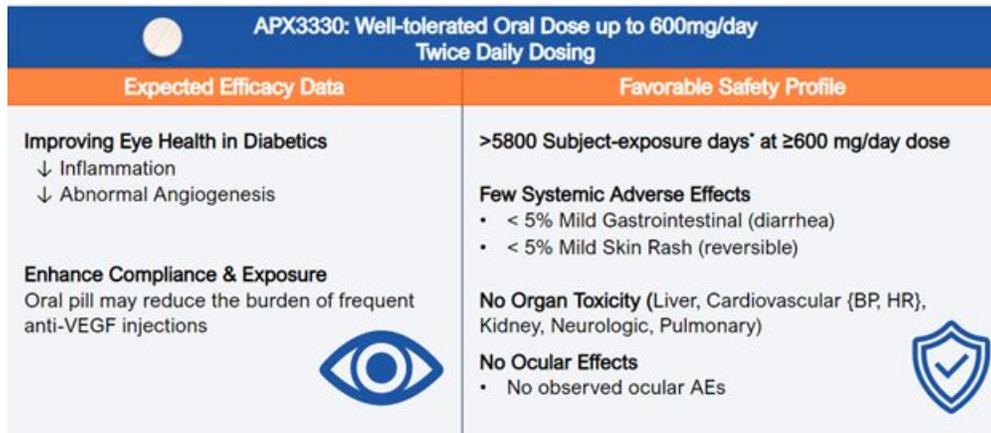
APX3330

APX3330 (E3330) is a twice a day oral tablet designed to target multiple pathways relevant to retinal and choroidal vascular diseases, such as diabetic retinopathy (DR) and diabetic macular edema (DME), which, if left untreated, may result in permanent visual acuity loss and eventual blindness. Mechanistic studies and prior clinical experience suggest that APX3330 is a promising candidate for clinical evaluation of its efficacy and safety in the treatment of these diseases, beginning with DR and DME. Ocuphire believes APX3330 shares desirable attributes for back of the eye therapies, including broad therapeutic applications, a convenient route of administration and cost-effective manufacturing process, without the need for uncomfortable intravitreal injections (**FIGURE 9**).

In preclinical studies, APX3330 has demonstrated the ability to decrease angiogenesis and inflammation in the retina whether delivered orally, systemically, or directly into the eye via intravitreal injections. In humans, APX3330 was shown to be clinically well-tolerated in multiple Phase 1 and 2 trials with fewer than 10% of the patients experiencing mild, self-limiting side effects, such as nausea or diarrhea. In addition, it was shown that significant amounts of oral APX3330 reach the bloodstream concentrations in humans and higher than the levels in mice which showed effects in the retina.

Ocuphire is initially pursuing a moderate-to-severe non-proliferative retinopathy (NPDR) or mild proliferative retinopathy (PDR) indication, as well as patients with DME without loss of central vision. Ocuphire may pursue other indications with APX3330 including broader DME population and wet AMD. Second-generation candidate, APX2009, may also be considered for intravitreal injections.

FIGURE 9. APX3330 Product Candidate Profile



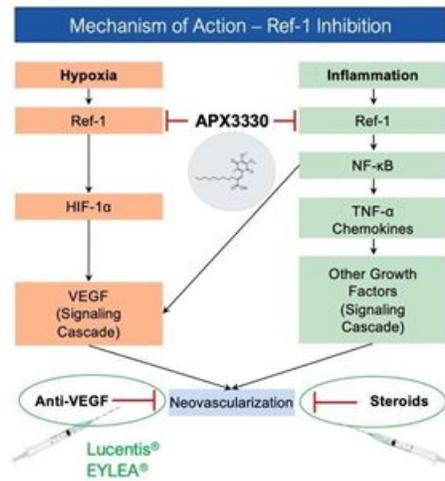
APX3330 Mechanism of Action

APX3330 is a highly selective small molecule that acts on the dual-functioning Apurinic/Apyrimidinic Endonuclease 1/Redox Effector Factor-1 (APE1/Ref-1) protein, referred to as Ref-1. This protein is implicated in both redox signaling and DNA repair. Because APX3330 selectively inhibits the redox function without affecting the molecule’s ability to carry out DNA repair, normal cell function is left intact. Moreover, interference of Ref-1 activity with APX3330 blocks angiogenesis and inflammation by simultaneously decreasing the activity of several important transcription factors such as HIF-1 α and NF- κ B (**FIGURE 10**). HIF-1 α regulates the expression of VEGF, a protein that is paramount for angiogenesis, and NF- κ B is an upstream regulator of proteins involved in inflammatory processes such as TNF α and chemokines.

The development of DR/DME involves leakage from retinal vessels, lack of blood flow to the retina, and release of angiogenic growth factors and inflammatory mediators. The downstream targets of HIF-1 α and NF- κ B serve as key mediators of these disease features and are targets of current therapy for diabetic eye disease and wAMD. Rather than inhibiting the action of VEGF protein, APX3330 has been shown in preclinical models to inhibit its formation; this is a key potential distinction of APX3330 from the drugs currently approved or under development for DR/DME such as Lucentis and EYLEA. APX3330’s potential ability to inhibit the activity of these two transcription factors may mitigate the need for frequent intravitreal anti-VEGF or steroid injections.

APX3330 has a dual mechanism that decreases both abnormal angiogenesis and inflammation. APX3330 blocks pathways downstream of Ref-1. Blocking HIF-1 α reduces VEGF signaling, and blocking NF- κ B modulates VEGF, TNF- α and other inflammatory cytokine production. In contrast, anti-VEGF agents solely inhibit the actions of VEGF (see **FIGURE 10**).

FIGURE 10. APX3330 Dual Mechanism of Action in Validated Disease Pathways



APX3330 Clinical Experience Summary

APX3330 has been studied in over 340 (of over 420 total) healthy volunteers or patients with hepatitis or cancer, over 220 of whom were given the product candidate for an average of 75 days or more. In these 11 Phase 1 and 2 non-ocular clinical trials, clinical data on safety, effect upon the Ref-1 molecular target, and pharmacodynamic characteristics were collected.

A summary of the 11 completed trials and the ongoing Phase 2b ZETA-1 trial can be found below (**TABLE 3**).

TABLE 3. Summary of APX3330 Completed and Ongoing Clinical Trials

Trial Number / Name	Patient / Indication	Phase	Trial Objectives	Doses	Number of Patients[^]	APX3330 Total Exposure Days	Dosing	Key Endpoints
APX_CLN_0001 (Eisai) Completed	Healthy Volunteers	1	Single-dose placebo-controlled trial of APX3330 to investigate safety and pharmacokinetics	10 mg 30 mg 60 mg 120 mg 180 mg 240 mg	APX3330 = 12 Placebo = 6	36 days	Single dose	Plasma Concentration of total quinone forms, safety
APX_CLN_0002 (Eisai) Completed	Healthy Volunteers	1	Repeat-dose placebo-controlled trial to investigate safety and pharmacokinetics	120 mg QD 120 mg BID	APX3330 = 12 Placebo = 6	96 days	8 days	Plasma Concentration of APX3330, safety
APX_CLN_0003 (Eisai) Completed	Healthy Volunteers	1	Repeat-dose trial to determine effects of food on pharmacokinetics	240 mg	APX3330 = 6	84 days	1 week	Plasma Concentration of APX3330, safety
APX_CLN_0004 (Eisai) Completed	Healthy Volunteers	1	Single-dose trial to determine the effects of meals on pharmacokinetics	120 mg	APX3330 = 6	6 days	Single dose	Plasma Concentration of APX3330, Safety
APX_CLN_0005 (Eisai) Completed	Chronic Hepatitis B Patients	2	Dose-escalation trial to investigate safety, efficacy and tolerability	20 mg 60 mg 120 mg 240 mg	APX3330 = 40	3360 days	12 weeks	Safety
APX_CLN_0006 (Eisai) Completed	Chronic Hepatitis C Patients	2	Dose-escalation trial to investigate safety, efficacy and tolerability	20 mg 60 mg 120 mg 240 mg	APX3330 = 51	4284 days	12 weeks	Safety

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APX_CLN_0007 (Eisai) Completed	Chronic Hepatitis C Patients	2	Double-masked, placebo-controlled trial to investigate safety, efficacy and tolerability	120 mg 240 mg	APX3330 = 128 Placebo = 68	10,752 days	Placebo = 82 days APX3330 120 mg = 79 days 240 mg = 78 days	Rate of change in GPT level, improvement in liver function, general performance
APX_CLN_0008 [^] (Eisai) Completed	Healthy Patients	1	Single-blind, single- dose, 3-step trial to investigate safety and pharmacokinetics of higher doses	300 mg 420 mg 600 mg	APX3330 = 18	54 days	Single dose	Plasma Concentration of APX3330, safety
APX_CLN_0009 (Eisai) Completed	Advanced Liver Cirrhosis Patients	2	Repeated-dose trial to investigate safety, efficacy and tolerability	120 mg	APX3330 = 30	420 days	2 weeks	Liver function, patient functional status, tolerability
APX_CLN_0010 (Eisai) Completed	Advanced Liver Cirrhosis Patients	2	Repeated-dose trial to investigate safety, efficacy and tolerability	120 mg	APX3330 = 18	504 days	4 weeks	Liver function, patient functional status, tolerability
APX_CLN_0011 (Apexian) Completed	Advanced Solid Tumor Patients	1	Multicenter, open- label, dose- escalation to investigate safety, efficacy, pharmacokinetics, and recommended Phase 2 dose	240 mg 360 mg 480 mg 600 mg 720 mg	APX3330 = 19	2354 days	21-day cycles until disease progression or study withdrawal	Tumor response, safety, PK, target engagement
ZETA-1 (Ocuphire) Ongoing, Masked	Diabetic Retinopathy and DME	2	Double-masked, randomized, placebo-controlled, multi-center trial	600mg	Pending data N= 103 APX3330 Placebo	>3,700 (estimated Jan 2022)	600mg daily for 24 weeks	≥ 2 step improvement on the DRSS score at week 24

[^] Total patient numbers will not equal to the sum of the subgroups in crossover studies

APX3330 – Ten Phase 1 and 2 Trials - Eisai (APX CLN 0001-0010)

Under the sponsorship of Eisai Co., Ltd., 10 clinical trials were conducted involving healthy volunteers as well as patients with chronic hepatitis diseases (i.e., Type C, B, alcohol-induced) in Japan with the intent of developing a TNF- α blocking agent. At the time of their clinical trials, the molecular target of APX3330 had not been confirmed and was not known to be the Ref-1 protein.

Across these 10 trials, it was found that APX3330 exhibits predictable pharmacokinetics that were consistent with the pharmacokinetic data obtained in non-clinical studies. In addition, there was a lack of significant acute toxicity at doses up to 600 mg/day. APX3330 has been demonstrated to be well-tolerated. Moreover, in two studies it was found that meals have no impact on the product candidate's pharmacokinetics. Safety tolerability measures showed no changes in vital signs and no changes in clinical laboratory values. Only adverse events included diarrhea and rash, which each occurred in <5% of patients and were mild. Liver function tests were used primarily to evaluate efficacy in Phase 2 studies of hepatitis patients and the overall assessment of liver function over time suggests that APX3330 had a minor positive, and no negative, effect. Additionally, there was a lack of acute neurologic, cardiovascular, hepatic, or pulmonary toxicity. Only a single ocular adverse event has been reported in APX3330 clinical trials; mild orbital region discomfort at 60 mg/day in CLN_0006. No mild, no moderate, and no severe rashes were observed in healthy patients dosed with APX3330.

APX3330 Phase 1 Oncology Trial - Apexian (APX CLN 0011)

Clinical development of APX3330 by Eisai Co., Ltd. in Japan was suspended with the in-licensing of anti-viral and biological agents for hepatitis C and rheumatoid arthritis. Later, while doing research on the Ref-1 protein, Dr. Mark Kelley from Indiana University and others identified that the molecular target of APX3330 was the Ref-1 protein. The elucidation of the mechanism of action with which APX3330 modulated the Ref-1 protein, and the concurrent advancement in understanding the role played by Ref-1 as a critical "gate-keeper" for controlling a variety of pro-inflammatory transcription factors, led to the establishment of Apexian in order to determine the utility of using APX3330 as a modulator of the Ref-1 protein in the treatment of inflammatory diseases. The clinical trial, APX_CLN_0011 under IND 125360 with the FDA Division of Oncology, was initiated by Apexian in order to identify the highest dose of APX3330 that could be safely administered in a chronic manner and to confirm molecular engagement of APX3330 with the Ref-1 protein by obtaining tumor biopsy samples and circulating tumor cell samples.

APX_CLN_0011 was a multi-center, open-label, dose-escalation Phase 1 oncology trial in patients with advanced solid tumors. Patients received daily oral doses of APX3330 each day of repeated 21-day cycles until disease progression or trial withdrawal. Nineteen patients received APX3330 in escalating doses from 240 mg/d dose to 720 mg/day in increments of 120mg/day. The highest dose tested (720 mg/day) produced a self-limiting, diffuse macular rash and was confirmed as the dose-limiting toxicity. The dose of 600 mg/day was then confirmed as a dose tolerable for chronic administration and for further clinical development as a modulator of Ref-1 activity in inflammatory diseases. Biopsy analyses of patients participating in the trial confirmed that APX3330 directly targets the Ref-1 protein and that the targeting produces subsequent regulation of transcription factors such as NF- κ B and HIF-1 α , regulators of VEGF and other inflammatory molecules. This mechanism of action provides significant rationale for testing APX3330 in diseases in which inflammation and neo-vascular development play a critical pathogenic role. APX3330 was also well-tolerated in cancer patients who were treated daily for up to 400 days (4% diarrhea/soft stool and 4% rash).

Overall, APX3330 demonstrated a favorable safety profile and was well tolerated. No effects of APX3330 on vital signs on laboratory measures have been observed. Across 11 Phase 1 and Phase 2 trials, the rate of adverse events was similar in APX3330 treated patients (N=346) and placebo treated patients, including a <3% difference between APX3330 and placebo in rates of diarrhea/soft stool and rash/pruritis. Among healthy patients and hepatitis patients (N=327), any adverse event occurred in 14% of patients receiving APX3330 and 14% of patients receiving placebo.

Given the favorable AE profile of APX3330 in diverse patient populations, Ocuphire expects administration of APX3330 to patients with retinal diseases may not result in any significant toxicity or safety issues that would interfere with chronic oral administration.

APX3330 Phase 2b Trial in DR/DME Patients (ZETA-1) (Ongoing)

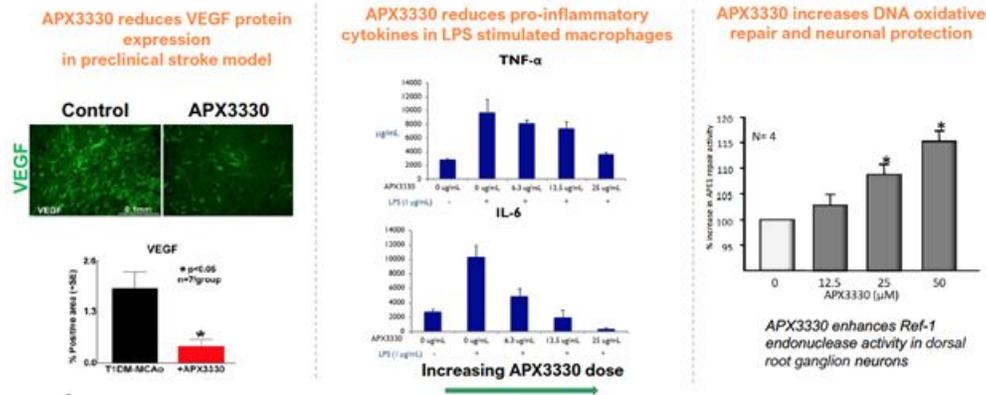
Ocuphire initiated ZETA-1, a Phase 2b double-masked, randomized, placebo-controlled, multi-center trial in patients with DR and DME in the first quarter of 2021. This study evaluates the effect of 600 mg daily dose of APX3330 (3 120 mg tablets in AM, and 2 120 mg tablets in PM) in treating patients with DR, including moderately severe NPDR to mild PDR, as well as patients with DME without loss of central vision. The primary endpoint is percent of patients with a ≥ 2 step improvement on the Diabetic Retinopathy Screening Score (DRSS) at week 24. Key secondary endpoints at multiple timepoints are central subfield thickness and low luminance high contrast distance visual acuity. Patient safety is assessed by AE monitoring, clinical laboratory evaluations, IOP, and vital sign assessments. In January 2022, Ocuphire reported masked safety data from the ongoing Phase 2 trial in DR/DME from 68 patients enrolled as of 1/12/2022. There were only 52 AEs in 28 patients (receiving APX3330 or placebo) and of the 52 AEs, only 6 AEs were considered probably or possibly related to study medication (4 mild: vertigo, rash, pruritus, frequent bowel movements and 2 moderate: diarrhea and DME). These safety data are consistent with safety data from the prior 11 clinical trials with total exposure experience now of over 5000 subject days with 600 mg daily dose of APX3330. In March 2022, Ocuphire reported enrollment completion at 103 patients in the ZETA-1 trial and expects to report top-line results from ZETA-1 DR/DME Phase 2b study in the second half of 2022.

APX3330 and Analogs Preclinical Efficacy Studies

Ref-1 is highly expressed within many cells in the diseased retina, including upregulation in the retina and choroid of human wAMD patient eyes compared with age-matched controls. Furthermore, in an *in vitro* study of adult human retinal pigment epithelium cells treated with oxLDL, an agent that upregulates factors involved in inflammation and angiogenesis, APX3330 reduced transcriptional activity of many of these key factors, namely HIF-1 α and NF- κ B. This reduces the activity of their downstream targets, VEGF, and that of inflammatory mediators.

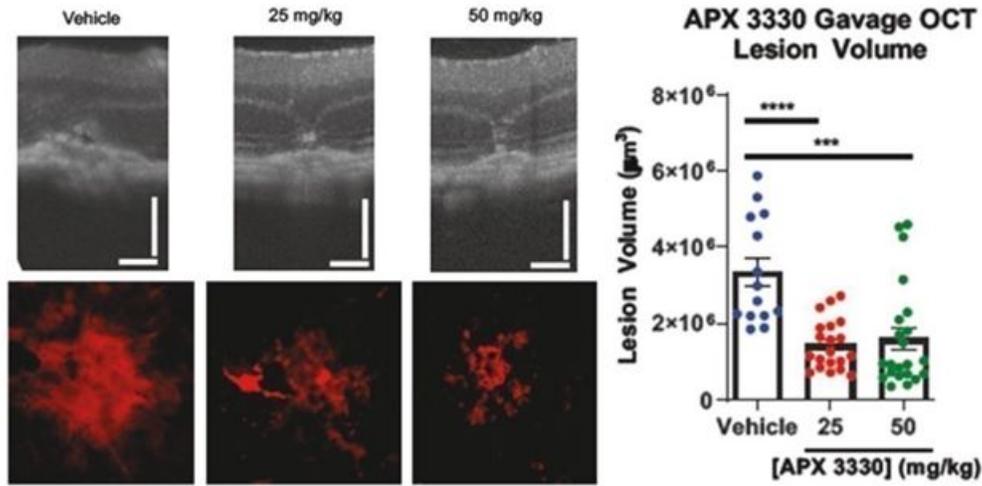
In animal studies, APX3330 delivered orally, intraperitoneally or intravitreally (directly into the eye), and APX2009 and APX2014 delivered intraperitoneally via injections reduced neovascularization in mouse models that recapitulate features of retinal neovascularization (seen in PDR and wAMD) called the L-CNV model. Although intravitreal injection is the delivery route of the standard-of-care anti-VEGF biologics and ensures that the drug gets to the affected area, in humans, it is labor-intensive, causes patient discomfort, and incurs a risk of potentially vision-threatening intraocular infections. As a result, systemic administration (intraperitoneal injections) of Ref-1 inhibitors were explored for similar effects as that seen by anti-VEGF biologics in mouse models. Treatment of APX3330 (10 mg/kg) via oral gavage in rats with type 1 diabetes and induced stroke (conditions that promote neovascularization) shows a significant decrease (~55%) of VEGF signaling (or lesion volume) as shown in **FIGURE 11** below. As seen in the first panel in **FIGURE 11**, expression of VEGF was lower in APX3330-treated cells compared to control cells in a stroke model. As seen in the second panel, APX3330 also demonstrated anti-inflammatory effects by reducing cytokines in LPS stimulated macrophages. The third panel demonstrates APX3330 increased DNA oxidative repair and neuronal protection by enhancing endonuclease activity.

FIGURE 11. APX3330 Reduces VEGF Levels and Inflammatory Cytokines and Provides Neuronal Protection (in-vitro)



While numerous published studies using APX3330 through intravitreal or systemic intraperitoneal administration have shown successful neovascularization reduction, additional studies with oral administration of 2 doses of APX3330 (25 mg/kg and 50 mg/kg per day) resulted in a more robust correction of the lesion volume in the L-CNV mouse model. As shown in **FIGURE 12** below, animals treated with APX3330 displayed a significant reduction (~55%) in the volume of the neovascular lesion (red staining).

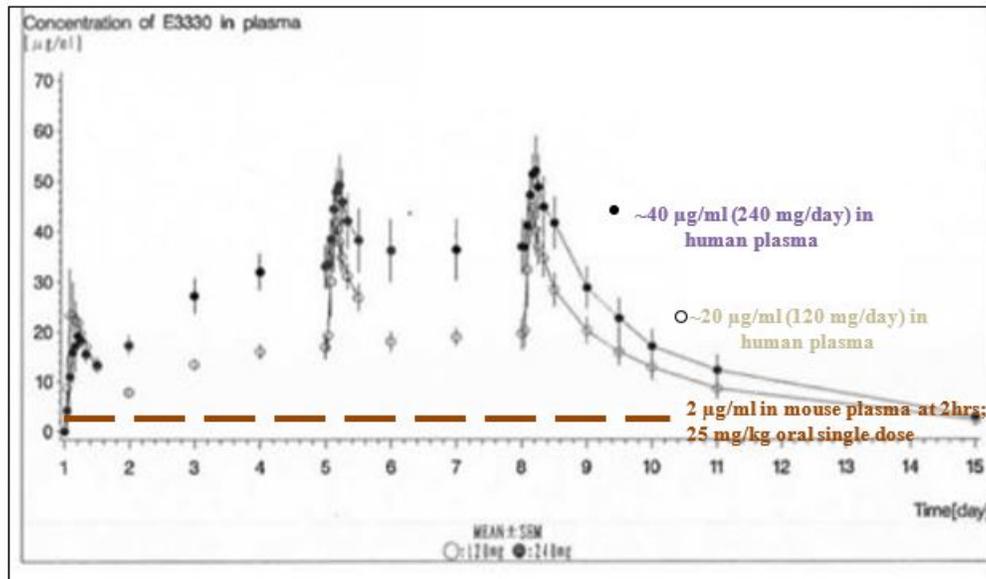
FIGURE 12. Lesion Size and Corresponding Fluorescent Stains in L-CNV Models Treated with APX3330



L-CNV mice treated with APX3330 at either 25 mg/kg or 50 mg/kg resulted in a decreased volume of neovascularization (lesion volume).

Human pharmacokinetics of APX3330 demonstrated plasma levels much greater than those seen in animals. Pharmacological studies with APX3330 in preclinical models demonstrated that, at a dose of 25 mg/kg, (equivalent to a 120 mg daily dose in humans), there was an APX3330 concentration (expressed as blood quinone) of 0.15-2 μg/ml, which resulted in an ocular effect in preclinical models. This plasma concentration was adequate to reach detectable levels in the retina and provide efficacy in reducing neovascularization. In support of these findings, APX3330 was detected in the eyes of mice using a lesser dose of 10 mg/kg. Furthermore, in clinical trials, a daily dose of 120 mg resulted in a peak blood concentration of 40 μg/ml, which is 20x times higher than those in mouse models (**FIGURE 13**). Doses of 120 mg per day and higher in humans were tolerable, as studied in the Phase 1 clinical trial, APX_CLN_011, where the maximally tolerated dose was 600 mg per day. Thus, the planned dose of 600 mg per day is five times above the 120 mg human equivalent dose shown to achieve retinal efficacy in animals.

FIGURE 13. Human Pharmacokinetics of APX3330



Human plasma concentrations of APX3330 after being given 120 mg per day for 8 days. Total quinone concentration refers to the amount of active form of APX3330 in the plasma. The peak and steady state blood concentration of APX3330 dosed at 120 mg per day is ~20 µg/mL and dosed at 120 mg twice a day is ~40 µg/mL. The dotted brown line refers to the maximum blood concentration of ~2 µg/mL at 2 hours post-dose of 25 mg/kg of APX3330 dosed orally in mouse. An oral dose of 25 mg/kg for 2 weeks in L-CNV mouse model showed 55% reduction in lesion volumes.

APX3330 Nonclinical Studies

Pharmacokinetics/Metabolism

Pharmacokinetic (PK) studies were conducted in rats and dogs to understand the absorption, distribution, and elimination of APX3330. APX3330 is well absorbed orally with a bioavailability of $\geq 60\%$. In the bloodstream, $\geq 99\%$ of the product candidate is bound to protein. Half-life after intravenous administration of APX3330 was 8 hours in rats, 7.8 to 8.7 hours in dogs, and 25.5 hours in monkeys. Excretion occurred mainly in bile, as a conjugate. In rats and beagles, APX3330 is excreted in stool as the unchanged compound.

Toxicology

APX3330 has been studied extensively in over 20 in-vitro and animal studies and demonstrated a favorable safety profile in each. APX3330 was not genotoxic and had no toxicologically significant effects in developmental studies. Over 15 single- and repeat- dose toxicology studies in rats and dogs up to 3 months duration have been conducted. Also, PK, ADME and safety pharmacology studies along with over 5 developmental, genotoxicity, and antigenicity studies have been completed. The FDA did not request any further toxicology studies to support the 24-week ZETA-1 clinical trial.

Ocuphire Clinical Development Plan

For Nyxol, the investigational new drug (IND) application was submitted to the FDA Division of Ophthalmology in July 2011 and is in effect (IND 70499). Nyxol has completed 9 trials (3 Phase 1 trials and 5 Phase 2 trials and 1 Phase 3 trial), mostly in young and older healthy volunteers as well as presbyopia, NVD and glaucoma patients. In May 2020, Ocuphire completed an EOP2 meeting with the FDA, which included a discussion and agreement around the design and scope of future registration trials for Nyxol across its indications. In June 2021, Ocuphire completed a Type C meeting with the FDA on CMC for Nyxol. In February 2022, Ocuphire completed a Type C meeting with the FDA which included discussion and guidance around the design of VEGA Phase 3 trials and registration package for Presbyopia for Nyxol alone and Nyxol with LDP as adjunctive therapy. Ocuphire anticipates engaging in similar discussions with other foreign regulatory authorities in the future.

For APX3330, the IND application for APX3330 to pursue retinal choroidal vascular diseases was submitted to the FDA Division of Ophthalmology in December 2018 and is in effect (IND 142152). APX3330 also has an IND with the FDA Division of Oncology for the treatment of pancreatic cancer (IND 125360). APX3330 has completed 11 trials (6 Phase 1 and 5 Phase 2 trials), mostly related to liver disease and patients with solid tumors.

Ocuphire has 4 studies ongoing across Nyxol and APX3330 from 2021 that have all completed enrollment as of first quarter 2022 (2 Phase 3 trials and 1 safety trial for Nyxol, and 1 Phase 2b trial for APX3330) Pending the results and timing of additional trials, Ocuphire intends to file a new drug application (NDA) for Nyxol for the RM indication in late 2022 and one or more indications for Nyxol in 2023 or later, and for APX3330 thereafter. The development programs for Ocuphire's targeted indications are described below.

Future Planned Nyxol Trials:

Nyxol Presbyopia: VEGA-2 & VEGA-3 Phase 3 Trials

The VEGA-2 and VEGA-3 trials are planned as a double-masked, randomized, placebo-controlled, multicenter trial in approximately 300 patients with presbyopia in each study. The registration trials will evaluate efficacy and safety and be similarly designed to achieve both labels - single agent Nyxol and LDP as adjunctive therapy to Nyxol. Key endpoints such as distance corrected near visual acuity, pupil diameter, and best corrected distance acuity will be measured at multiple timepoints after the first dose and multiple doses to assess the onset and duration of efficacy. The primary endpoint to establish the efficacy will be the percentage of patients who gain 15 or more letters of DCNVA without loss of 5 or more letters of BCDVA. Key secondary endpoints such as distance corrected near visual acuity, pupil diameter, and best corrected distance acuity will be measured at multiple timepoints after the first dose and multiple doses to assess the onset and duration of efficacy. A hierarchy analysis will be used to allow both single agent (compared to placebo) and combination (compared to individual components) endpoints to be evaluated with appropriate statistical significance. If the Vega Phase 3 program is successful, Ocuphire expects to file an NDA for Nyxol to treat presbyopia in 2023.

Nyxol Chronic Safety Trial: LYRA-1 Phase 3 Trial

For a NDA for Nyxol chronic indications, Ocuphire plans to conduct a long-term safety trial LYRA-1 which is expected to initiate after the FDA review of the 6-month repeated-dose toxicity study. The planned LYRA-1 Phase 3 trial evaluating chronic safety exposure is targeting 300 patients for 6 months, followed by 100 of the patients continuing for an additional 6 months in a double-masked, placebo-controlled design. Long-term endothelial cell count (ECC) clinical data will also be collected.

Nyxol NVD: LYNX-2 2nd Phase 3 Trial

Based on the results of the 1st Phase 3 trial, LYNX-1, and chronic indication priorities, Ocuphire may consider a 2nd registration trial for Nyxol for the treatment of NVD.

Potential Clinical Plans for APX3330:

Based on the Phase 2 safety, tolerability and efficacy results of APX3330 in patients with DR/DME, Ocuphire expects to request an EOP2 meeting with the FDA to finalize the design of the Phase 3 registration trials for APX3330 as first-line therapy in DR/DME in addition to defining the chronic safety exposure trial and any further animal toxicology studies necessary prior to an NDA submission. In addition, Ocuphire may consider evaluating APX3330 with currently approved intravitreal anti-VEGF therapies for the potential adjunctive treatment of DME, wAMD, RVO and GA, thereby reducing the burden of intravitreal injections and making treatment more accessible to patients in remote locations.

Future In-Licensing and Acquisition Opportunities

Ocuphire continually evaluates product candidates based on scientific merit, patent protection, regulatory pathways, and commercial opportunity. Its focus is on small molecule product candidates in the ophthalmology space.

Sales and Marketing

If any of Ocuphire's product candidates are approved in the United States or globally, Ocuphire has the option to either build out a commercial infrastructure directly or collaborate with established pharmaceutical partners. The company maintains discussions with a range of ophthalmic drug companies regarding development and commercialization of Nyxol and/or APX3330, including co-development, distribution, license, or mergers and acquisitions. As part of the pre-commercialization planning, Ocuphire has started market development activities which include engaging with Key Opinion Leaders as well as increased visibility and presence at ophthalmology medical and industry conferences. There are several global pharmaceuticals with major ophthalmic drug businesses as well as numerous other smaller global or regional companies that could provide significant reach in specific markets such as Europe or Asia. In addition, there are several ophthalmic drug sales and distribution companies in the U.S. with established specialty sales force that could market Nyxol or APX3330. The ophthalmic market is concentrated and therefore Ocuphire believes it is feasible to reach eye care providers (~20,000 ophthalmologists, ~46,000 optometrists, ~3,000 retinal specialists) via direct sales force (e.g., 30-100 representatives) or by multiple ophthalmic distributors and partners. Nyxol in RM indication has the potential for efficient adoption based on the GlobalData market research physician response, the lack of any reversal treatment options and minimal additional staff or patient training requirements.

Manufacturing

For Nyxol, APX3330, and for other product candidates that will be developed in the future, Ocuphire's contract manufacturers are currently producing, and will produce, its bulk drug substances and drug products for use in Ocuphire's preclinical studies and clinical trials, utilizing reliable and reproducible synthetic processes and common manufacturing techniques. Ocuphire does not have any long-term arrangements but intends to secure such arrangements for drug substances or drug products as appropriate, and currently uses purchase orders with multiple manufacturers. Ocuphire expects to enter into one or more Contract Development and Manufacturing Organization (CDMO) agreements in the near term. Ocuphire further intends to qualify its selected manufacturers to provide bulk drug substances and drug products in preparation for the NDA regulatory submission to the FDA. Ocuphire plans to continue to rely upon contract manufacturers and, potentially, collaboration partners to manufacture commercial quantities of its drug substances and drug products, if approved, for marketing by the applicable regulatory authorities. Ocuphire does not own or operate, and currently has no plans to establish, any manufacturing facilities.

Nyxol

The proprietary formulation of Nyxol is a sterile, preservative-free, isotonic, buffered aqueous solution containing phentolamine mesylate, mannitol, and sodium acetate. The drug substance phentolamine mesylate USP is a small molecule that can be manufactured by reliable and reproducible synthetic processes from readily available starting materials. Ocuphire obtains the active pharmaceutical ingredient for Nyxol from a single supplier in Italy and is presently taking steps to develop a second source. All lots of drug substance phentolamine mesylate and Nyxol drug product used in clinical trials are manufactured under current good manufacturing practices (cGMP), a quality-system regulating manufacturing, with processes registered by the supplier with FDA in an active Drug Master File (DMF). Ocuphire's product candidate was previously packaged in a single-use bottle with cap that was used as container closure system for Phase 1 and 2 clinical trials. Ocuphire has transitioned the container closure system to an industry standard, single-use preservative-free blow-fill-seal ("BFS") container for Nyxol, which is being formulated and filled by a leading U.S. manufacturer. Nyxol eye drops in the BFS container are classified by FDA as a drug-device combination product. The current manufacturing process has been scaled to a commercial capacity. Nyxol has demonstrated stability at 5°C refrigerated for a minimum of two years. Ocuphire is performing additional stability studies on lots of both the drug substance phentolamine mesylate and the drug product of Nyxol in order to establish expiry and to support regulatory submissions and commercial manufacturing. To supply eventual global markets and to avoid reliance on a single facility, Ocuphire is evaluating the establishment of second source manufacturing facilities for drug substance and drug product.

APX3330

APX3330 is an oral formulation of a small molecule drug substance that is synthesized from readily available raw materials and using conventional chemical processes. The APX3330 drug substance is currently obtained from a single supplier in India, although alternative manufacturing sources are available. The APX3330 drug product is manufactured in the U.S.. Process and analytical development of APX3330 drug product have been completed, and its production has been scaled-up under cGMP regulatory requirements. Previously, the APX3330 drug product manufacturer has performed pharmaceutical development to support the cGMP manufacturing campaign for tablets of 60 mg and 120 mg dose strengths, the latter being used in ongoing clinical trials. Under this tablet size, long-term ICH-stability studies of various strengths (60 and 120 mg tablet) have been conducted and have demonstrated a 3-year shelf life when stored at 25°C/60% relative humidity. Ocuphire is evaluating 300 mg tablets for convenient twice a day dosing. Ocuphire is also planning additional stability studies for future lots of both the drug substance and drug product of APX3330 in order to establish expiry and to support regulatory approval and commercial stage.

Apexian Sublicense Agreement

On January 21, 2020, Ocuphire entered into a sublicense agreement with Apexian pursuant to which it in-licensed patents and other intellectual property relating to the APX3330 product candidate and second-generation product candidates owned by Apexian, and intellectual property that Apexian in-licensed from Eisai, including certain study reports, manufacturing and analytical records, data, know-how, technical and other proprietary information relating to APX3330. This intellectual property constitutes a Ref-1 Inhibitor program focused on developing therapeutic applications to treat disorders related to ophthalmic and diabetes mellitus conditions. The lead compound in the Ref-1 Inhibitor program is APX3330, which Ocuphire intends to develop as an oral tablet therapeutic to treat DR and DME, and potentially wAMD. See “*Ocuphire Management’s Discussion and Analysis of Financial Condition and Results of Operations—Contractual Obligations and Commitments—Apexian Sublicense Agreement*” for more details regarding the Apexian Sublicense Agreement.

Intellectual Property

Nyxol

Ocuphire’s patent estate includes patents and patent applications to forms of phentolamine mesylate, methods of using phentolamine mesylate, and methods of manufacturing phentolamine mesylate. Ocuphire primarily protects its intellectual property through a combination of patents and patent applications on inventions, trademark protection on Ocuphire’s product name, and trade secret protection as Ocuphire deems appropriate. Ocuphire owns all of the worldwide rights to Nyxol for all indications.

As of March 1, 2022, Ocuphire’s patent estate relating to Nyxol contains eight U.S. patents, five pending U.S. non-provisional patent applications, two pending U.S. provisional patent applications, as well as issued patents in Australia, Canada, Europe, Japan, and Mexico and pending patent applications in Australia, Canada, Europe, Japan, China, and other foreign countries.

Ocuphire’s U.S. Patents 9,795,560; 10,278,918; 10,772,829 and 11,090,261 and counterpart Australian Canadian, European, and Japanese patents each contain composition of matter claims to aqueous phentolamine mesylate formulations and are scheduled to expire in year 2034. In the same patent family, Ocuphire also has 1 pending U.S. patent application with additional claims to aqueous phentolamine mesylate formulations, whereby a patent, if granted, would expire in year 2034. The patents and patent applications cover the current clinical formulation for the Nyxol product.

Ocuphire’s U.S. Patent Nos. 9,089,560; 9,789,088 and 11,000,509 contain claims directed to methods of improving visual performance using, for example, phentolamine mesylate and are scheduled to expire in year 2034. Counterpart patents have issued in Australia, Canada, Europe, and Japan, which are scheduled to expire in year 2034. In the same patent family, Ocuphire also has 1 pending U.S. patent application with additional claims to methods of improving visual performance using, for example, phentolamine mesylate, whereby a patent, if granted, based on this pending application would expire in year 2034. The patents and patent applications cover uses of the current clinical formulation for the Nyxol product.

Ocuphire has patent applications pending in the U.S., Australia, Canada, China, Europe, and Japan directed to treating glaucoma and other medical disorders using phentolamine mesylate. Patents, if granted, based on these pending applications would expire in year 2039.

Ocuphire's U.S. Patent 10,993,932 contains claims directed to methods of treating presbyopia using phentolamine mesylate with adjunctive pilocarpine and is scheduled to expire in year 2039. In the same patent family, Ocuphire has two pending U.S. patent applications, one with additional claims to treating presbyopia and the other U.S. application with claims to treating mydriasis. Counterpart patent applications are pending in Australia, Canada, China, Europe, Japan, and other foreign countries, whereby a patent, if granted, based on these pending U.S. and foreign patent applications would expire in year 2039.

Ocuphire has a pending U.S. provisional patent application and pending patent application in China directed to methods of making high-purity phentolamine mesylate and compositions resulting from such methods. Ocuphire also has a pending U.S. provisional patent application directed to additional methods for treating mydriasis and glaucoma. Patents, if granted, based on these U.S. provisional patent applications would expire in year 2042, and patents, if granted, based on the pending patent application in China would expire in year 2041.

Ocuphire also owns an issued patent in Mexico that is scheduled to expire in year 2025 and has claims to ophthalmic formulations.

Ocuphire has registered trademark protection in the United States for the mark NYXOL®.

APX3330

As of March 1, 2022, the patent estate that Ocuphire has in-licensed for APX3330 and related compounds contains six U.S. patents and four pending U.S. non-provisional patent applications, as well as issued patents in Europe, Japan, Canada, and Australia, and pending patent applications in Europe, Japan, Canada, China, South Korea and Australia. The license is for the use and commercialization of APX3330 and related composition of matter compounds covered by the subject patents and patent applications in the field of human health uses for ophthalmic and diabetes mellitus indications.

In-licensed U.S. patent 9,040,505 has claims to methods of treating diabetic retinopathy and other diseases using, for example, APX3330 and is scheduled to expire in year 2030. Counterpart patents have issued in Europe, Japan, Australia, and Canada, which are scheduled to expire in year 2028, and there is a related pending U.S. patent application with method of treatment claims that, if issued as a patent, would expire in year 2028. Pending US application 16,968,009 and pending applications in Europe, Japan, Canada, China, South Korea and Australia have claims to methods of treating wAMD and other diseases using, for example, APX3330, along with other formulations such as APX2009 and APX2014. These patents, if granted, would expire in year 2039. The U.S. and certain foreign countries permit extension of patent term for up to five years to compensate for patent term lost during the government regulatory review process for a new medicine. If U.S. patent 9,040,505 qualifies for the full five years of patent term extension, the expiration of U.S. patent 9,040,505 would be in year 2035. Whether U.S. patent 9,040,505 qualifies for the full five years of patent term extension depends in part on the date of FDA approval for the new medicine.

In-licensed patent applications directed to a combination therapy composition comprising an APE1/REF-1 inhibitor, such as APX3330, and a second therapeutic agent, and methods of using such combination therapy to treat retinal diseases and/or treat other indications are pending in the U.S. and Canada. Patents, if granted, would expire in year 2038. In-licensed patent applications directed to use of an APE1/REF-1 inhibitor, such as APX3330, in monotherapy or combination therapy to reduce neuronal sensitivity and/or treat other indications are pending in the U.S., Europe, Japan, and Canada, whereby patents, if granted based on these applications, would expire in year 2038.

U.S. patents that Ocuphire has in-licensed to derivatives of APX3330 include U.S. patents 9,089,605; 9,193,700; 9,877,936; 10,154,973; and 11,160,770. These U.S. patents are schedule to expire from 2029 to 2032. Foreign patents and patent applications that Ocuphire has in-licensed to derivatives of APX3330 include patents in Europe, Japan, China, and Canada that are scheduled to expire between the years 2028 to 2032, along with a pending patent application in Europe and Japan, whereby a patent, if granted, based on these pending applications would expire in year 2032.

In addition to patents and patent applications that Ocuphire has in-licensed, as of March 1, 2022, Ocuphire owns two pending U.S. provisional patent applications directed to methods of treating diabetic retinal diseases using APX3330. Patents, if granted, based on these pending U.S. provisional patent applications would expire in year 2042.

Additional Background

As background, the patent term is typically 20 years from the date of filing a non-provisional application. In the United States, a patent's term may be lengthened several ways. First, patent term adjustment (PTA) compensates a patentee for administrative delays by the USPTO in granting a patent. Second, in certain instances, a patent term extension (PTE) can be granted to recapture a portion of the term effectively lost as a result of the FDA regulatory review period, as provided under the Drug Price Competition and Patent Term Restoration Act of 1984, referred to as the Hatch-Waxman Act. This restoration period cannot be longer than 5 years for approval of a drug compound, and the total patent term, including the restoration period, must not exceed 14 years following FDA approval. Only patent(s) applicable to an approved drug is eligible for the PTE and the application for the extension must be submitted prior to the expiration of the patent and within 60 days from market approval. Independent of patent protection, in the United States, the Hatch-Waxman Act provides a 5-year period of non-patent data exclusivity within the United States to the first applicant to gain approval of an NDA for a new chemical entity (NCE). Under this provision, APX3330 may be eligible for up to 5 years of data and market exclusivity under the Hatch-Waxman Act, because it is considered an NCE as the FDA has not previously approved any other drug containing the active ingredient of APX3330.

In Europe, under the Data Exclusivity Directive, pharmaceutical companies may receive up to 11 years to market their product without risk of competition. In Japan, under the Pharmaceuticals Act of Japan, the market authorization holder, based on the length of a required study period reexamination, may have up to 10 years before a generic can enter the market. Further, the expiration date of certain patents may be extended for up to a maximum of 5 additional years to accommodate for time spent seeking government approval to market a new medicine, in those countries that permit extension of patent term to accommodate for time spent seeking government approval to market a new medicine.

Ocuphire also protects its proprietary information through written agreements. Ocuphire's employees, consultants, contractors, partners and other advisors are required to execute nondisclosure and assignment of invention agreements upon commencement of employment or engagement. In addition, Ocuphire protects its proprietary information through written confidentiality agreements with outside parties who may come into possession of Ocuphire's confidential information.

Competition

There is intense competition within the pharmaceutical industry. While Ocuphire believes that its product candidates, Nyxol and APX3330, are well positioned for development in each indication, Ocuphire will face competition from both branded and generic pharmaceutical companies as well as products that are currently in development. Many of these companies have significantly greater financial and human resources and experience in drug development, R&D, and commercialization. These competitors compete with Ocuphire in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites and patient enrollment for clinical trials as well as acquiring products, product candidates or other technologies complementary to Ocuphire program. Smaller and other early-stage companies may also prove to be significant competitors if they choose to partner with large, established companies.

Nyxol

The key competitive factors affecting the success of Nyxol, assuming Nyxol is approved, are likely to be the combination of efficacy, durability, tolerability, convenience, price (private pay), and stable, preservative-free formulation that will potentially allow it to compete effectively in these markets.

Competition in RM

There are currently no approved and commercially available drug treatments for RM, and Ocuphire is not aware of any in development. Rev-Eyes® (dapiprazole), an alpha-1 antagonist, was approved by the FDA in 1990 to reverse mydriasis induced by adrenergic or anticholinergic agents. Rev-Eyes was withdrawn in the past from the market for reasons unrelated to safety or efficacy, according to the FDA.

Competition in Presbyopia

The FDA approved Vuity™ eye drop for the treatment of presbyopia in October 2021. Vuity was launched in December 2021 and is marketed by Allergan, an AbbVie company. The competition also includes reading glasses, multifocal contact lenses, and monovision contact lenses (e.g., where one eye wears a near vision lens and the other eye wears a distance vision lens). Ocuphire will also compete against several pharmacological therapies in development for the temporary treatment of presbyopia, many of which are cholinergic agonist-based pupil management therapies, including:

- CSF-1, with low dose pilocarpine and a secondary agent (lubricant), developed by Orasis Pharmaceuticals Ltd.
- LNZ100 and LNZ101, with aceclidine (another miotic agent) and brimonidine, developed by Lenz Therapeutics.
- MicroLine®, which is a micro-dose delivery of pilocarpine using proprietary device developed by Eyenovia, Inc.
- KT-101, which uses pilocarpine in the AcuStream delivery system, developed by Kedalion Therapeutics, Inc.
- Brimochol™, with brimonidine and carbachol (both are miotic agents), developed by Visus Therapeutics, Inc.
- UNR844, which uses a mechanism that involves softening the lens to increase near visual acuity, developed by Novartis AG (originally Encore Vision, Inc.).

There are a few approved devices for presbyopia. One of these is the KAMRA Inlay, developed by AcuFocus, Inc. and marketed by SightLife Surgical, Inc. Another is the Eyelike NoanPinhole, developed by Koryo Eyetech, the first commercially available pinhole soft contact lens. Nyxol would not directly compete against these devices, but rather would be a non-invasive alternative for presbyopes who are averse to surgical intervention.

Competition in NVD

NVD is a new indication in which Nyxol would be the first approved moderate ‘miotic’ drug. There are currently no FDA-approved therapies for NVD nor is Ocuphire aware of any in development. Existing miotic agents are rarely used off-label given their limitations of tachyphylaxis (Alphagan P® (brimonidine), marketed by Allergan plc, an AbbVie company) and warning in the label of difficulties while driving at night or performing hazardous activities in poor illuminations (attributable to pilocarpine, a generic molecule marketed by various pharmaceutical companies at common doses of 1%, 2%, and 3%).

APX3330

The key competitive factors affecting the success of APX3330, assuming APX3330 is approved, are likely to be its oral dosage form, tolerability, durability, price, and the availability of coverage and reimbursement from government and other third-party payors.

Competition in Diabetic Retinopathy / Diabetic Macular Edema / wAMD

Ocuphire believes that APX3330, if approved, could have a competitive advantage in the DR/DME/wAMD markets because it is an oral tablet with a dual mechanism and potential to address multiple indications. However, Ocuphire may face potential competition from both existing therapies and those in development. Current therapies for these retinal diseases rely on suppressing the activity of vascular endothelial growth factors (VEGF) via intravitreal injection or by mitigating the inflammation via intravitreal corticosteroid-releasing implants including:

- Lucentis® (ranibizumab) and Avastin® (bevacizumab), which are anti-VEGF monoclonal antibody intravitreal injections, developed by Genentech, Inc and Roche AG.
- EYLEA® (aflibercept), a VEGF inhibitor intravitreal injection, developed by Regeneron Pharmaceuticals.
- Vabysmo® (Faricimab), a bispecific monoclonal antibody targeting VEGF-A and Ang-Tie2 pathway developed by Genentech, Inc and Roche AG.
- Beovu® (Brolucizumab), an anti-VEGF monoclonal antibody intravitreal injection, developed by Novartis AG.
- MACUGEN® (pegaptanib sodium injection), a selective inhibitor of VEGF-165, developed by Bausch + Lomb.
- Ozurdex® (dexamethasone), a corticosteroid IVT implant, developed by Allergan plc.
- Iluvien (fluocinolone acetonide), a corticosteroid IVT implant, developed by Alimera Sciences, Inc.

There are also several pharmacological therapies in development, including:

- Abicipar, an anti-VEGF intravitreal injection with a long duration of action, developed by Allergan plc and Molecular Partners.
- KSI-301, an anti-VEGF antibody intravitreal injection coupled with a biopolymer that is intended to increase the time between injections, developed by Kodiak Sciences.
- OPT-302, an intravitreal injection which binds to multiple types of VEGF receptors that could be used with other anti-VEGF agents, developed by Opthea Limited.
- ALG-1001, an integrin peptide therapy intravitreal injection that is being evaluated as a sequential or in-combination therapy with bevacizumab in patients with DME, developed by Allegro Ophthalmics, LLC.
- RG-7774, an orally administered selective CB2 (Cannabinoid 2) receptor agonist that is being evaluated in patients with moderately severe to severe non-proliferative diabetic retinopathy, developed by Hoffmann-LA Roche, AG.
- RZ402, an oral small molecule selective and potent plasma kallikrein inhibitor (PKI) for the chronic treatment of diabetic macular edema (DME), developed by Rezolute, Inc.
- Xiflam™, an oral small molecule drug for the treatment of dry form of Age-Related Macular Degeneration (AMD), Geographic Atrophy (GA), Diabetic Retinopathy (DR) manifesting Diabetic Macular Edema (DME), developed by InflammX.

- AKST4290, an oral small molecule CCR3 Eotaxin inhibitor for the treatment of diabetic retinopathy and wet AMD.
- BAY1101042, an oral guanylate cycles activator for the treatment of diabetic retinopathy.

Government Regulation and Product Approvals

Government authorities in the United States, at the federal, state and local level, and in other countries and jurisdictions, including the European Union (EU), extensively regulate, among other things, the research, development, testing, manufacture, quality control, approval, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, post-approval monitoring and reporting, and import and export of pharmaceutical products. The processes for obtaining regulatory approvals in the United States and in foreign countries and jurisdictions, along with subsequent compliance with applicable statutes and regulations and other regulatory authorities, require the expenditure of substantial time and financial resources.

The EMA is a decentralized agency governed by an independent management board responsible for the evaluation, supervision, and safety monitoring of medicines in the EU. The Medicines and Healthcare products Regulatory Agency (MHRA) regulates medicines, medical devices, and blood components in the United Kingdom (UK) and serves as a similar function to the EMA in the EU, following the exit of the UK from the EU in Brexit. The Japanese Pharmaceuticals and Medical Devices Agency serves a similar function to the FDA in the United States and is an independent administrative institution. The National Medical Products Administration (NMPA) is the Chinese agency for regulating drugs and medical devices (formerly the China Food and Drug Administration or CFDA).

Review and Approval of Drugs in the United States

In the United States, the FDA regulates drug products under the Federal Food, Drug, and Cosmetic Act, or FDCA, and implementing regulations. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations requires the expenditure of substantial time and financial resources. The failure to comply with applicable requirements under the FDCA and other applicable laws at any time during the product development process, approval process or after approval may subject an applicant and/or sponsor to a variety of administrative or judicial sanctions, including refusal by the FDA to approve pending applications, withdrawal of an approval, imposition of a clinical hold, issuance of warning letters and other types of letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement of profits, or civil or criminal investigations and penalties brought by the FDA and the Department of Justice or other governmental entities.

An applicant seeking approval to market and distribute a new drug product in the United States must typically undertake the following:

- completion of preclinical laboratory tests, animal studies and formulation studies in compliance, as applicable, with the Animal Welfare Act and FDA's good laboratory practice, or GLP, regulations;
- submission to the FDA of an IND, which must take effect before human clinical trials may begin;
- approval by an independent institutional review board, or IRB, representing each clinical site before each clinical trial may be initiated;
- performance of adequate and well-controlled human clinical trials in accordance with good clinical practices, or GCP, to establish the safety and efficacy of the proposed drug product for each indication;
- manufacturing, packaging, labelling, and distribution of drug substances and drug products consistent with the FDA's Good Manufacturing Practice (GMP) regulations which are utilized in the GLP non-clinical and GCP clinical studies to investigate the drug candidate;

- development of product label, package inserts, and prescriber information that is intended to be used and included with the commercial product;
- preparation and submission to the FDA of an NDA;
- review of the product by an FDA advisory committee, where appropriate or if applicable;
- satisfactory completion of one or more FDA inspections of the manufacturing facility or facilities at which the product, or components thereof, are produced to assess compliance with current Good Manufacturing Practices, or cGMP, requirements and to assure that the facilities, methods and controls are adequate to preserve the product's identity, strength, quality and purity;
- satisfactory completion of FDA audits of clinical trial sites to assure compliance with GCPs and the integrity of the clinical data;
- payment of user fees and securing FDA approval of the NDA; and
- compliance with any post-approval requirements, including Risk Evaluation and Mitigation Strategies, or REMS, and post-approval studies required by the FDA.

Preclinical Studies

Preclinical studies include laboratory evaluation of the purity and stability of the manufactured drug substance or active pharmaceutical ingredient and the formulated drug or drug product, as well as *in vitro* and *in vivo* animal studies to assess the safety and activity of the drug for initial testing in humans and to establish a rationale for therapeutic use. The conduct of preclinical studies is subject to federal regulations and requirements, including GLP regulations. The results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical trials, among other things, are submitted to the FDA as part of an IND. Some long-term preclinical testing, such as 6-month toxicology studies, may continue after the IND is submitted.

Companies usually must complete some long-term preclinical testing, such as 6-month or longer toxicology studies, and must also develop additional information about the chemistry and physical characteristics of the investigational product and finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the candidate product and, among other things, the manufacturer must develop methods for testing the identity, strength, quality and purity of the final product. Additionally, appropriate packaging must be selected and tested, and stability studies must be conducted to demonstrate that the candidate product does not undergo unacceptable deterioration over its shelf life.

The IND and IRB Processes

An IND is an exemption from the FDCA that allows an unapproved drug to be shipped in interstate commerce for use in an investigational clinical trial. In support of a request for an IND, applicants must submit a protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. In addition, the results of preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical trials, among other things, are submitted to the FDA as part of an IND. An IND goes into effect 30-days after its filing, unless during this 30-day period the FDA raises concerns or questions and imposes a clinical hold.

A clinical hold is an order issued by the FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. A partial clinical hold is a delay or suspension of only part of the clinical work requested under the IND. For example, a specific protocol or part of a protocol is not allowed to proceed, while other protocols may do so. No more than 30 days after imposition of a clinical hold or partial clinical hold, the FDA will provide the sponsor a written explanation of the basis for the hold. Following issuance of a clinical hold or partial clinical hold, an investigation may only resume after the FDA has notified the sponsor that the investigation may proceed. The FDA will base that determination on information provided by the sponsor correcting the deficiencies previously cited or otherwise satisfying the FDA that the investigation can proceed. The FDA may also place a clinical hold or partial clinical hold on a trial after a clinical trial has begun.

A sponsor may choose, but is not required, to conduct a foreign clinical trial under an IND. When a foreign clinical trial is conducted under an IND, all FDA IND requirements must be met unless waived. When the foreign clinical trial is not conducted under an IND, the sponsor must ensure that the trial complies with certain FDA regulatory requirements in order to use the trial as support for an IND or application for marketing approval, including that such trials must be conducted in accordance with GCP, including review and approval by an independent ethics committee, or IEC, and obtaining informed consent from patients. The GCP requirements in the final rule encompass both ethical and data integrity standards for clinical studies. The FDA's regulations are intended to help ensure the protection of human patients enrolled in non-IND foreign clinical studies, as well as the quality and integrity of the resulting data. They further help ensure that non-IND foreign studies are conducted in a manner comparable to that required for IND studies.

In addition, an IRB representing each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must exercise continuing supervision over the trial. The IRB must review and approve, among other things, the trial protocol and informed consent information to be provided to trial patients. An IRB must operate in compliance with FDA regulations. An IRB can suspend or terminate approval of a clinical trial at its institution, or an institution it represents, if the clinical trial is not being conducted in accordance with the IRB's requirements or if the product candidate has been associated with unexpected serious harm to patients.

Additionally, some trials are overseen by an independent group of qualified experts organized by the trial sponsor, known as a data safety monitoring board or committee. This group provides authorization for whether or not a trial may move forward at designated check points based on access that only the group maintains to available data from the trial. Suspension or termination of development during any phase of clinical trials can occur if it is determined that the participants or patients are being exposed to an unacceptable health risk. Other reasons for suspension or termination may be made by Ocuphire based on evolving business objectives and/or competitive climate.

Information about certain clinical trials must be submitted within specific timeframes to the National Institutes of Health, or NIH, for public dissemination on its ClinicalTrials.gov website.

Human Clinical Trials in Support of an NDA

Clinical trials involve the administration of the investigational product to human patients under the supervision of qualified investigators in accordance with GCP requirements, which include, among other things, the requirement that all research patients provide their informed consent in writing before their participation in any clinical trial. Clinical trials are conducted under written trial protocols detailing, among other things, the inclusion and exclusion criteria, the objectives of the trial, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated.

Human clinical trials are typically conducted in 3 sequential phases, but the phases may overlap.

- *Phase 1.* The drug is initially introduced into healthy human patients or, in certain indications such as cancer, patients with the target disease or condition and tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an early indication of its effectiveness and to determine optimal dosage.
- *Phase 2.* The drug is administered to a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance and optimal dosage.
- *Phase 3.* The drug is administered to an expanded patient population, generally at geographically dispersed clinical trial sites, in well-controlled clinical trials to generate enough data to statistically evaluate the efficacy and safety of the product for approval, to establish the overall risk-benefit profile of the product and to provide adequate information for the labeling of the product.

Reports detailing activities under, and the status of, an IND must be submitted at least annually to the FDA. In addition, IND safety reports must be submitted to the FDA for any of the following: serious and unexpected suspected adverse reactions; findings from other studies or animal or *in vitro* testing that suggest a significant risk in humans exposed to the drug; and any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, or at all. Furthermore, the FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution, or an institution it represents, if the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug has been associated with unexpected serious harm to patients. The FDA will typically inspect one or more clinical sites to assure compliance with GCP and the integrity of the clinical data submitted.

Concurrent with clinical trials, companies often complete additional animal studies and must also develop additional information about the chemistry and physical characteristics of the drug as well as finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the drug candidate and, among other things, must develop methods for testing the identity, strength, quality, purity, and potency of the final drug. Additionally, appropriate packaging must be selected and tested, and stability studies must be conducted to demonstrate that the drug candidate does not undergo unacceptable deterioration over its shelf life.

Submission of an NDA to the FDA

Assuming successful completion of required clinical testing and other requirements, the results of the preclinical studies and clinical trials, together with detailed information relating to the product's chemistry, manufacture, controls and proposed labeling, among other things, are submitted to the FDA as part of an NDA requesting approval to market the drug product for one or more indications. Under federal law, the submission of most NDAs is subject to an application user fee (up to a maximum of 5), which for federal fiscal year 2022 is \$3,117,281 for an application requiring clinical data. The sponsor of an approved NDA is also subject to an annual prescription drug program fee, which for fiscal year 2022 is \$369,413. Certain exceptions and waivers are available for some of these fees, such as an exception from the application fee for drugs with orphan designation and a waiver for certain small businesses. In November 2021, Ocuphire filed for a fee waiver for its first NDA as a small business entity, in compliance with the Prescription of Drug User Fee Act (PDUFA). If granted, the waiver would be available for 12 months following date of issuance, during which time the NDA application would need to be submitted to recognize benefit of the fee waiver. Denial of the waiver request would be followed by an appeal process described by the Code of Federal Regulations.

The FDA conducts a preliminary review of an NDA within 60 days of its receipt and informs the sponsor by the 74th day after the FDA's receipt of the submission to determine whether the application is sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an NDA for filing, and the sponsor receives a Refuse to File Notice. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA has agreed to certain performance goals in the review process of NDAs. The goal for review of most standard applications is within 10 months from the date of filing, and for "priority review" products the review goal is within 6 months of filing. The review process may be extended by the FDA for 3 additional months to consider new information or clarification provided by the applicant to address an outstanding deficiency identified by the FDA following the original submission.

Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is or will be manufactured. These pre-approval inspections (PAIs) may cover all facilities associated with an NDA submission, including drug component manufacturing (such as active pharmaceutical ingredients), finished drug product manufacturing, and control testing laboratories. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications at the commercial scale. Additionally, before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP.

In addition, as a condition of approval, the FDA may require an applicant to develop a Risk Evaluation and Mitigation Strategies (REMS). REMS uses risk minimization strategies to ensure that the benefits of the product outweigh the potential risks. REMS can include medication guides, physician communication plans for healthcare professionals, and elements to assure safe use, or ETASU. ETASU may include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring, and the use of patient registries. The FDA may require a REMS at the time of approval or post-approval if it becomes aware of a serious risk associated with use of the product. The requirement for a REMS can materially affect the potential market and profitability of a product.

The FDA may refer an application for a novel drug to an advisory committee or explain why such referral was not made. Typically, an advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates and provides a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

Fast Track, Breakthrough Therapy, and Priority Review Designations

The FDA is authorized to designate certain products for expedited review if they are intended to address an unmet medical need in the treatment of a serious or life-threatening disease or condition. These programs are referred to as fast-track designation, breakthrough therapy designation, and priority review designation.

Specifically, the FDA may designate a product for Fast Track review if it is intended, whether alone or in combination with one or more other products, for the treatment of a serious or life-threatening disease or condition, and it demonstrates the potential to address unmet medical needs for such a disease or condition. For Fast Track products, sponsors may have greater interactions with the FDA and the FDA may initiate review of sections of a Fast Track product's application before the application is complete. The sponsor must also provide, and the FDA must approve, a schedule for the submission of the remaining information and the sponsor must pay applicable user fees. However, the FDA's time period goal for reviewing a Fast Track application does not begin until the last section of the application is submitted. In addition, the Fast Track designation may be withdrawn by the FDA if the FDA believes that the designation is no longer supported by data emerging in the clinical trial process.

Second, a product may be designated as a Breakthrough Therapy if it is intended, either alone or in combination with one or more other products, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The FDA may take certain actions with respect to Breakthrough Therapies, including holding meetings with the sponsor throughout the development process; providing timely advice to the product sponsor regarding development and approval; involving more senior staff in the review process; assigning a cross-disciplinary project lead for the review team; and taking other steps to design the clinical trials in an efficient manner.

Third, the FDA may designate a product for Priority Review if it is a product that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. The FDA determines, on a case-by-case basis, whether the proposed product represents a significant improvement when compared with other available therapies. Significant improvement may be illustrated by evidence of increased effectiveness in the treatment of a condition, elimination or substantial reduction of a treatment-limiting product reaction, documented enhancement of patient compliance that may lead to improvement in serious outcomes, and evidence of safety and effectiveness in a new subpopulation. A priority designation is intended to direct overall attention and resources to the evaluation of such applications, and to shorten the FDA's goal for taking action on a marketing application from 10 months to 6 months.

The FDA's Decision on an NDA

On the basis of the FDA's evaluation of the NDA and accompanying information, including the results of the inspection of the manufacturing facilities, the FDA may issue an approval letter, or a complete response letter (CRL). An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. A complete response letter generally outlines the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application. If and when those deficiencies have been addressed to the FDA's satisfaction in a resubmission of the NDA, the FDA may issue an approval letter. The FDA has committed to reviewing such resubmissions in 2 or 6 months depending on the type of information included. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

If the FDA approves a product, it may limit the approved indications for use for the product, require that contraindications, warnings or precautions be included in the product labeling, require that post-approval studies, including Phase 4 clinical trials, be conducted to further assess the drug's safety after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms, including REMS, which can materially affect the potential market and profitability of the product. The FDA may prevent or limit further marketing of a product based on the results of post-market studies or surveillance programs. After approval, many types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further testing requirements and FDA review and approval.

Post-Approval Requirements

Drugs manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting (such as annual reports and quarterly safety reports for the first 3 years), product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims, are subject to prior FDA review and approval. There also are continuing user fee requirements for any marketed products, as well as new application fees for supplemental applications with clinical data.

In addition, drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and state agencies and are subject to periodic unannounced inspections by the FDA and these state agencies for compliance with cGMP requirements. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon the sponsor and any third-party manufacturers that the sponsor may decide to use. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance.

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls;
- fines, warning letters or holds on post-approval clinical trials;

- refusal of the FDA to approve pending NDAs or supplements to approved NDAs, or suspension or revocation of product license approvals;
- product seizure or detention, or refusal to permit the import or export of products; or
- injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. Drugs may be promoted only for the approved indications and in accordance with the provisions of the approved label. All promotional materials must be submitted to FDA prior to the time of their first use. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability.

In addition, the distribution of prescription pharmaceutical products is subject to the Prescription Drug Marketing Act, or PDMA, which regulates the distribution of drug samples at the federal level, and sets minimum standards for the registration and regulation of drug sample distributors by the states. Both the PDMA and state laws limit the distribution of prescription pharmaceutical product samples and impose requirements to ensure accountability in distribution.

Section 505(b)(2) NDAs

NDAs for most new drug products are based on 2 adequate and well-controlled clinical trials which must contain substantial evidence of the safety and efficacy of the proposed new product. These applications are submitted under Section 505(b)(1) of the FDCA. The FDA is, however, authorized to approve an alternative type of NDA under Section 505(b)(2) of the FDCA. This type of application allows the applicant to rely, in part, on the FDA's previous findings of safety and efficacy for a similar product, or published literature. Specifically, Section 505(b)(2) applies to an NDA for a drug for which the investigations to show whether the drug is safe and effective and relied upon by the applicant for approval of the application "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted."

Thus, Section 505(b)(2) authorizes the FDA to approve an NDA based in part on safety and effectiveness data that were not developed by the applicant. Section 505(b)(2) may provide an alternate and potentially more expeditious pathway to FDA approval for new or improved formulations or new uses of previously approved products. If the Section 505(b)(2) applicant can establish that reliance on the FDA's previous approval is scientifically appropriate, the applicant may eliminate the need to conduct certain preclinical studies or clinical trials of the new product. The FDA may also require companies to perform additional studies or measurements to support the change from the approved product. The FDA may then approve the new drug candidate for all or some of the label indications for which the referenced product has been approved, as well as for any new indication sought by the Section 505(b)(2) applicant.

Abbreviated New Drug Applications for Generic Drugs

In 1984, with passage of the Hatch-Waxman Amendments to the FDCA, Congress authorized the FDA to approve generic drugs that are the same as drugs previously approved by the FDA under the NDA provisions of the statute. To obtain approval of a generic drug, an applicant must submit an abbreviated new drug application, or ANDA, to the agency. In support of such applications, a generic manufacturer may rely on the preclinical and clinical testing previously conducted for a drug product previously approved under an NDA, known as the reference-listed drug, or RLD.

Specifically, in order for an ANDA to be approved, the FDA generally must find that the generic version is identical to the RLD with respect to the active ingredients, the route of administration, the dosage form, and the strength of the drug. The FDA must also determine that the generic drug is "bioequivalent" to the innovator drug. Under the statute, a generic drug is bioequivalent to an RLD if "the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug."

Upon approval of an ANDA, the FDA indicates whether the generic product is “therapeutically equivalent” to the RLD in its publication Approved Drug Products with Therapeutic Equivalence Evaluations, also referred to as the Orange Book. Clinicians and pharmacists often consider a therapeutic equivalent generic drug to be fully substitutable for the RLD. In addition, by operation of certain state laws and numerous health insurance programs, the FDA’s designation of therapeutic equivalence often results in substitution of the generic drug without the knowledge or consent of either the prescribing clinicians or patient.

Under the Hatch-Waxman Amendments, the FDA may not approve an ANDA until any applicable period of non-patent exclusivity for the RLD has expired. The FDCA provides a period of five years of non-patent data exclusivity for a new drug containing a new chemical entity. For the purposes of this provision, a new chemical entity, or NCE, is a drug that contains no active moiety that has previously been approved by the FDA in any other NDA. An active moiety is the molecule or ion responsible for the physiological or pharmacological action of the drug substance. In cases where such NCE exclusivity has been granted, an ANDA may not be filed with the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification, in which case the applicant may submit its application four years following the original product approval.

The FDCA also provides for a period of three years of exclusivity if the NDA includes reports of one or more new clinical investigations, other than bioavailability or bioequivalence studies, that were conducted by or for the applicant and are essential to the approval of the application. This three-year exclusivity period applies to the condition(s) of use for which the new clinical investigation was conducted, and often protects changes to a previously approved drug product, such as a new dosage form, route of administration, combination or indication. Three-year exclusivity would be available for a drug product that contains a previously approved active moiety, provided the statutory requirement for a new clinical investigation is satisfied. Unlike five-year NCE exclusivity, an award of three-year exclusivity does not block the FDA from accepting ANDAs seeking approval for generic versions of the drug as of the date of approval of the original drug product.

Hatch-Waxman Patent Certification and the 30-Month Stay

Upon approval of an NDA or a supplement thereto, NDA sponsors are required to list with the FDA each patent with claims that cover the applicant’s product or an approved method of using the product. Each of the patents listed by the NDA sponsor is published in the Orange Book. When an ANDA applicant files its application with the FDA, the applicant is required to certify to the FDA concerning any patents listed for the reference product in the Orange Book, except for patents covering methods of use for which the ANDA applicant is not seeking approval. To the extent that the Section 505(b)(2) applicant is relying on studies conducted for an already approved product, the applicant is required to certify to the FDA concerning any patents listed for the approved product in the Orange Book to the same extent that an ANDA applicant would.

Specifically, the applicant must certify with respect to each patent that: (1) the required patent information has not been filed, (2) the listed patent has expired, (3) the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or (4) the listed patent is invalid, unenforceable or will not be infringed by the new product.

A certification that the new product will not infringe the already approved product’s listed patents or that such patents are invalid or unenforceable is called a Paragraph IV certification. If the applicant does not challenge the listed patents or indicates that it is not seeking approval of a patented method of use, the ANDA or 505(b)(2) application will not be approved until all the listed patents claiming the referenced product have expired (other than method of use patents involving indications for which the applicant is not seeking approval).

If the ANDA applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA and patent holders once the ANDA has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days after the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA until the earlier of 30 months after the receipt of the Paragraph IV notice, expiration of the patent, or a decision in the infringement case that is favorable to the ANDA applicant.

To the extent that the Section 505(b)(2) applicant is relying on studies conducted for an already approved product, the applicant is required to certify to the FDA concerning any patents listed for the approved product in the Orange Book to the same extent that an ANDA applicant would. As a result, approval of a Section 505(b)(2) NDA can be stalled until all the listed patents claiming the referenced product have expired, until any non-patent exclusivity, such as exclusivity for obtaining approval of a new chemical entity, listed in the Orange Book for the referenced product has expired, and, in the case of a Paragraph IV certification and subsequent patent infringement suit, until the earlier of 30 months, settlement of the lawsuit or a decision in the infringement case that is favorable to the Section 505(b)(2) applicant.

505(b)(2) and NCE Data Exclusivity in U.S.

In the United States, the Hatch-Waxman Act provides a 3-year period of non-patent data exclusivity within the United States to the first applicant to gain approval through a 505(b)(2) application seeking regulatory approval of, for example, a new indication, dosage, or strength of an existing drug. This three-year exclusivity covers only the conditions of use associated with the new clinical investigation and does not prohibit the FDA from approving an ANDA for drugs containing the original active agent. Under this provision, Nyxol for use in treating presbyopia, mydriasis, or NVD may be eligible for 3 years of data exclusivity under the Hatch-Waxman Act.

In the United States, the Hatch-Waxman Act provides period of 5-years of non-patent data exclusivity for a new drug containing a new chemical entity. For the purposes of this provision, a new chemical entity, or NCE, is a drug that contains no active moiety that has previously been approved by the FDA in any other NDA. An active moiety is the molecule or ion responsible for the physiological or pharmacological action of the drug substance. In cases where such NCE exclusivity has been granted, an ANDA may not be filed with the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification, in which case the applicant may submit its application four years following the original product approval.

Pediatric Studies and Exclusivity

Under the Pediatric Research Equity Act of 2003, an NDA or supplement thereto must contain data that are adequate to assess the safety and effectiveness of the drug product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. With enactment of the Food and Drug Administration Safety and Innovation Act or FDASIA, in 2012, sponsors must also submit pediatric trial plans prior to the assessment data. Those plans must contain an outline of the proposed pediatric trial or studies the applicant plans to conduct, including trial objectives and design, any deferral or waiver requests, and other information required by regulation. The applicant, the FDA, and the FDA's internal review committee must then review the information submitted, consult with each other, and agree upon a final plan. The FDA or the applicant may request an amendment to the plan at any time.

The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements. Additional requirements and procedures relating to deferral requests and requests for extension of deferrals are contained in FDASIA. Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan designation.

Pediatric exclusivity is another type of non-patent marketing exclusivity in the United States and, if granted, provides for the attachment of an additional 6 months to the term of any patent or regulatory exclusivity, including orphan exclusivity. This 6-month exclusivity may be granted if an NDA sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The data do not need to show the product to be effective in the pediatric population studied; rather, if the clinical trial is deemed to fairly respond to the FDA's request, the additional protection is granted. If reports of requested pediatric studies are submitted to and accepted by the FDA within the statutory time limits, the latest statutory or regulatory period of exclusivity or patent covering the product is extended by 6 months. This is not a patent term extension, but it effectively extends the regulatory period during which the FDA cannot approve another application.

Orphan Drug Designation and Exclusivity

Under the Orphan Drug Act, the FDA may designate a drug product as an “orphan drug” if it is intended to treat a rare disease or condition (generally meaning that it affects fewer than 200,000 individuals in the United States, or more in cases in which there is no reasonable expectation that the cost of developing and making a drug product available in the United States for treatment of the disease or condition will be recovered from sales of the product). A company must request orphan product designation before submitting an NDA. If the request is granted, the FDA will disclose the identity of the therapeutic agent and its potential use. Orphan product designation does not convey any advantage in or shorten the duration of the regulatory review and approval process.

If a product with orphan status receives the first FDA approval for the disease or condition for which it has such designation or for a select indication or use within the rare disease or condition for which it was designated, the product generally will receive orphan drug exclusivity. Orphan drug exclusivity means that the FDA may not approve any other applications for the same product for the same indication for 7 years, except in certain limited circumstances. Competitors may receive approval of different products for the indication for which the orphan product has exclusivity and may obtain approval for the same product but for a different indication. If a drug or drug product designated as an orphan product ultimately receives marketing approval for an indication broader than what was designated in its orphan product application, it may not be entitled to exclusivity.

Patent Term Restoration and Extension

A patent claiming a new drug product may be eligible for a limited patent term extension under the Hatch-Waxman Act, which permits a patent restoration of up to 5 years for patent term lost during product development and the FDA regulatory review. The restoration period granted is typically one-half the time between the effective date of an IND and the submission date of an NDA, plus the time between the submission date of an NDA and the ultimate approval date. Patent term restoration cannot be used to extend the remaining term of a patent past a total of 14 years from the product’s approval date. Only one patent applicable to an approved drug product is eligible for the extension, and the application for the extension must be submitted prior to the expiration of the patent in question. A patent that covers multiple drugs for which approval is sought can only be extended in connection with one of the approvals. The U.S. Patent and Trademark Office reviews and approves the application for any patent term extension or restoration in consultation with the FDA. Ocuphire cannot provide any assurance that any patent term extension with respect to any U.S. patent will be obtained and, if obtained, the duration of such extension, in connection with any of its product candidates.

The 21st Century Cures Act

On December 13, 2016, President Obama signed the Cures Act into law. The Cures Act is designed to modernize and personalize healthcare, spur innovation and research, and streamline the discovery and development of new therapies through increased federal funding of particular programs. It authorizes increased funding for the FDA to spend on innovation projects. The new law also amends the Public Health Service Act to reauthorize and expand funding for the NIH. The Act establishes the NIH Innovation Fund to pay for the cost of development and implementation of a strategic plan, early-stage investigators and research. It also charges NIH with leading and coordinating expanded pediatric research. Further, the Cures Act directs the Centers for Disease Control and Prevention to expand surveillance of neurological diseases.

With amendments to the FDCA and the Public Health Service Act, or PHS Act, Title III of the Cures Act seeks to accelerate the discovery, development, and delivery of new medicines and medical technologies. To that end, and among other provisions, the Cures Act reauthorizes the existing priority review voucher program for certain drugs intended to treat rare pediatric diseases until 2020; creates a new priority review voucher program for drug applications determined to be material national security threat medical countermeasure applications; revises the FDCA to streamline review of combination product applications; requires FDA to evaluate the potential use of “real world evidence” to help support approval of new indications for approved drugs; and provides a new “limited population” approval pathway for antibiotic and antifungal drugs intended to treat serious or life-threatening infections.

Review and Approval of Drug Products in the European Union

In order to market any product outside of the United States, a company must also comply with numerous and varying regulatory requirements of other countries and jurisdictions regarding quality, safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of products. Whether or not it obtains FDA approval for a product, Ocuphire would need to obtain the necessary approvals by the comparable foreign regulatory authorities before it can commence clinical trials or marketing of the product in those countries or jurisdictions. The approval process ultimately varies between countries and jurisdictions and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries and jurisdictions might differ from and be longer than that required to obtain FDA approval. Regulatory approval in one country or jurisdiction does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country or jurisdiction may negatively impact the regulatory process in others.

Procedures Governing Approval of Drug Products in the European Union

Pursuant to the European Clinical Trials Directive, a system for the approval of clinical trials in the European Union has been implemented through national legislation of the member states. Under this system, an applicant must obtain approval from the competent national authority of a European Union member state in which the clinical trial is to be conducted. Furthermore, the applicant may only start a clinical trial after a competent ethics committee has issued a favorable opinion. Clinical trial application must be accompanied by an investigational medicinal product dossier with supporting information prescribed by the European Clinical Trials Directive and corresponding national laws of the member states and further detailed in applicable guidance documents.

To obtain marketing approval of a product under European Union regulatory systems, an applicant must submit a marketing authorization application, or MAA, either under a centralized or decentralized procedure. The centralized procedure provides for the grant of a single marketing authorization by the European Commission that is valid for all European Union member states. The centralized procedure is compulsory for specific products, including for medicines produced by certain biotechnological processes, products designated as orphan medicinal products, advanced therapy products and products with a new active substance indicated for the treatment of certain diseases. For products with a new active substance indicated for the treatment of other diseases and products that are highly innovative or for which a centralized process is in the interest of patients, the centralized procedure may be optional.

Under the centralized procedure, the Committee for Medicinal Products for Human Use, or the CHMP, established at the European Medicines Agency, or EMA, is responsible for conducting the initial assessment of a product. The CHMP is also responsible for several post-authorization and maintenance activities, such as the assessment of modifications or extensions to an existing marketing authorization. Under the centralized procedure in the European Union, the maximum timeframe for the evaluation of an MAA is 210 days, excluding clock stops, when additional information or written or oral explanation is to be provided by the applicant in response to questions of the CHMP. Accelerated evaluation might be granted by the CHMP in exceptional cases when a medicinal product is of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation. In this circumstance, the EMA ensures that the opinion of the CHMP is given within 150 days.

The decentralized procedure is available to applicants who wish to market a product in various European Union member states where such product has not received marketing approval in any European Union member states before. The decentralized procedure provides for approval by one or more other, or concerned, member states of an assessment of an application performed by one-member state designated by the applicant, known as the reference member state. Under this procedure, an applicant submits an application based on identical dossiers and related materials, including a draft summary of product characteristics, and draft labeling and package leaflet, to the reference member state and concerned member states. The reference member state prepares a draft assessment report and drafts of the related materials within 210 days after receipt of a valid application. Within 90 days of receiving the reference member state's assessment report and related materials, each concerned member state must decide whether to approve the assessment report and related materials.

If a member state cannot approve the assessment report and related materials on the grounds of potential serious risk to public health, the disputed points are subject to a dispute resolution mechanism and may eventually be referred to the European Commission, whose decision is binding on all member states.

Within this framework, manufacturers may seek approval of hybrid medicinal products under Article 10(3) of Directive 2001/83/EC. Hybrid applications rely, in part, on information and data from a reference product and new data from appropriate pre-clinical tests and clinical trials. Such applications are necessary when the proposed product does not meet the strict definition of a generic medicinal product, or bioavailability studies cannot be used to demonstrate bioequivalence, or there are changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration of the generic product compared to the reference medicinal product. In such cases the results of tests and trials must be consistent with the data content standards required in the Annex to the Directive 2001/83/EC, as amended by Directive 2003/63/EC.

Hybrid medicinal product applications have automatic access to the centralized procedure when the reference product was authorized for marketing via that procedure. Where the reference product was authorized via the decentralized procedure, a hybrid application may be accepted for consideration under the centralized procedure if the applicant shows that the medicinal product constitutes a significant therapeutic, scientific or technical innovation, or the granting of a community authorization for the medicinal product is in the interest of patients at the community level.

Clinical Trial Approval in the European Union

Requirements for the conduct of clinical trials in the European Union including Good Clinical Practice, or GCP, are set forth in the Clinical Trials Directive 2001/20/EC and the GCP Directive 2005/28/EC. Pursuant to Directive 2001/20/EC and Directive 2005/28/EC, as amended, a system for the approval of clinical trials in the European Union has been implemented through national legislation of the E.U. member states. Under this system, approval must be obtained from the competent national authority of each E.U. member state in which a trial is planned to be conducted. To this end, a CTA is submitted, which must be supported by an investigational medicinal product dossier, or IMPD, and further supporting information prescribed by Directive 2001/20/EC and Directive 2005/28/EC and other applicable guidance documents. Furthermore, a clinical trial may only be started after a competent ethics committee has issued a favorable opinion on the clinical trial application in that country.

In April 2014, the E.U. passed the new Clinical Trials Regulation (EU) No 536/2014. The new Clinical Trials Regulation, which will replace the Clinical Trials Directive, introduces a complete overhaul of the existing regulation of clinical trials for medicinal products in the E.U., including a new coordinated procedure for authorization of clinical trials that is reminiscent of the mutual recognition procedure for marketing authorization of medicinal products, and increased obligations on sponsors to publish clinical trial results. The entry into application of the Clinical Trials Regulation has been delayed. The Clinical Trials Directive may be replaced with the new Clinical Trials Regulation in late 2022. The new Clinical Trials Regulation aims to simplify and streamline the approval of clinical trials in the European Union. The main characteristics of the regulation include: a streamlined application procedure via a single entry point, the E.U. portal; a single set of documents to be prepared and submitted for the application as well as simplified reporting procedures that will spare sponsors from submitting broadly identical information separately to various bodies and different member states; a harmonized procedure for the assessment of applications for clinical trials, which is divided into two parts (Part I is assessed jointly by all member states concerned, and Part II is assessed separately by each member state concerned); strictly defined deadlines for the assessment of clinical trial applications; and the involvement of the ethics committees in the assessment procedure in accordance with the national law of the member state concerned but within the overall timelines defined by the Clinical Trials Regulation.

Periods of Authorization and Renewals

Marketing authorization is valid for five years in principle and the marketing authorization may be renewed after five years on the basis of a re-evaluation of the risk-benefit balance by the EMA or by the competent authority of the authorizing member state. To this end, the marketing authorization holder must provide the EMA or the competent authority with a consolidated version of the file in respect of quality, safety and efficacy, including all variations introduced since the marketing authorization was granted, at least six months before the marketing authorization ceases to be valid. Once renewed, the marketing authorization is valid for an unlimited period, unless the European Commission or the competent authority decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal. Any authorization which is not followed by the actual placing of the drug on the European Union market (in case of centralized procedure) or on the market of the authorizing member state within three years after authorization ceases to be valid (the so-called sunset clause).

Data and Market Exclusivity in the European Union

In the European Union, new chemical entities qualify for eight years of data exclusivity upon marketing authorization and an additional two years of market exclusivity. This data exclusivity, if granted, prevents regulatory authorities in the European Union from referencing the innovator's data to assess a generic (abbreviated) application for eight years, after which generic marketing authorization can be submitted, and the innovator's data may be referenced, but not approved for two years. The overall ten-year period will be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies. Even if a compound is considered to be a new chemical entity and the sponsor is able to gain the prescribed period of data exclusivity, another company nevertheless could also market another version of the product if such company can complete a full MAA with a complete database of pharmaceutical test, preclinical tests and clinical trials and obtain marketing approval of its product.

Orphan Drug Designation and Exclusivity

Regulation 141/2000 provides that a drug shall be designated as an orphan drug if its sponsor can establish: that the product is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in ten thousand persons in the European Community when the application is made, or that the product is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the European Community and that without incentives it is unlikely that the marketing of the drug in the European Community would generate sufficient return to justify the necessary investment. For either of these conditions, the applicant must demonstrate that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorized in the European Community or, if such method exists, the drug will be of significant benefit to those affected by that condition.

Regulation 847/2000 sets out criteria and procedures governing designation of orphan drugs in the European Union. Specifically, an application for designation as an orphan product can be made any time prior to the filing of an application for approval to market the product. Marketing authorization for an orphan drug leads to a ten-year period of market exclusivity. This period may, however, be reduced to six years if, at the end of the fifth year, it is established that the product no longer meets the criteria for orphan drug designation, for example because the product is sufficiently profitable not to justify market exclusivity. Market exclusivity can be revoked only in very selected cases, such as consent from the marketing authorization holder, inability to supply sufficient quantities of the product, demonstration of "clinically relevant superiority" by a similar medicinal product, or, after a review by the Committee for Orphan Medicinal Products, requested by a member state in the fifth year of the marketing exclusivity period (if the designation criteria are believed to no longer apply). Medicinal products designated as orphan drugs pursuant to Regulation 141/2000 shall be eligible for incentives made available by the European Community and by the member states to support research into, and the development and availability of, orphan drugs.

Regulatory Requirements after Marketing Authorization

As in the United States, both marketing authorization holders and manufacturers of medicinal products are subject to comprehensive regulatory oversight by the EMA and the competent authorities of the individual EU Member States both before and after grant of the manufacturing and marketing authorizations. The holder of an EU marketing authorization for a medicinal product must, for example, comply with EU pharmacovigilance legislation and its related regulations and guidelines which entail many requirements for conducting pharmacovigilance, or the assessment and monitoring of the safety of medicinal products. The manufacturing process for medicinal products in the European Union is also highly regulated and regulators may shut down manufacturing facilities that they believe do not comply with regulations. Manufacturing requires a manufacturing authorization, and the manufacturing authorization holder must comply with various requirements set out in the applicable EU laws, including compliance with EU cGMP standards when manufacturing medicinal products and active pharmaceutical ingredients.

In the European Union, the advertising and promotion of approved products are subject to EU Member States' laws governing promotion of medicinal products, interactions with clinicians, misleading and comparative advertising and unfair commercial practices. In addition, other legislation adopted by individual EU Member States may apply to the advertising and promotion of medicinal products. These laws require that promotional materials and advertising in relation to medicinal products comply with the product's Summary of Product Characteristics, or SmPC, as approved by the competent authorities. Promotion of a medicinal product that does not comply with the SmPC is considered to constitute off-label promotion, which is prohibited in the European Union.

Pharmaceutical Coverage, Pricing and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of products approved by the FDA and other government authorities. Sales of products will depend, in part, on the extent to which third-party payors, including government health programs in the United States such as Medicare and Medicaid, commercial health insurers and managed care organizations, provide coverage, and establish adequate reimbursement levels for, such products. The process for determining whether a payor will provide coverage for a product may be separate from the process for setting the price or reimbursement rate that the payor will pay for the product once coverage is approved. Third-party payors are increasingly challenging the prices charged, examining the medical necessity, and reviewing the cost-effectiveness of medical products and services and imposing controls to manage costs. Third-party payors may limit coverage to specific products on an approved list, or formulary, which might not include all of the approved products for a particular indication.

In order to secure coverage and reimbursement for any product that might be approved for sale, a company may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of the product, in addition to the costs required to obtain FDA or other comparable regulatory approvals. Nonetheless, product candidates may not be considered medically necessary or cost effective. Additionally, a payor's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Further, one payor's determination to provide coverage for a drug product does not assure that other payors will also provide coverage for the drug product. Third-party reimbursement may not be sufficient to maintain price levels high enough to realize an appropriate return on investment in product development.

The containment of healthcare costs also has become a priority of federal, state and foreign governments and the prices of drugs have been a focus in this effort. Governments have shown significant interest in implementing cost-containment programs, including price controls, restrictions on reimbursement and requirements for substitution of generic products. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit a company's revenue generated from the sale of any approved products. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which a company or its collaborators receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

Outside the United States, ensuring adequate coverage and payment for its product candidates will face challenges. Pricing of prescription pharmaceuticals is subject to governmental control in many countries. Pricing negotiations with governmental authorities can extend well beyond the receipt of regulatory marketing approval for a product and may require Ocuphire to conduct a clinical trial that compares the cost effectiveness of its product candidates or products to other available therapies. The conduct of such a clinical trial could be expensive and result in delays in Ocuphire's commercialization efforts.

In the European Union, pricing and reimbursement schemes vary widely from country to country. Some countries provide that drug products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost-effectiveness of a particular drug candidate to currently available therapies. For example, the European Union provides options for its member states to restrict the range of drug products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. European Union member states may approve a specific price for a drug product, or it may instead adopt a system of direct or indirect controls on the profitability of Ocuphire placing the drug product on the market. Other member states allow companies to fix their own prices for drug products but monitor and control company profits. The downward pressure on healthcare costs in general, particularly prescription drugs, has become intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, in some countries, cross-border imports from low-priced markets exert competitive pressure that may reduce pricing within a country. Any country that has price controls or reimbursement limitations for drug products may not allow favorable reimbursement and pricing arrangements.

Healthcare Law and Regulation

Healthcare providers and third-party payors play a primary role in the recommendation and prescription of drug products that are granted regulatory approval. Arrangements with providers, consultants, third-party payors and customers are subject to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain Ocuphire's business and/or financial arrangements. Such restrictions under applicable federal and state healthcare laws and regulations, include the following:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made, in whole or in part, under a federal healthcare program such as Medicare and Medicaid;
- the federal civil and criminal false claims laws, including the civil False Claims Act, and civil monetary penalties laws, which prohibit individuals or entities from, among other things, knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created additional federal criminal laws that prohibit, among other things, knowingly and willingly executing, or attempting to execute, a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act and its implementing regulations, which also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;
- the federal transparency requirements known as the federal Physician Payments Sunshine Act, under the Patient Protection and Affordable Care Act, as amended by the Health Care Education Reconciliation Act, or the Affordable Care Act, which requires certain manufacturers of drugs, devices, biologics and medical supplies to report specially to the Centers for Medicare & Medicaid Services, or CMS, within the U.S. Department of Health and Human Services, information related to payments and other transfers of value to clinicians and teaching hospitals and clinician ownership and investment interests; and
- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws, which may apply to healthcare items or services that are reimbursed by non-governmental third-party payors, including private insurers.

Some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring drug manufacturers to report information related to payments to clinicians and other healthcare providers or marketing expenditures. State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Healthcare Reform

A primary trend in the United States healthcare industry and elsewhere is cost containment. There have been several federal and state proposals during the last few years regarding the pricing of pharmaceutical products, limiting coverage and reimbursement for drugs and other medical products, government control and other changes to the healthcare system in the United States.

In March 2010, the United States Congress enacted the Affordable Care Act, or ACA, which, among other things, includes changes to the coverage and payment for products under government healthcare programs. Among the provisions of the ACA of importance to Ocuphire's potential drug candidates are:

- a special, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs, although this fee would not apply to sales of certain products approved exclusively for orphan indications;
- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to certain individuals with income at or below 133% of the federal poverty level, thereby potentially increasing a manufacturer's Medicaid rebate liability;
- expanded manufacturers' rebate liability under the Medicaid Drug Rebate Program by increasing the minimum rebate for both branded and generic drugs and revising the definition of "average manufacturer price," or AMP, for calculating and reporting Medicaid drug rebates on outpatient prescription drug prices and extending rebate liability to prescriptions for individuals enrolled in Medicare Advantage plans; addressed a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected;
- expanded the types of entities eligible for the 340B drug discount program;
- established the Medicare Part D coverage gap discount program by requiring manufacturers to provide a 50% point-of-sale-discount off the negotiated price of applicable brand drugs to eligible beneficiaries during their coverage gap period as a condition for the manufacturers' outpatient drugs to be covered under Medicare Part D;
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research;
- the Independent Payment Advisory Board, or IPAB, which has authority to recommend certain changes to the Medicare program to reduce expenditures by the program that could result in reduced payments for prescription drugs. However, the IPAB implementation has not been clearly defined. The ACA provided that under certain circumstances, IPAB recommendations will become law unless Congress enacts legislation that will achieve the same or greater Medicare cost savings; and
- established the Center for Medicare and Medicaid Innovation within CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending.

Other legislative changes have been proposed and adopted in the United States since the ACA was enacted. For example, in August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least \$1.2 trillion for the years 2012 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers of up to 2% per fiscal year, which went into effect in April 2013 and will remain in effect through 2024 unless additional Congressional action is taken. In January 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, further reduced Medicare payments to several providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. Further, on March 11, 2021, President Biden signed the American Rescue Plan Act of 2021 into law, which eliminates the statutory Medicaid drug rebate cap for single source and innovator multiple source drugs, beginning January 1, 2024. In addition, Congress is considering additional health reform measures, such as capping the costs for prescription drugs covered by Medicare Part D and by setting the annual out-of-pocket limit at \$2,000 beginning in 2024, as part of other health reform initiatives.

There may be additional legislative changes, including potentially repeal and replacement of certain provisions of the ACA. It remains to be seen, however, whether new legislation will be enacted and, if so, precisely what any new legislation will provide and what impact it will have on the availability of healthcare and containing or lowering the cost of healthcare. It is possible that any repeal and replacement initiatives, if enacted into law, could ultimately result in fewer individuals having health insurance coverage or in individuals having insurance coverage with less generous benefits. While the timing and scope of any potential future legislation to repeal and replace ACA provisions is highly uncertain in many respects, it is also possible that some of the ACA provisions that generally are not favorable for the research-based pharmaceutical industry could also be repealed along with ACA coverage expansion provisions.

Human Capital Resources

As of December 31, 2021, Ocuphire had eight full-time employees, with the following assignments: two engaged in clinical research and development activities, one of whom holds a Ph.D. degree, three engaged in research and development activities and also business development and finance, and three engaged in finance, human resources, and administrative support. Ocuphire is evaluating candidates for several senior full-time positions but plans to continue to utilize expert consultants and contract organizations to execute the day-to-day operations. None of Ocuphire's employees are represented by labor unions or covered by collective bargaining agreements. Ocuphire believes that it maintains good relations with its employees.

ITEM 1A. RISK FACTORS

An investment in our securities has a high degree of risk. Before you invest you should carefully consider the risks and uncertainties described below and the other information in this Annual Report. Any of the risks and uncertainties set forth herein could materially and adversely affect our business, results of operations and financial condition, which in turn could materially and adversely affect the trading price or value of our securities. Additional risks not currently known to us or which we consider immaterial based on information currently available to us may also materially adversely affect us. As a result, you could lose all or part of your investment.

Risks Related to Development of Ocuphire's Product Candidates

Ocuphire currently depends entirely on the success of Nyxol and APX3330, its only product candidates. Ocuphire may never receive marketing approval for, or successfully commercialize, Nyxol, APX3330, or other product candidates it may pursue in the future for any indication.

Ocuphire currently has only two product candidates, Nyxol and APX3330, in clinical development, and its business depends on their successful clinical development, regulatory approval and commercialization. The research, testing, manufacturing, labeling, approval, sale, marketing and distribution of a drug product are subject to extensive regulation by the FDA and other regulatory authorities in the United States and other countries, where regulations may differ. Ocuphire is not permitted to market its product candidates in the United States until it receives approval of an NDA from the FDA or in any foreign countries until it receives the requisite approval from such countries. Ocuphire has not submitted an NDA to the FDA or comparable applications to other regulatory authorities or received marketing approval for its product candidates. Before obtaining regulatory approval for the commercial sale of its product candidates for a particular indication, Ocuphire must demonstrate through preclinical testing and clinical trials that the applicable product candidate is safe and effective for use in that target indication. This process can take many years and may be followed by post-marketing studies and surveillance together which will require the expenditure of substantial resources beyond the proceeds raised in Ocuphire's equity and debt financings to date. Of the large number of drugs in development in the United States, only a small percentage of drugs successfully complete the FDA regulatory approval process and are commercialized. Accordingly, even if Ocuphire is able to complete development of its product candidates, Ocuphire cannot assure you that its product candidates will be approved or commercialized.

Obtaining approval of an NDA is an extensive, lengthy, expensive and uncertain process, and the FDA may delay, limit or deny approval of Ocuphire's product candidates for many reasons, including:

- the data collected from preclinical studies and clinical trials of Ocuphire's product candidates may not be sufficient to support the submission of an NDA;
- Ocuphire may not be able to demonstrate to the satisfaction of the FDA that its product candidates are safe and effective for any indication;
- the results of clinical trials may not meet the level of statistical significance or clinical significance required by the FDA for approval;
- the FDA may disagree with the number, design, size, conduct, or implementation of Ocuphire's clinical trials;
- the FDA may not find the data from preclinical studies and clinical trials sufficient to demonstrate that Ocuphire's product candidates' clinical and other benefits outweigh the safety risks;
- the FDA may disagree with Ocuphire's interpretation of data from preclinical studies or clinical trials;
- the FDA may not accept data generated at Ocuphire's clinical trial sites;

- the FDA may have difficulties scheduling an advisory committee meeting in a timely manner or the advisory committee may recommend against approval of Ocuphire’s application or may recommend that the FDA require, as a condition of approval, additional preclinical studies or clinical trials, limitations on approved labeling or distribution and use restrictions;
- the FDA may require development of a Risk Evaluation and Mitigation Strategy (REMS) as a condition of approval;
- the FDA may identify deficiencies in the manufacturing processes or facilities of third-party manufacturers with which Ocuphire enters into agreements for clinical and commercial supplies; or
- the FDA may change its approval policies or adopt new regulations.

The results of previous clinical trials may not be predictive of future results, and the results of Ocuphire’s current and planned clinical trials may not satisfy the requirements of the FDA or non-U.S. regulatory authorities.

The results from the prior preclinical studies and clinical trials for Nyxol and APX3330 discussed elsewhere in this Annual Report may not necessarily be predictive of the results of future preclinical studies or clinical trials. Even if Ocuphire is able to complete its planned clinical trials of its product candidates according to its current development timeline, the results from its prior clinical trials of its product candidates may not be replicated in these future trials. Many companies in the pharmaceutical and biotechnology industries (including those with greater resources and experience than Ocuphire) have suffered significant setbacks in late-stage clinical trials after achieving positive results in early-stage development, and Ocuphire cannot be certain that it will not face similar setbacks. These setbacks have been caused by, among other things, preclinical findings made while clinical trials were underway or safety or efficacy observations made in clinical trials, including previously unreported adverse events (“AEs”). Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that believed their product candidates performed satisfactorily in preclinical studies and clinical trials nonetheless have failed to obtain FDA approval. If Ocuphire fails to produce positive results in its clinical trials of any of its product candidates, the development timelines, regulatory approvals, and commercialization prospects for its product candidates, as well as Ocuphire’s business and financial prospects, would be adversely affected. Further, Ocuphire’s product candidates may not be approved even if they achieve their respective primary endpoints in additional Phase 3 registration trials. The FDA or non-U.S. regulatory authorities may disagree with Ocuphire’s trial designs or its interpretation of data from preclinical studies and clinical trials. In addition, any of these regulatory authorities may change requirements for the approval of a product candidate even after reviewing and providing comments or advice on a protocol for a pivotal clinical trial that has the potential to result in approval by the FDA or another regulatory authority. Furthermore, any of these regulatory authorities may also approve Ocuphire’s product candidate for fewer or more limited indications than it requests or may grant approval contingent on the performance of costly post-marketing clinical trials.

If Ocuphire’s future clinical and preclinical trials (as described elsewhere in this Annual Report) are successful, Ocuphire plans to eventually seek regulatory approvals of Nyxol and APX3330 initially in the United States, Canada, and Europe, and may seek approvals in other geographies. Before obtaining regulatory approvals for the commercial sale of any product candidate for any target indication, Ocuphire must demonstrate with substantial evidence gathered in preclinical studies and adequate and well-controlled clinical studies, and, with respect to approval in the United States, to the satisfaction of the FDA, that the product candidate is safe and effective for use for that target indication. Ocuphire cannot assure you that the FDA or non-U.S. regulatory authorities would consider its planned clinical trials to be sufficient to serve as the basis for approval of its product candidates for any indication. The FDA and non-U.S. regulatory authorities retain broad discretion in evaluating the results of Ocuphire’s clinical trials and in determining whether the results demonstrate that its product candidates are safe and effective. If Ocuphire is required to conduct clinical trials of its product candidates in addition to those it has planned prior to approval, Ocuphire will need substantial additional funds, and cannot assure you that the results of any such outcomes trial or other clinical trials will be sufficient for approval.

Additional data and/or time may be required to obtain U.S. regulatory approval for any of Ocuphire's product candidates that are deemed to be a drug/device combination product candidate.

Ocuphire's eye drop product candidates are now considered combination products with both drug and device components. The FDA requires both the drug and device components of combination product candidates to be reviewed as part of an NDA submission. Given this is a recent development with very few examples, the FDA's application of the regulations is evolving for drug/device combination products including single-use and multi-dose eye droppers. Ocuphire may experience request for additional data and/or delays in the development and commercialization of its drug led combination product candidates, due to regulatory uncertainties in the product development and approval process.

If clinical trials of Ocuphire's product candidates fail to demonstrate safety and efficacy to the satisfaction of regulatory authorities or do not otherwise produce positive results, Ocuphire may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of such product candidates.

Before obtaining marketing approval from regulatory authorities for the sale of Nyxol, Ocuphire must complete registration Phase 3 clinical trials to demonstrate the safety and efficacy in humans. In addition, for Nyxol chronic indications, Ocuphire must complete a six-month toxicology study in rabbits, which has completed the in-life portion. Clinical testing is expensive, difficult to design and implement, can take many years to complete, and is uncertain as to outcome. A failure of one or more clinical trials can occur at any stage of development. In addition, based on the Phase 2 safety, tolerability and efficacy results for APX3330, Ocuphire would need to conduct further animal toxicology studies and additional Phase 2 and Phase 3 clinical trials before obtaining marketing approval from regulatory authorities for the sale of APX3330.

Ocuphire may continue to experience delays in manufacturing and its clinical trials, and Ocuphire, or its future collaborators, may experience numerous unforeseen events during, or as a result of, clinical trials that could result in increased development costs and delay, and could limit or prevent its ability to receive marketing approval or commercialize its product candidates, including:

- regulators or IRBs may not authorize Ocuphire or its investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site including due to the ongoing COVID-19 pandemic or other public health emergency;
- government or regulatory delays and changes in regulatory requirements, policy and guidelines may require Ocuphire to perform additional clinical trials or use substantial additional resources to obtain regulatory approval, including due to the ongoing COVID-19 pandemic or other public health emergency;
- Ocuphire may have delays in reaching or fail to reach agreement on acceptable clinical trial contracts or clinical trial protocols with prospective trial sites, including due to the ongoing COVID-19 pandemic or other public health emergency;
- clinical trials may produce negative or inconclusive results, and Ocuphire may decide, or regulators may require it, to conduct additional clinical trials or abandon product development programs, including due to the ongoing COVID-19 pandemic or other public health emergency;
- the number of patients required for clinical trials may be larger, enrollment in these clinical trials may be slower or participants may drop out of these clinical trials at a higher rate than Ocuphire anticipates, including due to the ongoing COVID-19 pandemic or other public health emergency;
- Ocuphire's third-party contractors may fail to comply with regulatory requirements or meet their contractual obligations to Ocuphire in a timely manner, or at all;

- Ocuphire’s patients or medical investigators may be unwilling to follow its clinical trial protocols;
- Ocuphire might have to suspend or terminate clinical trials for various reasons, including a finding that the participants are being exposed to unacceptable health risks;
- the cost of clinical trials may be greater than Ocuphire anticipates, including due to the ongoing COVID-19 pandemic or other public health emergency;
- the supply or quality of any product candidate or other materials necessary to conduct clinical trials may be insufficient or inadequate;
- the product candidate may have undesirable side effects or other unexpected characteristics, causing Ocuphire or its investigators, regulators or IRBs to suspend or terminate the trials;
- clinical trials may be delayed or terminated because of the ongoing COVID-19 pandemic or another public health emergency; and
- federal agencies may, due to reduced manpower or diverted resources to the COVID-19 pandemic, require more time to review clinical trial protocols and INDs.

If Ocuphire experiences delays or difficulties in the enrollment of patients in clinical trials, Ocuphire’s ability to conduct and complete those clinical trials, and its ability to seek and receive necessary regulatory approvals, could be delayed or prevented.

Ocuphire or its future collaborators may not be able to initiate or continue clinical trials for its product candidates if Ocuphire is unable to locate and enroll a sufficient number of eligible patients to participate in these trials as required by the FDA or analogous regulatory authorities outside the United States. Patient enrollment can be affected by many factors, including:

- severity of the disease under investigation;
- availability and efficacy of medications already approved for the disease under investigation;
- eligibility criteria for the trial in question;
- competition for eligible patients with other companies conducting clinical trials for product candidates seeking to treat the same indication or patient population;
- its payments for conducting clinical trials;
- perceived risks and benefits of the product candidate under study;
- efforts to facilitate timely enrollment in clinical trials;
- patient referral practices of physicians;
- the ability to monitor patients adequately during and after treatment;
- proximity and availability of clinical trial sites for prospective patients;
- the ability of patients to safely participate in clinical trials during the COVID-19 pandemic or other public health emergencies; and

- the ability to monitor patients adequately during periods in which social distancing is required or recommended due to the COVID-19 pandemic.

The recent COVID-19 pandemic may also increase the time required to recruit patients for a study, and may also diminish the ability to monitor patients during the clinical trial. Ocuphire's inability to enroll a sufficient number of patients for its clinical trials or retain sufficient enrollment through the completion of its trials would result in significant delays or may require Ocuphire to abandon one or more clinical trials altogether. Enrollment delays in Ocuphire's clinical trials may result in increased development costs for its product candidates and cause its stock price to decline.

Ocuphire or others could discover that Ocuphire's product candidates lack sufficient efficacy, or that they cause undesirable side effects that were not previously identified, which could delay or prevent regulatory approval or commercialization.

Because both Nyxol and APX3330 have been tested in relatively small patient populations, at a limited range of daily doses up to 0.75% Phentolamine Ophthalmic Solution (which is the same as 1.0% Phentolamine Mesylate Ophthalmic Solution) and up to 720 mg respectively, and for limited durations to date, it is possible that Ocuphire's clinical trials have or will indicate an apparent positive effect of Nyxol or APX3330 that is greater than the actual positive effect, if any, or that additional and unforeseen side effects may be observed as its development progresses. The discovery that either Nyxol (alone or in combination with LDP) or APX3330 lacks sufficient efficacy, or that they cause undesirable side effects (including side effects not previously identified in Ocuphire's completed clinical trials), could cause Ocuphire or regulatory authorities to interrupt, delay, or discontinue clinical trials, and could result in the denial of regulatory approval by the FDA or other non-U.S. regulatory authorities for any or all targeted indications.

The discovery that Ocuphire's product candidates lack sufficient efficacy or that they cause undesirable side effects that were not previously identified could prevent Ocuphire from commercializing such product candidates and generating revenues from sales. In addition, if Ocuphire receives marketing approval for its product candidates and Ocuphire or others later discover that it is less effective, or identify undesirable side effects caused by its product candidates:

- regulatory authorities may withdraw their approval of the product;
- Ocuphire may be required to recall the product, change the way this product is administered, conduct additional clinical trials, or change the labeling or distribution of the product (including REMS);
- additional restrictions may be imposed on the marketing of, or the manufacturing processes for, the product;
- Ocuphire may be subject to fines, injunctions, or the imposition of civil or criminal penalties;
- Ocuphire could be sued and held liable for harm caused to patients;
- the product may be rendered less competitive and sales may decrease; or
- Ocuphire's reputation may suffer generally both among clinicians and patients.

Any one or a combination of these events could prevent Ocuphire from achieving or maintaining market acceptance of the affected product candidate or could substantially increase the costs and expenses of commercializing the product candidate, which in turn could delay or prevent Ocuphire from generating significant, or any, revenues from the sale of the product candidate.

Changes in regulatory requirements or FDA guidance, or unanticipated events during Ocuphire's clinical trials, may result in changes to clinical trial protocols or additional clinical trial requirements, which could result in increased costs to Ocuphire or delays in its development timeline.

Changes in regulatory requirements or FDA guidance, or unanticipated events during Ocuphire's clinical trials, may require Ocuphire to amend clinical trial protocols or the FDA may impose additional clinical trial requirements. Amendments to Ocuphire's clinical trial protocols would require resubmission to the FDA and IRBs for review and approval, and may adversely impact the cost, timing or successful completion of a clinical trial. If Ocuphire experiences delays completing, or if it terminates, any Phase 2 or Phase 3 trials, or if it is required to conduct additional clinical trials, the commercial prospects for its product candidates may be harmed and its ability to generate product revenues will be delayed.

If Ocuphire fails to receive regulatory approval for any of its planned indications for its product candidates or fails to develop additional product candidates, Ocuphire's commercial opportunity will be limited.

Ocuphire is initially focused on the development of its product candidates for its target indications, the reversal of pharmacologically-induced mydriasis, treatment of presbyopia, NVD, DR and DME. However, Ocuphire cannot assure you that it will be able to obtain regulatory approval of its product candidates for any indication, or successfully commercialize its product candidates, if approved. If Ocuphire does not receive regulatory approval for, or successfully commercialize, its product candidates for one or more of its targeted or other indications, Ocuphire's commercial opportunity will be limited.

Ocuphire may pursue clinical development of additional acquired or in-licensing product candidates. Developing, obtaining regulatory approval for and commercializing additional product candidates will require substantial additional funding beyond the net proceeds of Ocuphire's completed equity and debt financings, and are prone to the risks of failure inherent in drug product development. Ocuphire cannot assure you that it will be able to successfully advance any additional product candidates through the development process.

Even if it obtains FDA approval to market additional product candidates, Ocuphire cannot assure you that any such product candidates will be successfully commercialized, widely accepted in the marketplace, or more effective than other commercially available alternatives. If Ocuphire is unable to successfully develop and commercialize additional product candidates, its commercial opportunity will be limited.

Ocuphire has limited drug research and discovery capabilities and may need to acquire or license product candidates from third parties to expand its product candidate pipeline.

Ocuphire currently has limited drug research and discovery capabilities. Accordingly, if it is to expand its product candidate pipeline beyond Nyxol and APX3330 and its pipeline candidates, Ocuphire may need to acquire or license product candidates from third parties. Ocuphire would face significant competition in seeking to acquire or license promising product candidates. Many of its competitors for such promising product candidates may have significantly greater financial resources and more extensive experience in preclinical testing and clinical trials, obtaining regulatory approvals, and manufacturing and marketing pharmaceutical products, and thus, may be a more attractive option to a potential licensor than Ocuphire. If Ocuphire is unable to acquire or license additional promising product candidates, it may not be able to expand its product candidate pipeline.

If Ocuphire is able to acquire or license other product candidates, such license agreements will likely impose various obligations upon it, and its licensors may have the right to terminate the license thereunder in the event of a material breach or, in some cases, at will. A termination of a future license could result in Ocuphire's loss of the right to use the licensed intellectual property, which could adversely affect Ocuphire's ability to develop and commercialize a future product candidate, if approved, as well as harm its competitive business position and its business prospects.

Ocuphire may expend its limited resources to pursue a particular indication and fail to capitalize on indications that may be more profitable or for which there is a greater likelihood of success.

Because Ocuphire has limited financial and managerial resources, it is currently focusing only on development programs that it identifies for specific indications for its product candidates. As a result, Ocuphire may forego or delay pursuit of opportunities for other indications, or with other potential product candidates that later prove to have greater commercial potential. Ocuphire's resource allocation decisions may cause it to fail to capitalize on viable commercial products or profitable market opportunities. Ocuphire's spending on current and future research and development programs for specific indications or future product candidates may not yield any commercially viable product. If Ocuphire does not accurately evaluate the commercial potential or target market for its product candidates, it may not gain approval or achieve market acceptance of that candidate, and its business and financial results will be harmed.

Changes in tax laws or regulations that are applied adversely to us may have a material adverse effect on our business, cash flow, financial condition or results of operations.

New tax laws, statutes, rules, regulations or ordinances could be enacted at any time, which could adversely affect our business operations and financial performance. Further, existing tax laws, statutes, rules, regulations or ordinances could be interpreted, changed, modified or applied adversely to us. For example, the Tax Act, as modified by the Coronavirus Aid, Relief, and Economic Security Act (the "CARES Act") enacted in March 2020, enacted many significant changes to the U.S. tax laws. Future guidance from the Internal Revenue Service and other tax authorities with respect to the Tax Act may affect us, and certain aspects of the Tax Act could be repealed or modified in future legislation. For example, the CARES Act, modified certain provisions of the Tax Act and proposals have recently been made in Congress (which have not yet been enacted) to make tax law changes that could have a material adverse impact on us.

Risks Related to Ocuphire's Financial Position and Need for Additional Capital

Ocuphire has incurred only losses since inception. Ocuphire expects to incur losses for the foreseeable future and may never achieve or maintain profitability.

Since inception, Ocuphire incurred only operating losses. Ocuphire's net losses were \$56.7 million and \$24.6 million for the years ended December 31, 2021 and 2020, respectively. As of December 31, 2021, Ocuphire had an accumulated deficit of \$89.4 million. Ocuphire has funded its operations primarily through issuance of promissory notes and convertible notes in private placements, and then common stock and warrants after becoming a publicly-traded company. It has devoted substantially all of its financial resources and efforts to the clinical development of its product candidates. Even assuming Ocuphire obtains regulatory approval for one or more of its product candidates, Ocuphire expects that it will be at least eighteen months before it has a product candidate ready for commercialization. Ocuphire expects to continue to incur significant expenses and increased operating losses for the foreseeable future.

To become and remain profitable, Ocuphire must develop and eventually commercialize a product with market potential. This will require Ocuphire to be successful in a range of challenging activities, including completing preclinical testing and clinical trials, obtaining regulatory approval for a product candidate, manufacturing, marketing, and selling any drug for which it may obtain regulatory approval and satisfying any post-marketing requirements. Ocuphire is in the early stages of most of these activities. Ocuphire may never succeed in these activities and, even if it does, it may never generate revenues that are significant or large enough to achieve profitability.

If Ocuphire does achieve profitability, it may not be able to sustain or increase profitability on an annual basis. Its failure to become or remain profitable may decrease Ocuphire's value and could impair its ability to raise capital, maintain its research and development efforts, expand its business, or continue its operations.

Ocuphire has not generated any revenue from sales of any products and may never be profitable.

Ocuphire has no products approved for commercial sale, and does not anticipate generating any product revenue, unless and until either Nyxol, APX3330 or another product candidate receives the regulatory approvals necessary for commercialization in one or more jurisdictions. Ocuphire's ability to generate revenue depends on a number of factors, including its ability to:

- obtain favorable results from and complete the clinical development of both Nyxol and APX3330 for their planned indications, including successful completion of additional clinical trials for these indications;
- submit applications to regulatory authorities for both product candidates and receive timely marketing approvals in the United States and foreign countries;
- establish and maintain commercially viable supply and manufacturing relationships with third parties that can provide adequate, in both amount and quality, products and services to support clinical development and meet the market demand for product candidates that we develop, if approved;

- establish sales and marketing capabilities to effectively market and sell its product candidates in the United States or other markets, either alone or with a pharmaceutical partner;
- address any competing products and technological and market developments;
- obtain coverage and adequate reimbursement for customers and patients from government and third-party payors for product candidates that we develop; and
- achieve market acceptance of its product candidates.

Even if Ocuphire's product candidates are approved for commercial sale in one or all of the initial indications that it is pursuing, they may not gain market acceptance or achieve commercial success. In addition, Ocuphire anticipates incurring significant costs associated with commercializing its product candidates. Ocuphire may not achieve profitability soon after generating product revenue, if ever, and may be unable to continue operations without continued funding.

Ocuphire's recurring operating losses have raised substantial doubt regarding its ability to continue as a going concern.

Ocuphire's recurring operating losses raise substantial doubt about its ability to continue as a going concern. For the fiscal year ended December 31, 2021, its independent registered public accounting firm has issued its report on Ocuphire's financial statements and has expressed substantial doubt about its ability to continue as a going concern. Ocuphire has no current source of revenue to sustain its present activities, and it does not expect to generate revenue until and unless the FDA or other applicable regulatory authorities approves, and it successfully commercializes, its product candidates. Accordingly, Ocuphire's ability to continue as a going concern will require it to obtain additional financing to fund its operations. Uncertainty surrounding Ocuphire's ability to continue as a going concern may make it more difficult for it to obtain financing for the continuation of its operations and could result in a loss of confidence by investors, suppliers, contractors, and employees.

Ocuphire's relatively short operating history may make it difficult for investors to evaluate the success of its business to date and to assess its future viability.

Ocuphire is a clinical-stage company, and its operations to date have been limited to organizing and staffing its company, business planning, raising capital, and developing its product candidates. Ocuphire has not yet demonstrated its ability to successfully complete a Phase 3 program, obtain regulatory approval, manufacture a product at commercial scale, or conduct sales and marketing activities necessary for successful product commercialization.

Additionally, there is no operating history on which investors may evaluate this business and its prospects. Investment in a start-up company such as Ocuphire is inherently subject to many risks. These risks and difficulties include challenges in accurate financial planning as a result of: (a) accumulated losses; (b) uncertainties resulting from a relatively limited time period in which to develop and evaluate business strategies as compared to companies with longer operating histories; (c) compliance with regulations required to commence sales on future products; (d) reliance on third parties for clinical, manufacturing, analytical laboratory work, preclinical, regulatory, commercialization or other activities; (e) financing the business; and (f) meeting the challenges of the other risk factors described herein. Ocuphire has no operating history upon which investors may base an evaluation of its performance; therefore, it is subject to all risks incident to the creation and development of a new business. There can be no assurance that Ocuphire can realize its plans on its projected timetable in order to reach sustainable or profitable operations.

Ocuphire will need substantial additional capital in the future. If additional capital is not available, it will have to delay, reduce or cease operations.

Ocuphire will need to raise additional capital to continue to fund the further development of its product candidates and operations. Its future capital requirements may be substantial and will depend on many factors including:

- the scope, size, rate of progress, results, and costs of researching and developing its product candidates, and initiating and completing its preclinical studies and clinical trials;
- the cost, timing and outcome of its efforts to obtain marketing approval for its product candidates in the United States and other countries, including to fund the preparation and filing of NDAs with the FDA for its product candidates and to satisfy related FDA requirements and regulatory requirements in other countries;
- the number and characteristics of any additional product candidates it develops or acquires, if any;
- Ocuphire's ability to establish and maintain collaborations on favorable terms, if at all;
- the amount of revenue, if any, from commercial sales, should its product candidates receive marketing approval;
- the costs associated with commercializing its product candidates, if Ocuphire receives marketing approval, including the cost and timing of developing sales and marketing capabilities or entering into strategic collaborations to market and sell its product candidates;
- the cost of manufacturing its product candidates or products Ocuphire successfully commercializes; and
- the costs associated with general corporate activities, such as the cost of filing, prosecuting and enforcing patent claims and making regulatory filings.

Changing circumstances may cause Ocuphire to consume capital significantly faster than it currently anticipates. Because the outcome of any clinical trial is highly uncertain, Ocuphire cannot reasonably estimate the actual amounts necessary to successfully complete the development, regulatory approval and commercialization of its product candidates. Additional financing may not be available when Ocuphire needs it, or may not be available on terms that are favorable to Ocuphire. In addition, Ocuphire may seek additional capital due to favorable market conditions or strategic considerations, even if Ocuphire believes it has sufficient funds for its current or future operating plans. If adequate funds are unavailable to it on a timely basis, or at all, Ocuphire may not be able to continue the development of its product candidates, or commercialize its product candidates, if approved, unless it finds a strategic partner.

Worldwide economic and social instability could adversely affect Ocuphire's revenue, financial condition, or results of operations.

The health of the global economy, and the equity and credit markets in particular, as well as the stability of the social fabric of our society, affects our business and operating results. For example, the equity and credit markets may be adversely affected by the current conflict between Russia and Ukraine and measures taken in response thereto. If the equity and credit markets are not favorable, we may be unable to raise additional financing when needed or on favorable terms. Our vendors and development partners may experience financial difficulties or be unable to borrow money to fund their operations, which may adversely impact their ability to purchase our products or to pay for our products on a timely basis, if at all. In addition, adverse economic conditions, such as recent supply chain disruptions and labor shortages and persistent inflation, have affected, and may continue to adversely affect our suppliers' ability to provide our manufacturers with materials and components, which may negatively impact our business. These economic conditions make it more difficult for us to accurately forecast and plan our future business activities.

Raising additional capital may cause dilution to Ocuphire's stockholders, restrict Ocuphire's operations, or require Ocuphire to relinquish rights to its technologies or product candidates.

Until such time, if ever, as Ocuphire can generate substantial product revenues, it expects to finance its cash needs through a combination of equity and debt financings as well as potential strategic collaborations and licensing arrangements. It does not have any committed external source of funds. Debt financing or preferred equity financing, if available, may involve agreements that include covenants limiting or restricting Ocuphire's ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends.

If Ocuphire raises funds through strategic collaborations or marketing, distribution, or licensing arrangements with third parties, it may have to relinquish valuable rights to its technologies, future revenue streams, research programs or product candidates or to grant licenses on terms that may not be favorable to it. If it is unable to raise additional funds when needed, Ocuphire may be required to delay, limit, reduce or terminate its product development or future commercialization efforts or grant rights to develop and market product candidates that it would otherwise prefer to develop and market itself. This may reduce the value of its common stock.

Risks Related to Government Regulation

The FDA requires the completion of a toxicology study of similar duration before trials longer than six months can be conducted such as Phase 3 safety exposure trials for chronic indications or efficacy trials with such six-month endpoints. This may lead to a significant delay in the commencement of long-term clinical trials by Ocuphire or the failure of its product candidates to obtain marketing approval.

At this time, Ocuphire can run trials using Nyxol up to 28 days in duration based on its completed 28-day rabbit toxicology study. Therefore, the planned Phase 3 registration efficacy trials for presbyopia and NVD, with dosing for 7 to 14 days, may be conducted without further toxicology studies. Until Ocuphire has completed a six-month toxicology study for Nyxol, FDA regulations restrict it from conducting clinical trials longer than 6 months in duration targeting chronic indications, which at this time is a planned 1-year Phase 3 safety exposure trial to support chronic indications of presbyopia and NVD. Ocuphire completed the in-life portion of the six-month toxicology study in rabbits for Nyxol in the fourth quarter of 2021, with an expected completion and draft report in mid-2022. For APX3330, the drug has already been dosed for more than a year in humans and completed over 15 single- and repeat-dose toxicology studies in rats and dogs (including 2 studies up to 3 months in duration); with this data Ocuphire initiated its 24-week clinical trial for APX3330 without the need for further toxicology studies requested by the FDA. Ocuphire expects to complete further toxicology studies for future clinical trials prior to any marketing approval from regulatory authorities for the sale of APX3330. Clinical trials may be delayed due to these clinical restrictions and additional oversight by the FDA. In addition, the findings in the toxicology studies could affect the outcome of NDA reviews, and, if approved, labels and uses of Ocuphire's product candidates.

Even if it receives marketing approval for its product candidates in the United States, Ocuphire may never receive regulatory approval to market such product candidates outside of the United States.

In addition to the United States, Ocuphire intends to seek regulatory approval to market its product candidates in Europe, Japan, Canada, and Australia, and potentially other markets. If Ocuphire pursues additional product candidates in the future, it may seek regulatory approval of such product candidates outside the United States. In order to market any product outside of the United States, however, Ocuphire must establish and comply with the numerous and varying safety, efficacy and other regulatory requirements of these other countries. Approval procedures vary among countries and can involve additional product candidate testing and additional administrative review periods. The time required to obtain approvals in other countries might differ from that required to obtain FDA approval. The marketing approval processes in other countries may include all of the risks detailed above regarding FDA approval in the United States as well as other risks. In particular, in many countries outside of the United States, products must receive pricing and reimbursement approval before the product can be commercialized. Obtaining this approval can result in substantial delays in bringing products to market in such countries. Marketing approval in one country does not ensure marketing approval in another, but a failure or delay in obtaining marketing approval in one country may have a negative effect on the regulatory process in others. Failure to obtain marketing approval in other countries or any delay or other setback in obtaining such approval would impair Ocuphire's ability to market its product candidates in such foreign markets. Any such impairment would reduce the size of Ocuphire's potential market, which could have an adverse impact on its business, results of operations and prospects.

Even if Ocuphire obtains marketing approval for its product candidates, such product candidates could be subject to post-marketing, obligations, restrictions or withdrawal from the market, and Ocuphire may be subject to substantial penalties if it fails to comply with regulatory requirements or experience unanticipated problems with a product following approval.

Any product candidate for which Ocuphire, or its future collaborators, obtains marketing approval in the future, as well as the manufacturing processes, post-approval studies and measures, labeling, advertising, and promotional activities for such drug, among other things, will be subject to continual requirements of and review by the FDA and other regulatory authorities. These requirements include submissions of safety and other post-marketing information and reports, registration and listing requirements, requirements relating to manufacturing, quality control, quality assurance and corresponding maintenance of records and documents, requirements regarding the distribution of samples to physicians and recordkeeping. Even if marketing approval of a product candidate is granted, the approval may be subject to limitations on the indicated uses for which the drug may be marketed or to the conditions of approval, including the requirement to implement a REMS, which could include requirements for a restricted distribution system.

The FDA may also impose requirements for costly post-marketing studies or clinical trials and surveillance to monitor the safety or efficacy of a product candidate. The FDA and other agencies, including the Department of Justice, closely regulate and monitor the post-approval marketing and promotion of drugs to ensure that they are manufactured, marketed, and distributed only for the approved indications and in accordance with the provisions of the approved labeling. The FDA imposes stringent restrictions on manufacturers' communications regarding off-label use and if Ocuphire, or any future collaborator, does not market a product candidate for which it receives marketing approval for only its approved indications, Ocuphire, or the collaborator, may be subject to warnings or enforcement action for off-label promotion. Violation of the Federal Food, Drug, and Cosmetic Act ("FDCA") and other statutes, including the False Claims Act, relating to the promotion and advertising of prescription drugs, may lead to investigations or allegations of violations of federal or state healthcare fraud and abuse laws and state consumer protection laws.

In addition, later discovery of previously unknown AEs or other problems with Ocuphire's product candidates or its manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may yield various results, including:

- litigation involving patients taking Ocuphire's drugs;
- restrictions on such drugs, manufacturers, or manufacturing processes;
- restrictions on the labeling or marketing of a drug;
- restrictions on drug distribution or use;
- requirements to conduct post-marketing studies or clinical trials;
- warning letters or untitled letters;
- withdrawal of the drugs from the market;
- refusal to approve pending applications or supplements to approved applications that Ocuphire submits;
- product recall or public notification or medical product safety alerts to healthcare professionals;
- fines, restitution, or disgorgement of profits or revenues;
- suspension or withdrawal of marketing approvals;
- damage to relationships with any potential collaborators;

- unfavorable press coverage and damage to Ocuphire’s reputation;
- refusal to permit the import or export of drugs;
- product seizure; or
- injunctions or the imposition of civil or criminal penalties.

Ocuphire may seek to avail itself of mechanisms to expedite the development or approval for product candidates it may pursue in the future, such as fast track or breakthrough designation, but such mechanisms may not actually lead to a faster development or regulatory review or approval process.

Ocuphire may seek fast track designation, breakthrough designation, orphan drug designation, priority review, or accelerated approval for product candidates it may pursue in the future. For example, if a drug is intended for the treatment of a serious or life-threatening condition and the drug demonstrates the potential to address unmet medical needs for this condition, the drug sponsor may apply for FDA fast track designation. However, the FDA has broad discretion with regard to these mechanisms, and even if Ocuphire believes a particular product candidate is eligible for any such mechanism, it cannot guarantee that the FDA would decide to grant it. Even if it does obtain fast track or priority review designation or pursue an accelerated approval pathway, Ocuphire may not experience a faster development process, review, or approval compared to conventional FDA procedures. The FDA may withdraw a particular designation if it believes that the designation is no longer supported by data from Ocuphire’s clinical development program.

A breakthrough therapy is defined as a drug that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. Designation as a breakthrough therapy is within the discretion of the FDA. Accordingly, even if Ocuphire believes a product candidate meets the criteria for designation as a breakthrough therapy, the FDA may disagree and instead determine not to make such designation. Ocuphire cannot be sure that its evaluation of a product candidate as qualifying for breakthrough therapy designation will meet the FDA’s requirements. In any event, the receipt of a breakthrough therapy designation for a product candidate may not result in a faster development process, review, or approval compared to conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, even if one or more product candidates qualifies as a breakthrough therapy, the FDA may later decide that the product candidate no longer meets the conditions for qualification or may decide that the time period for FDA review or approval will not be shortened.

Recently enacted and future legislation may increase the difficulty and cost for Ocuphire and its future collaborators to obtain marketing approval of its product candidates and affect their pricing.

In the United States and some foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of a product candidate, restrict or regulate post-approval activities and affect Ocuphire’s ability, or the ability of its future collaborators, to profitably sell any drug for which it, or they, obtains marketing approval. Ocuphire expects that current laws, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and cause downward pressure on the price that Ocuphire, or its future collaborators, may charge for any approved drug.

For example, in March 2010, the United States Congress enacted the Patient Protection and Affordable Care Act (“ACA”), and the Health Care and Education Reconciliation Act, or the Healthcare Reform Act, which expanded health care coverage through Medicaid expansion and the implementation of the individual mandate for health insurance coverage and which included changes to the coverage and reimbursement of drug products under government healthcare programs.

There have also been efforts by federal and state government officials or legislators to implement measures to regulate prices or payment for pharmaceutical products, including legislation on drug importation. Recently, there has been considerable public and government scrutiny of pharmaceutical pricing and proposals to address the perceived high cost of pharmaceuticals. There have also been recent state legislative efforts to address drug costs, which generally have focused on increasing transparency around drug costs or limiting drug prices.

General legislative cost control measures may also affect reimbursement for Ocuphire's product candidates. The Budget Control Act, as amended, resulted in the imposition of 2% reductions in Medicare (but not Medicaid) payments to providers in 2013 and will remain in effect through 2027 unless additional Congressional action is taken. Any significant spending reductions affecting Medicare, Medicaid or other publicly funded or subsidized health programs that may be implemented and/or any significant taxes or fees that may be imposed on Ocuphire could have an adverse impact on results of operations.

Adoption of new legislation at the federal or state level could affect demand for, or pricing of, Ocuphire's current or future products if approved for sale. Ocuphire cannot, however, predict the ultimate content, timing or effect of any changes to the Healthcare Reform Act or other federal and state reform efforts. There is no assurance that federal or state health care reform will not adversely affect Ocuphire's future business and financial results.

There have been judicial and congressional challenges and amendments to certain aspects of the ACA, and Ocuphire expects there will be additional challenges and amendments to the ACA in the future, as well as efforts to repeal and replace it. In addition, other legislative changes have been proposed and adopted since the ACA was enacted. These new laws have resulted in additional reductions in Medicare and other healthcare funding and otherwise may affect the prices Ocuphire may obtain for any product candidate for which marketing approval is obtained. Any reduction in reimbursement from Medicare or other government-funded programs may result in a similar reduction in payments from private payors. Moreover, recently there has been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products. The implementation of cost containment measures or other healthcare reforms may prevent Ocuphire from being able to generate revenue, attain profitability, or commercialize its drugs. Further, on March 11, 2021, President Biden signed the American Rescue Plan Act of 2021 into law, which eliminates the statutory Medicaid drug rebate cap for single source and innovator multiple source drugs, beginning January 1, 2024. In addition, Congress is considering additional health reform measures, such as capping the costs for prescription drugs covered by Medicare Part D and by setting the annual out-of-pocket limit at \$2,000 beginning in 2024, as part of other health reform initiatives.

Legislative and regulatory proposals have been made to expand post-approval requirements and restrict sales and promotional activities for pharmaceutical products. Ocuphire cannot be sure whether additional legislative changes will be enacted, or whether the FDA regulations, guidance, or interpretations will be changed, or what the impact of such changes on the marketing approvals of a product candidate, if any, may be. In addition, increased scrutiny by the U.S. Congress of the FDA's approval process may significantly delay or prevent marketing approval or subject Ocuphire or its future collaborators to more stringent drug labeling and post-marketing testing and other requirements.

Governments outside of the United States tend to impose strict price controls, which may adversely affect Ocuphire's revenues from the sales of a drug, if any.

In some countries, particularly in the European Union, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a drug. To obtain reimbursement or pricing approval in some countries, Ocuphire, or its future collaborators, may be required to conduct a clinical trial that compares the cost-effectiveness of its products to other available therapies. If reimbursement of Ocuphire's drugs is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, its business could be harmed.

Ocuphire's relationships with healthcare providers and third-party payors will be subject to applicable fraud and abuse and other healthcare laws and regulations, which could expose Ocuphire to criminal sanctions, civil penalties, contractual damages, reputational harm, and diminished profits and future earnings, among other penalties and consequences.

Healthcare providers and third-party payors will play a primary role in the recommendation and prescription of any product candidate for which Ocuphire obtains marketing approval. Ocuphire's current and future arrangements with third-party payors and customers may expose Ocuphire to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which it markets, sells, and distributes product candidates for which it obtains marketing approval. Restrictions and obligations under applicable federal and state healthcare laws and regulations include the following:

- the federal Anti-Kickback Statute prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made under a federal healthcare program such as Medicare and Medicaid;
- the federal false claims and civil monetary penalties laws, including the civil False Claims Act, impose criminal and civil penalties, including civil whistleblower or qui tam actions, against individuals or entities for knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent or making a false statement to avoid, decrease, or conceal an obligation to pay money to the federal government;
- HIPAA imposes criminal and civil liability for, among other things, executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, and its implementing regulations, also imposes obligations, including mandatory contractual terms, on certain people and entities with respect to safeguarding the privacy, security, and transmission of individually identifiable health information;
- the federal Physician Payments Sunshine Act under the Affordable Care Act requires certain manufacturers of drugs, devices, biologics, and medical supplies for which payment is available under Medicare, Medicaid, or the Children's Health Insurance Program, with specific exceptions, to report specially to the Centers for Medicare & Medicaid Services within the U.S. Department of Health and Human Services information related to physician payments and other transfers of value and physician ownership and investment interests; and
- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers, and some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government, in addition to requiring drug manufacturers to report information related to payments to physicians and other healthcare providers or marketing expenditures. Certain state and foreign laws also govern the privacy and security of health information in ways that differ from each other and often are not preempted by HIPAA, thus complicating compliance efforts.

Efforts to ensure that Ocuphire's current and future business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that Ocuphire's business practices may not comply with current or future statutes, regulations, or case law involving applicable fraud and abuse or other healthcare laws and regulations. If Ocuphire's operations are found to be in violation of any of these laws or any other governmental regulations that may apply to it, it may be subject to significant civil, criminal, and administrative penalties, damages, fines, exclusion from government funded healthcare programs, such as Medicare and Medicaid, disgorgement, individual imprisonment, contractual damages, reputational harm, diminished profits and future earnings, and the curtailment or restructuring of its operations. If any of the physicians or other providers or entities with whom Ocuphire expects to do business are found to not be in compliance with applicable laws, they may be subject to criminal, civil, and administrative sanctions, including exclusions from government funded healthcare programs. Defending against any such actions can be costly, time-consuming, and may require significant financial and personnel resources. Therefore, even if Ocuphire is successful in defending against any such actions that may be brought against it, its business may be impaired.

Ocuphire is subject to U.S. and certain foreign export and import controls, sanctions, embargoes, anti-corruption laws, and anti-money laundering laws and regulations. Compliance with these legal standards could impair its ability to compete in domestic and international markets. Ocuphire could face criminal liability and other serious consequences for violations which could harm its business.

Ocuphire is subject to export control and import laws and regulations, including the U.S. Export Administration Regulations, U.S. Customs regulations, various economic and trade sanctions regulations administered by the U.S. Treasury Department's Office of Foreign Assets Controls, the U.S. Foreign Corrupt Practices Act of 1977, as amended, the U.S. domestic bribery statute contained in 18 U.S.C. § 201, the U.S. Travel Act, the USA PATRIOT Act, and other state and national anti-bribery and anti-money laundering laws in the countries in which Ocuphire conducts activities. Anti-corruption laws are interpreted broadly and prohibit companies and their employees, agents, contractors, and other partners from authorizing, promising, offering, or providing, directly or indirectly, improper payments or anything else of value to recipients in the public or private sector. Ocuphire may engage third parties for clinical trials outside of the United States, to sell its products abroad once it enters a commercialization phase, and/or to obtain necessary permits, licenses, patent registrations, and other regulatory approvals. Ocuphire has direct or indirect interactions with officials and employees of government agencies or government-affiliated hospitals, universities, and other organizations. Ocuphire can be held liable for the corrupt or other illegal activities of its employees, agents, contractors, and other partners, even if it does not explicitly authorize or have actual knowledge of such activities. Any violations of the laws and regulations described above may result in substantial civil and criminal fines and penalties, imprisonment, the loss of export or import privileges, debarment, tax reassessments, breach of contract and fraud litigation, reputational harm, and other consequences.

Ocuphire employees or representatives may engage in misconduct or other improper activities, including violating applicable regulatory standards and requirements or engaging in insider trading, which could significantly harm Ocuphire's business.

Ocuphire is exposed to the risk of employee fraud or other misconduct. Misconduct by employees could include intentional failures to:

- comply with the regulations of the FDA and applicable non-U.S. regulators;
- provide accurate information to the FDA and applicable non-U.S. regulators;
- comply with healthcare fraud and abuse laws and regulations in the United States and abroad;
- report financial information or data accurately; or
- disclose unauthorized activities to Ocuphire.

In particular, sales, marketing, and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing, and other abusive practices. These laws and regulations restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs, and other business arrangements. Employee misconduct could also involve the improper use of, including trading on, information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to Ocuphire's reputation. It is not always possible to identify and deter employee misconduct, and the precautions Ocuphire takes to detect and prevent this activity may be ineffective in controlling unknown or unmanaged risks or losses or in protecting it from governmental investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. If any such actions are instituted against Ocuphire, and Ocuphire is not successful in defending itself or asserting its rights, those actions could have a significant impact on its business, including the imposition of significant civil, criminal, and administrative penalties, damages, fines, exclusion from government funded healthcare programs such as Medicare and Medicaid, disgorgement, individual imprisonment, contractual damages, reputational harm, diminished profits and future earnings, and the curtailment or restructuring of its operations.

The FDA and other regulatory agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses. If found to have improperly promoted off-label uses, Ocuphire may become subject to significant liability.

The FDA and other regulatory agencies strictly regulate the promotional claims that may be made about prescription products. In particular, a product may not be promoted for uses that are not approved by the FDA or such other regulatory agencies as reflected in the product's approved labeling. If Ocuphire receives marketing approval for its product candidates for a certain indication, physicians may nevertheless prescribe such products to their patients in a manner that is inconsistent with the approved label. If Ocuphire is found to have promoted such off-label uses, it may become subject to significant liability. The federal government has levied large civil and criminal fines against companies for improper promotion and has enjoined several companies from engaging in off-label promotion. The FDA has also requested that companies enter into consent decrees or permanent injunctions under which specified promotional conduct is changed or curtailed. If Ocuphire cannot successfully manage the promotion of its product candidates, if approved, it could become subject to significant liability, which would adversely affect its business and financial condition.

Risks Related to Commercialization of Ocuphire's Product Candidates

Ocuphire faces substantial competition, which may result in others discovering, developing, or commercializing products before or more successfully than it does.

The development and commercialization of new drug products is highly competitive. Ocuphire expects to face competition with respect to its product candidates, if approved, and will face competition with respect to any future product candidates that it may seek to develop or commercialize from major pharmaceutical companies, specialty pharmaceutical companies, biotechnology companies, universities and other research institutions, and government agencies worldwide. The ophthalmic therapies market is highly competitive and dynamic. Ocuphire's success will depend, in part, on its ability to obtain a share of the market for its planned indications.

Nyxol

Ocuphire is developing Nyxol for use in three different indications: the reversal of pharmacologically induced mydriasis ("RM"), the treatment of presbyopia and the treatment of NVD. In addition to currently approved therapies, any product that is developed for any of the three indications could compete with Nyxol. Such a product could reduce the overall market opportunity for Nyxol. Other pharmaceutical companies may develop therapies for the same indications that would compete with Nyxol, if approved, and that would not infringe the claims of Ocuphire's patents, pending patent applications, or other proprietary rights, which could adversely affect its business and results of operations.

RM

Currently, there are no available and approved pharmacological therapies for NVD or RM and Ocuphire is not aware of any in development. Rev-Eyes® (dapiprazole), an alpha-1 antagonist, was approved by the FDA in 1990 to reverse mydriasis induced by adrenergic or anticholinergic agents. Rev-Eyes was withdrawn in the past from the market for reasons unrelated to safety or efficacy, according to the FDA.

Presbyopia

The FDA approved Vuity™ eye drop for the treatment of presbyopia in October 2021. Vuity was launched in December 2021 and is marketed by Allergan, an AbbVie company. The competition also includes reading glasses, multifocal contact lenses, and monovision contact lenses (e.g., where one eye wears a near vision lens and the other eye wears a distance vision lens). Ocuphire will also compete against several pharmacological therapies in development for the temporary treatment of presbyopia, many of which are cholinergic agonist-based pupil management therapies, including:

- CSF-1, with low dose pilocarpine and a secondary agent (lubricant), developed by Orasis Pharmaceuticals Ltd.
- LNZ100 and LNZ101, with aceclidine (another miotic agent), developed by Lenz Therapeutics.
- MicroLine®, which is a micro-dose delivery of pilocarpine using proprietary device developed by Eyenovia, Inc.
- KT-101, which uses pilocarpine in the AcuStream delivery system, developed by Kedalion Therapeutics, Inc.
- Brimochol™, with brimonidine and carbachol (both are miotic agents), developed by Visus Therapeutics, Inc.
- UNR844, which uses a mechanism that involves softening the lens to increase near visual acuity, developed by Novartis AG (originally Encore Vision, Inc.).

There are approved devices for presbyopia. One of these is the KAMRA Inlay, developed by AcuFocus, Inc. and marketed by SightLife Surgical, Inc. Another is the Eyelike NoanPinhole, developed by Koryo Eyetech, the first commercially available pinhole soft contact lens. Nyxol would not directly compete against these devices, but rather would be a non-invasive alternative for presbyopes who are averse to surgical intervention.

APX3330

Ocuphire is developing APX3330 for use in two different indications initially: the treatment of DR and DME, and potentially later the treatment of wAMD. In addition to currently approved therapies, any product that is developed for either of the three indications could directly compete directly with APX3330. Such a product could reduce the overall market opportunity for APX3330. Other pharmaceutical companies may develop therapies for the same indications that would compete with APX3330, if approved, and that would not infringe the claims of Ocuphire's in-licensed patents, pending patent applications, or other proprietary rights, which could adversely affect its business and results of operations.

Competition in Diabetic Retinopathy / Diabetic Macular Edema / wAMD

Ocuphire may face potential competition from both existing therapies and those in development. Current therapies for these retinal diseases rely on suppressing VEGF activity via intravitreal injection or by mitigating the inflammation via intravitreal corticosteroid-releasing implants including:

- Lucentis® (ranibizumab) and Avastin® (bevacizumab), which are anti-VEGF monoclonal antibody intravitreal injections, developed by Genentech, Inc and Roche AG.
- EYLEA® (aflibercept), a VEGF inhibitor intravitreal injection, developed by Regeneron Pharmaceuticals.
- Vabysmo® (Faricimab), a bispecific monoclonal antibody targeting VEGF-A and Ang-Tie2 pathway developed by Genentech, Inc and Roche AG.
- Beovu® (Brolucizumab), an anti-VEGF monoclonal antibody intravitreal injection, developed by Novartis AG.

- MACUGEN® (pegaptanib sodium injection), a selective inhibitor of VEGF-165, developed by Bausch + Lomb.
- Ozurdex® (dexamethasone), a corticosteroid IVT implant, developed by Allergan plc.
- Iluvien (fluocinolone acetonide), a corticosteroid IVT implant, developed by Alimera Sciences, Inc

There are also several pharmacological therapies in development, including:

- Abicipar, an anti-VEGF intravitreal injection with a long duration of action, developed by Allergan plc and Molecular Partners.
- KSI-301, an anti-VEGF antibody intravitreal injection coupled with a biopolymer that is intended to increase the time between injections, developed by Kodiak Sciences.
- OPT-302, an intravitreal injection which binds to multiple types of VEGF receptors that could be used with other anti-VEGF agents, developed by Opthea Limited.
- ALG-1001, an integrin peptide therapy intravitreal injection that is being evaluated as a sequential or in-combination therapy with bevacizumab in patients with DME, developed by Allegro Ophthalmics, LLC.
- RG-7774, an orally administered selective CB2 (Cannabinoid 2) receptor agonist that is being evaluated in patients with moderately severe to severe non-proliferative diabetic retinopathy, developed by Hoffmann-LA Roche, AG.
- RZ402, a small molecule selective and potent plasma kallikrein inhibitor (PKI) for the chronic treatment of diabetic macular edema (DME), developed by Rezolute, Inc.
- Xiflam™, an oral small molecule drug for the treatment of dry form of Age-Related Macular Degeneration (AMD), Geographic Atrophy (GA), Diabetic Retinopathy (DR) manifesting Diabetic Macular Edema (DME), developed by InflammX.
- AKST4290, an oral small molecule CCR3 Eotaxin inhibitor for the treatment of diabetic retinopathy and wet AMD.
- BAY1101042, an oral guanylate cycles activator for the treatment of diabetic retinopathy.

Ocuphire's competitors may develop products that are more effective, safer, more convenient, or less costly than any that it is developing, or that would render its product candidates obsolete or non-competitive. Ocuphire's competitors may also render its technologies obsolete by advances in existing technological approaches or the development of new or different approaches, potentially eliminating the advantages in Ocuphire's drug discovery process. Ocuphire's competitors may also obtain marketing approval from the FDA or other regulatory authorities for its products more rapidly than Ocuphire obtains approval for its products, which could result in Ocuphire's competitors establishing a strong market position before Ocuphire is able to enter the market.

Many of Ocuphire's competitors have significantly greater name recognition, financial resources, and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals, and marketing approved products than Ocuphire does. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of Ocuphire's competitors. Smaller and other early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These companies compete with Ocuphire in recruiting, hiring, and retaining qualified scientific and management personnel, engaging contract service providers, manufacturers and consultants, establishing clinical trial sites, recruiting patients for clinical trials, and entering into strategic transactions, as well as in acquiring technologies complementary to, or necessary for, Ocuphire's programs.

Ocuphire lacks experience in commercializing products, which may have an adverse effect on its business.

If its product candidates receive marketing approval, Ocuphire will need to transition from a company with a development focus to a company capable of supporting commercial activities, and it may not be successful in making that transition. Ocuphire has never filed an NDA and has not yet demonstrated the ability to obtain marketing approval for, or to commercialize, any product candidate. As a result, its clinical development and regulatory approval activities, and its ability to successfully commercialize any approved products, may involve more inherent risk, take longer, and cost more than would be the case if it were a company with experience obtaining marketing approval for and commercializing a product candidate.

If Ocuphire is unable to establish sales and marketing capabilities or enter into agreements with third parties to sell, market, and distribute its product candidates, if approved, it may not be successful in commercializing such product candidates if and when they are approved.

Ocuphire does not have any sales or marketing infrastructure and has no capabilities in place at the present time for the sale, marketing, or distribution of pharmaceutical products. To achieve commercial success for any approved product for which it retains sales and marketing responsibilities, Ocuphire must either develop a sales and marketing organization or outsource part or all of these functions to other third parties.

There are risks involved with Ocuphire both establishing its own sales and marketing capabilities and entering into arrangements with third parties to perform these services. For example, recruiting and training a sales force is expensive and time-consuming, which could delay any product launch. If the commercial launch of a product candidate for which Ocuphire recruits a sales force and establish marketing capabilities is delayed or does not occur for any reason, it would have prematurely or unnecessarily incurred these commercialization expenses. This may be costly, and Ocuphire's investment would be lost if it cannot retain or reposition its sales and marketing personnel.

Factors that may inhibit Ocuphire's efforts to commercialize its product candidates on its own include:

- the inability to recruit and retain adequate numbers of effective sales and marketing personnel or enter into distribution agreements with third parties;
- the inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe its product candidate;
- the lack of complementary products to be offered by sales personnel, which may put Ocuphire at a competitive disadvantage relative to companies with more extensive product lines;
- unforeseen costs and expenses associated with creating an independent sales and marketing organization; and
- the inability to obtain sufficient coverage and reimbursement from third-party payors and governmental agencies.
- If it enters into arrangements with third parties to perform sales, marketing, and distribution services, Ocuphire's product revenues or the profitability of these product revenues to it are likely to be lower than if it were to market and sell a product that Ocuphire developed itself. In addition, Ocuphire may not be successful in entering into arrangements with third parties to sell and market any product candidate or may be unable to do so on terms that are favorable to it. Ocuphire likely will have little control over such third parties, and any of them may fail to devote the necessary resources and attention to sell and market a drug effectively. If Ocuphire does not establish sales and marketing capabilities successfully, either on its own or in collaboration with third parties, it will not be successful in commercializing its product candidates.

Ocuphire's future commercial success depends upon attaining significant market acceptance of its product candidates, if approved, among physicians, patients, third-party payors, and others in the medical community.

Even if Ocuphire's product candidates receive marketing approval, they may nonetheless fail to gain sufficient market acceptance by physicians, patients, healthcare payors, or others in the medical community. If such product candidates do not achieve an adequate level of acceptance, Ocuphire may not generate significant product revenues and may not become profitable. The degree of market acceptance of a product candidate, if approved for commercial sale, will depend on a number of factors, including:

- efficacy and potential advantages compared to alternative treatments;
- the ability to offer Ocuphire's product for sale at competitive prices;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- any restrictions on the use of Ocuphire's product together with other medications;
- interactions of its product with other medicines patients are taking;
- inability of certain types of patients to take Ocuphire's product;
- demonstrated ability to treat patients and, if required by any applicable regulatory authority in connection with the approval for target indications as compared with other available therapies;
- the relative convenience and ease of administration as compared with other treatments available for approved indications;
- the prevalence and severity of any adverse side effects;
- limitations or warnings contained in the labeling approved by the FDA;
- availability of alternative treatments already approved or expected to be commercially launched in the near future;
- the effectiveness of Ocuphire's sales and marketing strategies;
- Ocuphire's ability to increase awareness through marketing efforts;
- guidelines and recommendations of organizations involved in research, treatment and prevention of various diseases that may advocate for alternative therapies;
- Ocuphire's ability to obtain sufficient third-party coverage and adequate reimbursement;
- the willingness of patients to pay out-of-pocket in the absence of third-party coverage; and
- physicians or patients may be reluctant to switch from existing therapies even if potentially more effective, safe or convenient.

Ocuphire has not yet sold any of its products. Ocuphire cannot assure investors that there is a sufficient market demand for its products. Achieving market acceptance for its products will require substantial marketing efforts and expenditure of funds to create awareness and demand by participants in the industry. Ocuphire has not conducted any independent market research to determine the extent of any demand that exists for the products to be provided by it and there is no guarantee that a sufficient interest in the market will exist for the products and services being produced by, or for, it. Any lack of sufficient demand for the products contemplated to be provided by Ocuphire will have a material adverse effect on it.

If the FDA or a comparable foreign regulatory authority approves generic versions of Ocuphire's product candidates that receive marketing approval, or if such authorities do not grant Ocuphire's product candidates appropriate periods of exclusivity before approving generic versions of Ocuphire's products, the sales of Ocuphire's products could be adversely affected.

Once an NDA is approved, the product covered thereby becomes a "reference listed drug" in the FDA's publication, "Approved Drug Products with Therapeutic Equivalence Evaluations." Manufacturers may seek approval of generic versions of reference listed drugs through submission of abbreviated new drug applications ("ANDAs") in the United States. In support of an ANDA, a generic manufacturer need not conduct clinical studies. Rather, the applicant generally must show that its product has the same active ingredient(s), dosage form, strength, route of administration, and conditions of use or labeling as the reference listed drug ("RLD") and that the generic version is bioequivalent to the RLD, meaning it is absorbed in the body at the same rate and to the same extent. Generic products may be significantly less costly to bring to market than the RLD, and companies that produce generic products are generally able to offer them at lower prices. Thus, following the introduction of a generic drug, a significant percentage of the sales of any branded product or RLD may be lost to the generic product.

The FDA may not approve an ANDA for a generic product until any applicable period of non-patent exclusivity for the reference listed drug has expired. The FDC Act provides a period of five years of non-patent exclusivity for a new drug containing a new chemical entity ("NCE"). Specifically, in cases where such exclusivity has been granted, an ANDA may not be filed with the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification that a patent covering the reference listed drug is either invalid or will not be infringed by the generic product, in which case the applicant may submit its application four years after approval of the RLD. It is unclear whether the FDA will treat the active ingredients in its product candidates as NCEs and, therefore, afford them five years of NCE exclusivity if they are approved. If any product Ocuphire develops does not receive five years of NCE exclusivity, it may nonetheless be eligible for three years of exclusivity, which means that the FDA may approve generic versions of such product three years after its date of approval. Manufacturers may seek to launch these generic products following the expiration of the applicable marketing exclusivity period, even if Ocuphire still has patent protection for its product.

Competition that Ocuphire's product candidates would face from generic versions could materially and adversely impact its future revenue, profitability, and cash flows and substantially limit its ability to obtain a return on the investments it has made in any such product candidate.

Even if Ocuphire is able to commercialize its product candidates, their profitability will likely depend in significant part on third-party reimbursement practices, which, if unfavorable, would harm its business.

Ocuphire's ability to commercialize a drug successfully will depend in part on the extent to which coverage and adequate reimbursement will be available from government health administration authorities, private health insurers and other organizations. Government authorities and third-party payors, such as private health insurers and health maintenance organizations, decide which medications they will pay for and establish reimbursement levels. Government authorities and third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for certain medications. Increasingly, third-party payors are requiring that drug companies provide them with predetermined discounts from list prices and are challenging the prices charged for medical products. Ocuphire cannot be sure that coverage will be available for any product candidate that Ocuphire commercializes and, if coverage is available, whether the level of reimbursement will be adequate. Assuming Ocuphire obtains coverage for its product candidates, if approved, by a third-party payor, the resulting reimbursement payment rates may not be adequate or may require co-payments that patients find unacceptably high. Patients who are prescribed medications for the treatment of their conditions, and their prescribing physicians, generally rely on third-party payors to reimburse all or some of the costs associated with their prescription drugs. Patients are unlikely to use a product candidate, if approved, unless coverage is provided and reimbursement is adequate to cover all or a significant portion of the cost of its products. Therefore, coverage and adequate reimbursement are critical to new product acceptance. If reimbursement is not available or is available only to limited levels, Ocuphire may not be able to successfully commercialize any product candidate for which it obtains marketing approval. Furthermore, drug pricing and access policies in the United States and internationally may change and negatively impact our product candidates' commercial viability. Proposed policy changes, including the potential for Medicare to negotiate with drug manufacturers, may limit our ability to competitively price our product candidates, if approved.

There may be significant delays in obtaining reimbursement for newly approved drugs, and coverage may be more limited than the purposes for which a product candidate is approved by the FDA or similar regulatory authorities outside the United States. Moreover, eligibility for reimbursement does not imply that any product will be paid for in all cases or at a rate that covers Ocuphire's costs, including research, development, manufacture, sale, and distribution. Interim reimbursement levels for a new product, if applicable, may also not be sufficient to cover Ocuphire's costs and may not be made permanent. Reimbursement rates may vary according to the use of the product and the clinical setting in which it is used, may be based on reimbursement levels already set for lower cost medicines, and may be incorporated into existing payments for other services. Net prices for products may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future relaxation of laws that presently restrict imports of medicines from countries where they may be sold at lower prices than in the United States. Third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement policies. However, there is no uniform policy requirement for coverage and reimbursement for drug products among third-party payors in the United States. Therefore, coverage and reimbursement for drug products can differ significantly from payor to payor. As a result, the coverage determination process is often time-consuming and costly, and it will require Ocuphire to provide scientific and clinical support for the use of its products to each payor separately. There is no assurance that coverage and adequate reimbursement will be applied consistently or obtained in the first instance.

Any inability to promptly obtain coverage and profitable payment rates from government-funded or private payors for any approved products that Ocuphire develops could have an adverse effect on its operating results, its ability to raise capital needed to commercialize products, and its overall financial condition.

Product liability lawsuits against Ocuphire, or its suppliers and manufacturers, could cause it to incur substantial liabilities and could limit commercialization of any product candidate that it may develop.

Ocuphire faces an inherent risk of product liability exposure related to the testing of its product candidates in human clinical trials and will face an even greater risk if it commercially sells any products that it may develop. Product liability claims might be brought against Ocuphire by patients, healthcare providers, or others selling or otherwise coming into contact with its product candidates during product testing, manufacturing, marketing, or sale. For example, Ocuphire may be sued under allegations that a product candidate caused injury or that the product was otherwise unsuitable. Any such product liability claims may include allegations of manufacturing or design defects, failure to warn of dangers inherent in the product, such as interactions with alcohol or other drugs, negligence, or breach of warranty. Claims could also be asserted under state consumer protection acts. If Ocuphire cannot successfully defend itself against claims that its product candidate caused injuries, it could incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

- decreased demand for any product candidate that Ocuphire is developing;
- injury to Ocuphire's reputation and significant negative media attention;
- withdrawal of clinical trial participants;
- increased FDA warnings on product labels;
- significant costs to defend the related litigation;
- substantial monetary awards to trial participants or patients;

- distraction of management’s attention from Ocuphire’s primary business;
- loss of revenue; and
- the inability to commercialize any product candidate that Ocuphire may develop.

Its product liability and/or clinical trial insurance coverage may not be adequate to cover all liabilities that Ocuphire may incur. Ocuphire may need to increase its insurance coverage as it expands clinical trials and if it successfully commercializes its product candidates. Insurance coverage is increasingly expensive, and it may not be able to obtain product liability insurance on commercially reasonable terms or for a sufficient amount to satisfy liabilities that may arise.

Similarly, Ocuphire may be a party to, or may be otherwise responsible for, pending or threatened lawsuits or other claims related to products purchased from its manufacturers and suppliers. Although Ocuphire intends to require its providers to have product liability insurance, the ability to obtain such coverage and the sufficiency thereof is uncertain. Such cases and claims may raise difficult and complex factual and legal issues and may be subject to many uncertainties and complexities, including, but not limited to, the facts and circumstances of each particular case or claim, the jurisdiction in which each suit is brought, and differences in applicable law. Such litigation could result in additional expense and exposure in excess of Ocuphire’s anticipated reserves, especially if such matters are not covered by insurance. Upon resolution of any pending legal matters or other claims, Ocuphire may incur charges in excess of established reserves. Product liability lawsuits and claims, safety alerts or product recalls in the future, regardless of their ultimate outcome, could have a material adverse effect on the business and reputation and on Ocuphire’s ability to attract and retain customers and strategic partners. The business, profitability and growth prospects could suffer if Ocuphire faces such negative publicity.

If Ocuphire or its third-party manufacturers fail to comply with environmental or health and safety laws and regulations, Ocuphire could become subject to fines or penalties or incur costs that could have an adverse effect on the success of its business.

Ocuphire’s research and development activities involve the controlled use of potentially hazardous substances, including chemical and biological materials, by itself and its third-party manufacturers. Ocuphire’s manufacturers are subject to federal, state, and local laws and regulations in the United States and abroad governing laboratory procedures and the use, manufacture, storage, handling, and disposal of medical and hazardous materials. Although Ocuphire believes that its manufacturers’ procedures for using, handling, storing, and disposing of these materials comply with legally prescribed standards, it cannot eliminate the risk of contamination or injury resulting from medical or hazardous materials. As a result of any such contamination or injury, Ocuphire may incur liability, or federal, state, city, or local authorities may curtail its use of these materials and interrupt its business operations. In the event of an accident, Ocuphire could be held liable for damages or fined, and such liability or fines could exceed its resources. Ocuphire does not have insurance for liabilities arising from medical or hazardous materials. Although Ocuphire maintains workers’ compensation insurance for costs and expenses that it may incur due to injuries to its employees resulting from the use of hazardous materials, this insurance may not provide adequate coverage against potential liabilities. Compliance with applicable environmental and health and safety laws and regulations is expensive, and current or future environmental regulations may impair Ocuphire’s research, development, and production efforts, which could harm its business, prospects, financial condition, or results of operations.

Federal legislation and actions by state and local governments could permit reimportation of drugs from foreign countries into the United States, which could adversely affect Ocuphire’s operating results when the drugs are sold at lower prices in foreign countries than in the United States.

Ocuphire may face competition for its product candidates, if approved, from other therapies sourced from foreign countries that have price controls on pharmaceutical products. The Medicare Modernization Act contains provisions that may change U.S. reimportation laws and expand pharmacists’ and wholesalers’ ability to import cheaper versions of approved drugs or competing products from Canada, where there are government price controls. These changes to U.S. importation laws would not take effect unless and until the Secretary of Health and Human Services certifies that the changes would pose no additional risk to the public’s health and safety and would result in a significant reduction in the cost of products to consumers. The Secretary of Health and Human Services has so far declined to approve a reimportation plan. Proponents of drug reimportation may attempt to pass legislation that would directly allow reimportation under certain circumstances. Legislation or regulations allowing the reimportation of drugs, if enacted, could decrease the price Ocuphire receives for any product it may develop and adversely affect its future revenues and prospects for profitability.

Risks Related to Ocuphire's Reliance on Third Parties

Ocuphire will be unable to control all aspects of its non-clinical studies and its clinical trials due to its reliance on CROs and other third parties that assist Ocuphire in conducting non-clinical studies and clinical trials.

Ocuphire relies on third-party CROs and other third parties to assist in managing, monitoring, and otherwise carrying out its non-clinical studies and clinical trials. Ocuphire expects to continue to rely on third parties, such as CROs, clinical data management organizations, medical institutions, and clinical investigators, to conduct its non-clinical studies and clinical trials in the future, including its Phase 3 development program for Nyxol. Ocuphire competes with many other companies for the resources of these third parties.

As a result, Ocuphire will have limited control over the conduct, timing, and completion of these non-clinical studies and clinical trials and the management of data developed through the non-clinical studies and clinical trials. Ocuphire has experienced in the past, and may experience in the future, schedule disruptions due to events affecting the performance of third parties on which it relies. Communicating with outside parties can also be challenging, potentially leading to mistakes as well as difficulties in coordinating activities. Additionally, the ongoing COVID-19 pandemic may affect the ability of third parties to fulfill their obligations to Ocuphire. Outside parties may:

- have staffing difficulties;
- fail to comply with contractual obligations;
- experience regulatory compliance issues;
- undergo changes in ownership or management;
- undergo changes in priorities or become financially distressed; or
- form relationships with other entities, some of which may be Ocuphire's competitors.

These factors may adversely affect the willingness or ability of third parties to conduct Ocuphire's clinical trials and may subject Ocuphire to unexpected cost increases that are beyond its control.

While Ocuphire's reliance on these third parties for research and development activities will reduce its control over these activities, it will not relieve Ocuphire of its responsibilities and requirements. For example, the FDA requires Ocuphire to comply with standards, commonly referred to as good clinical practices ("GCP"), for conducting, recording, and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity, and confidentiality of clinical trial participants are protected.

Problems with the timeliness or quality of the work of any CRO may lead Ocuphire to seek to terminate its relationship with any such CRO and use an alternative service provider. Making this change may be costly or delay Ocuphire's clinical trials, and contractual restrictions may make such a change difficult or impossible. If Ocuphire must replace any CRO that is conducting its clinical trials, its clinical trials may have to be suspended until it finds another CRO that offers comparable services. The time that it would take Ocuphire to find alternative organizations may cause a delay in the commercialization of its product candidates, or it may cause it to incur significant expenses to replicate any lost data. Although Ocuphire does not believe that any CRO on which it would rely would offer services that are not available elsewhere, it may be difficult to find a replacement organization that can conduct Ocuphire's clinical trials in an acceptable manner and at an acceptable cost. Any delay in or inability to complete Ocuphire's clinical trials could significantly compromise its ability to secure regulatory approval for its product candidates and preclude its ability to commercialize its product candidates, thereby limiting or preventing its ability to generate sales revenue.

Ocuphire relies completely on third parties to supply and manufacture bulk drug substances and to formulate and package preclinical and clinical drug supplies of its product candidates as well as to conduct analytical testing of drug substances and products in the manufacturing processes, and intends to rely on third parties to produce and test commercial supplies of its current and any future product candidates.

Ocuphire does not currently have, nor does it plan to acquire, the infrastructure or capability to internally manufacture its clinical drug supply of product candidates for use in the conduct of its preclinical studies and clinical trials. Ocuphire lacks the internal resources and the capability to manufacture any product candidates on a clinical or commercial scale. The process of manufacturing drug products is complex, highly regulated, and subject to several risks. For example, the facilities used by Ocuphire's contract manufacturers to manufacture and conduct analytical testing of the active pharmaceutical ingredient (or drug substance) and final drug product for product candidates must be inspected by the FDA and other comparable foreign regulatory agencies in connection with Ocuphire's submission of an NDA or relevant foreign regulatory submission to the applicable regulatory agency. In addition, the manufacturing of drug substance or product is susceptible to product loss due to contamination, equipment failure, improper installation or operation of equipment, or vendor or operator error. Moreover, the manufacturing facilities in which product candidates are made could be adversely affected by equipment failures, labor shortages, natural disasters, power failures, or other factors. Manufacturing timelines may be negatively affected by material shortages, construction delays and supply chain challenges due to, among other factors, global supply chain shortages due to COVID-19 or other reasons.

Ocuphire does not control the manufacturing and testing processes of its contract manufacturers and analytical labs, and is completely dependent on them to comply with current good manufacturing practices ("cGMP") for manufacture and good lab practices ("GLP") of both active drug substances and finished drug products. If Ocuphire's contract manufacturers and analytical labs cannot successfully manufacture and test materials that conform to its specifications and the strict regulatory requirements of the FDA or applicable foreign regulatory agencies, Ocuphire will not be able to secure and/or maintain regulatory approval for its products. In addition, Ocuphire has no control over its contract manufacturers' and analytical labs' ability to maintain adequate quality control, quality assurance, and qualified personnel. Failure to satisfy the regulatory requirements for the production and testing of those materials and products may affect the regulatory clearance of Ocuphire's contract manufacturers' and analytical labs' facilities generally. If the FDA or a comparable foreign regulatory agency does not approve these facilities for the manufacture and testing of product candidates, or if it withdraws its approval in the future, Ocuphire may need to find alternative manufacturing and testing facilities, which would adversely impact Ocuphire's ability to develop, obtain regulatory approval for, or market product candidates. Furthermore, all of Ocuphire's contract manufacturers and analytical labs are engaged with other companies to supply and/or manufacture and/or test materials or products for such companies, which exposes its manufacturers to regulatory and sourcing risks for the production of such materials and products. To the extent practicable, Ocuphire attempts to identify more than one supplier. However, some raw materials are available only from a single source or only one supplier has been identified, even in instances where multiple sources exist.

Ocuphire has relied and will rely upon third-party manufacturers and testing labs in the United States and overseas for the manufacture and testing of Nyxol and APX3330 for preclinical and clinical testing purposes and intends to continue to do so in the future for Nyxol, APX3330, Nyxol with adjunctive low-dose pilocarpine, and any other product candidates, including for commercial purposes. If Ocuphire's third-party manufacturers and analytical labs are unable to supply or test drug substance and/or drug product on a commercial basis, Ocuphire may not be able to successfully produce and market product candidates, if approved, or it could be delayed in doing so. For instance, Ocuphire presently relies on one supplier in Italy for the drug substance for Nyxol, and one manufacturer in India for APX3330 drug substance. If there is any delay or problem with the manufacture of these drug substance or if there is a delay in producing finished drug product from these drug substances, the development and possible approval of Ocuphire's product candidates and potential commercial launch may be delayed or otherwise adversely affected. Ocuphire will rely on comparison of product specifications (identity, strength, quality, and potency) to demonstrate equivalence of the current drug substance and/or drug product to the drug substance and/or drug product used in previously completed preclinical and clinical testing. If Ocuphire is unable to demonstrate such equivalence, it may be required to conduct additional preclinical and/or clinical testing of its product candidates. The formulation of the low-dose pilocarpine as adjunctive product candidate with Nyxol is still in development. Also, due to the current COVID-19 pandemic, disruptions of global supply chains are more likely to occur, which could delay the clinical development of Ocuphire's product candidates. Ocuphire has already experienced a few interruptions in its manufacturing, supply chain, research and development operations, regulatory and financial position, including, for example, the acceleration of the shipment of active pharmaceutical ingredient supply from overseas.

Due to these and other potential problems, Ocuphire is exploring the possibility of establishing additional sources of supply, with U.S. manufacturers, for the active pharmaceutical ingredients of both Nyxol and APX3330. Establishing these additional sources, including qualifying their manufacturing processes and demonstrating the equivalence of their products, may be costly, time-consuming, and difficult to effectuate, and may delay Ocuphire's research and development activities. If Ocuphire must replace any manufacturer, its research and development activities may have to be suspended until it finds another manufacturer that offers comparable services. The time that it takes Ocuphire to find alternative organizations may cause a delay in the development and commercialization of product candidates.

Ocuphire may form or seek strategic alliances or enter into licensing arrangements in the future, and may not realize benefits from such alliances or licensing arrangements.

Ocuphire may form or seek strategic alliances, create joint ventures or collaborations or enter into additional licensing arrangements with third parties that it believes will complement or augment its development and commercialization efforts with respect to product candidates. Any of these relationships may require Ocuphire to incur non-recurring and other charges, increase its near- and long-term expenditures, or issue securities that dilute Ocuphire's existing stockholders, which may disrupt its management and business. Ocuphire's likely collaborators include large, mid-size, regional, or national pharmaceutical companies and biotechnology companies. If Ocuphire enters into any such arrangements with any third parties, it will likely have limited control over the amount and timing of resources that its collaborators dedicate to the development or commercialization of product candidates. Ocuphire's ability to generate revenues from these arrangements will depend on its collaborators' abilities to successfully perform the functions assigned to them in these arrangements. Ocuphire cannot be certain that, following a strategic transaction or license, it will achieve the revenue or specific net income that justifies such transaction. Collaborations involving product candidates pose the following risks to Ocuphire:

- collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations;
- collaborators may not perform their obligations as expected;
- collaborators may not pursue development and commercialization or may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in the collaborator's strategic focus or available funding, or external factors such as an acquisition that diverts resources or creates competing priorities;
- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials, or require a new formulation of a product candidate for clinical testing;
- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with its product candidate if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more attractive than Ocuphire's;
- a collaborator with marketing and distribution rights to one or more product candidates may not commit sufficient resources to the marketing or distribution of any such product candidate;
- collaborators may not properly maintain or defend Ocuphire's intellectual property rights or may use its proprietary information in such a way as to invite litigation that could jeopardize or invalidate Ocuphire's proprietary information or expose Ocuphire to litigation;

- collaborators may infringe the intellectual property rights of third parties, which may expose Ocuphire to litigation and potential liability;
- disputes may arise between the Ocuphire and collaborators that result in the delay or termination of research, development, or commercialization of its product candidates, or in litigation or arbitration that diverts management attention and resources;
- Ocuphire may lose certain valuable rights under circumstances identified in its collaborations, including if it undergoes a change of control;
- collaborations may be terminated and such terminations may create a need for additional capital to pursue further development or commercialization of the applicable product candidates;
- collaborators may learn about Ocuphire's discoveries and use this knowledge to compete with Ocuphire in the future;
- the results of collaborators' preclinical or clinical studies could harm or impair other development programs;
- there may be conflicts between different collaborators that could negatively affect those collaborations and potentially others;
- the number and nature of Ocuphire's collaborations could adversely affect its attractiveness to potential future collaborators or acquirers;
- collaboration agreements may not lead to development or commercialization of its product candidate in the most efficient manner or at all. If a present or future collaborator of Ocuphire were to be involved in a business combination, the continued pursuit and emphasis on its product development or commercialization program under such collaboration could be delayed, diminished, or terminated; and
- collaborators may be unable to obtain the necessary marketing approvals.

If future collaboration partners fail to develop or effectively commercialize product candidates for any of these reasons, such product candidates may not be approved for sale and Ocuphire's sales of such product candidates, if approved, may be limited, which would have an adverse effect on Ocuphire's operating results and financial condition.

If Ocuphire is not able to establish new collaborations on commercially reasonable terms, it may have to alter its development, manufacturing, and commercialization plans.

Ocuphire faces significant competition in attracting collaborators for development, manufacturing or commercialization plans. Whether it reaches a definitive agreement for collaboration will depend, among other things, upon its assessment of the proposed collaborator's resources, expertise, and evaluation of a number of factors related to the associated product candidate, as well as the terms and conditions of the proposed collaboration. Those factors may include the design or results of clinical trials, the likelihood of approval by the FDA or similar regulatory authorities outside the United States, the potential market for the product candidate, the costs and complexities of manufacturing and delivering such product candidate to patients, the potential of competing products, the existence of uncertainty with respect to Ocuphire's ownership of technology, which may exist if there is a challenge to such ownership without regard to the merits of the challenge, and industry and market conditions generally. The collaborator may also consider alternative product candidates or technologies for similar indications that may be available for collaborations and whether such a collaboration could be more attractive than one with Ocuphire. Ocuphire may not be able to enter into these agreements on commercially reasonable terms, or at all.

Much of the potential revenue from future commercial collaborations may consist of contingent payments, such as payments for achieving regulatory milestones or royalties payable on sales of Ocuphire's product candidate, if approved. The milestone and royalty revenue that Ocuphire may receive under these collaborations would depend upon its collaborators' ability to successfully develop, introduce, market and sell its product candidate, if approved. In addition, collaborators may decide to enter into arrangements with third parties to commercialize products developed under collaborations related to its product candidate, which could reduce the milestone and royalty revenue received, if any.

Ocuphire may also be restricted under existing collaboration agreements from entering into future agreements on certain terms with potential collaborators. Collaborations are complex and time-consuming to negotiate and document. In addition, there have been a significant number of recent business combinations among large pharmaceutical companies that have resulted in a reduced number of potential future collaborators.

Ocuphire may not be able to negotiate collaborations on a timely basis and on acceptable terms, or at all. If Ocuphire is unable to do so, it may have to curtail the development of the product candidate for which it is seeking to collaborate, reduce or delay its development program or that of one or more of its other development programs, delay its potential commercialization or reduce the scope of any sales or marketing activities, or increase its expenditures and undertake development or commercialization activities at its own expense. If Ocuphire elects to increase its expenditures to fund development or commercialization activities on its own, it may need to obtain additional capital, which may not be available to Ocuphire on acceptable terms or at all. If Ocuphire does not have sufficient funds, it may not be able to further develop its product candidate or bring it to market and generate product revenue.

If Ocuphire engages in acquisitions, in-licensing or strategic partnerships, this may increase its capital requirements, dilute its stockholders, cause it to incur debt or assume contingent liabilities and subject it to other risks.

Ocuphire may engage in various acquisitions and strategic partnerships, including licensing or acquiring complementary products, intellectual property rights, technologies, or businesses. Any acquisition or strategic partnership may entail numerous risks, including:

- increased operating expenses and cash requirements;
- the assumption of indebtedness or contingent liabilities;
- the issuance of Ocuphire's equity securities which would result in dilution to Ocuphire stockholders;
- assimilation of operations, intellectual property, products and product candidates of an acquired company, including difficulties associated with integrating new personnel;
- the diversion of management's attention from Ocuphire's existing product candidates and initiatives in pursuing such an acquisition or strategic partnership;
- retention of key employees, the loss of key personnel, and uncertainties in Ocuphire's ability to maintain key business relationships;
- risks and uncertainties associated with the other party to such a transaction, including the prospects of that party and their existing products or product candidates and regulatory approvals; and
- Ocuphire's inability to generate revenue from acquired intellectual property, technology and/or products sufficient to meet its objectives or even to offset the associated transaction and maintenance costs.

In addition, if Ocuphire undertakes such a transaction, it may incur large one-time expenses and acquire intangible assets that could result in significant future amortization expense.

Risks Related to Ocuphire's Intellectual Property

If Ocuphire is unable to obtain and maintain sufficient patent protection for its product candidates, its competitors could develop and commercialize products or technology similar or identical to those of Ocuphire, which would adversely affect Ocuphire's ability to successfully commercialize any product candidates it may develop, its business, results of operations, financial condition and prospects.

Ocuphire primarily protects its intellectual property through a combination of patents and patent applications on inventions, trademark protection on its product name, and trade secret protection as it deems appropriate.

As of March 1, 2022, Ocuphire's patent estate relating to the Nyxol product candidate contains eight U.S. patents, five pending U.S. non-provisional patent applications, two pending U.S. provisional patent applications, as well as issued patents in Australia, Canada, Europe, Japan, and Mexico and pending patent applications in Australia, Canada, Europe, Japan, China, and other foreign countries, all of which are owned by Ocuphire.

Ocuphire's U.S. Patents 9,795,560; 10,278,918; 10,772,829 and 11,090,261 and counterpart Australian, Canadian, European, and Japanese patents each contain composition of matter claims to aqueous phentolamine mesylate formulations and are scheduled to expire in year 2034. In the same patent family, Ocuphire also has 1 pending U.S. patent application with additional claims to aqueous phentolamine mesylate formulations, whereby a patent, if granted, based on this patent application would expire in year 2034. The patents and patent applications cover the current clinical formulation for the Nyxol product.

Ocuphire's U.S. Patent Nos. 9,089,560; 9,789,088; and 11,000,509 contain claims directed to methods of improving visual performance using, for example, phentolamine mesylate and are scheduled to expire in year 2034. Counterpart patents have issued in Australia, Canada, Europe and Japan, which are scheduled to expire in year 2034. In the same patent family, Ocuphire also has 1 pending U.S. patent application with additional claims to methods of improving visual performance using, for example, phentolamine mesylate, whereby a patent, if granted from this pending patent application, would expire in year 2034. The patents and patent applications cover uses of the current clinical formulation for the Nyxol product.

Ocuphire has patent applications pending in the U.S., Australia, Canada, China, Europe, and Japan directed to treating glaucoma and other medical disorders using phentolamine mesylate. Patents, if granted, based on these pending applications would expire in year 2039.

Ocuphire's U.S. Patent 10,993,932 contains claims directed to methods of treating presbyopia using phentolamine mesylate in combination with pilocarpine and is scheduled to expire in year 2039. In the same patent family, Ocuphire has two pending U.S. patent applications, one with additional claims to treating presbyopia and the other U.S. application with claims to treating mydriasis. Counterpart patent applications are pending in Australia, Canada, China, Europe, Japan, and other foreign countries, whereby a patent, if granted, based on these pending U.S. and foreign patent applications would expire in year 2039.

Ocuphire has a pending U.S. provisional patent application and pending patent application in China directed to methods of making high purity phentolamine mesylate and compositions resulting from such methods. Ocuphire also has a pending U.S. provisional patent application directed to additional methods for treating mydriasis and glaucoma. Patents, if granted, based on these U.S. provisional patent applications would expire in year 2042, and patents, if granted, based on the pending patent application in China would expire in year 2041.

Ocuphire also owns an issued patent in Mexico that is scheduled to expire in year 2025 and has claims to ophthalmic formulations.

Ocuphire has in-licensed a patent estate directed to APX3330 and related compounds that, as of March 1, 2022, contains six U.S. patents, four pending U.S. non-provisional patent applications, as well as issued patents in Europe, Japan, Canada, and Australia, and pending patent applications in Europe, Japan, Canada, China, South Korea and Australia. Ocuphire's in-licensed U.S. patent 9,040,505 has claims to methods of treating diabetic retinopathy and other diseases using, for example, APX3330 and is scheduled to expire in year 2030. Counterpart patents have issued in Europe, Japan, Australia, and Canada, which are scheduled to expire in year 2028, and there is a related pending U.S. patent application with method of treatment claims that, if issued as a patent, would expire in year 2028. Ocuphire's in-licensed pending U.S. patent application 16,968,009 and pending applications in Europe, Japan, Canada, South Korea and Australia have claims to methods of treating wAMD and other diseases using, for example, APX3330, whereby patents, if granted based on these pending patent applications, would expire in year 2039. Ocuphire's in-licensed patent applications directed to a combination therapy composition comprising an APE1/REF-1 inhibitor, such as APX3330, and a second therapeutic agent, and are pending in the U.S. and Canada, whereby patents, if granted based on these pending patent applications, would expire in year 2038. In-licensed patent applications directed to use of an APE1/REF-1 inhibitor, such as APX3330, in monotherapy or combination therapy to reduce neuronal sensitivity and/or treat other indications are pending in the U.S., Europe, Japan, and Canada, whereby patents, if granted based on these applications, would expire in year 2038. Patents to derivatives of APX3330 have issued in the U.S., Europe, and other countries that are scheduled to expire from year 2028 to 2032, and patent applications to derivatives of APX3330 are pending in Europe and Japan whereby a patent, if granted based on these pending patent applications, would expire in year 2032.

In addition to patents and patent applications that Ocuphire has in-licensed, as of March 1, 2022, Ocuphire owns two pending U.S. provisional patent applications directed to methods of treating diabetic retinal diseases using APX3330. Patents, if granted, based on these pending U.S. provisional patent applications would expire in year 2042.

The patent prosecution process is expensive and time-consuming, and Ocuphire and its future licensors, licensees, or collaboration partners may not be able to prepare, file, and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that Ocuphire or any future licensors, licensees, or collaboration partners may fail to identify patentable aspects of inventions made in the course of development and commercialization activities before it is too late to obtain patent protection on them. Ocuphire and its licensors' patent applications cannot be enforced against third parties practicing the technology claimed in such applications unless and until a patent issues from such applications, and then only to the extent the issued claims cover the technology.

Ocuphire cannot assure you that any of its patents have matured, or that any of its pending patent applications will mature, into issued patents that will include, claims with a scope sufficient to protect its product candidates. Others have developed technologies that may be related or competitive to Ocuphire's approach, and may have filed or may file patent applications and may have received or may receive patents that overlap or conflict with Ocuphire's patent applications, for example by claiming the same compounds, methods or formulations or by claiming subject matter that could dominate the patents that Ocuphire owns or in-licenses. The patent positions of biotechnology and pharmaceutical companies, including Ocuphire's patent position, involve complex legal and factual questions, and, therefore, the issuance, scope, validity, and enforceability of any patent claims that Ocuphire may obtain cannot be predicted with certainty. Patents, if issued, may be challenged, deemed unenforceable, invalidated, or circumvented. U.S. patents and patent applications may also be subject to interference proceedings, *ex parte* reexamination, or *inter partes* review proceedings, supplemental examination and challenges in district court. Patents may be subjected to opposition, post-grant review, or comparable proceedings in various national and regional patent offices. These proceedings could result in either loss of the patent or denial of the patent application or loss or reduction in the scope of one or more of the claims of the patent or patent application. In addition, such interference, re-examination, opposition, post-grant review, *inter partes* review, supplemental examination, or revocation proceedings may be costly or time-consuming. Thus, any patents that Ocuphire may own or exclusively license may not provide any protection against competitors. Furthermore, an adverse decision in an interference proceeding can result in a third party receiving the patent right sought by Ocuphire, which in turn could affect its ability to develop, market or otherwise commercialize its product candidates.

Furthermore, the issuance of a patent, while presumed valid, is not conclusive as to its validity or its enforceability and it may not provide Ocuphire with adequate proprietary protection or competitive advantages against competitors with similar products. Competitors may also be able to design around Ocuphire's patents. Other parties may develop and obtain patent protection for more effective technologies, designs, or methods. Ocuphire may not be able to prevent the unauthorized disclosure or use of any technical knowledge or trade secrets by consultants, vendors, former employees, or current employees. The laws of some foreign countries do not protect proprietary rights to the same extent as do the laws of the United States, and Ocuphire may encounter significant problems in protecting its proprietary rights in these countries. If these developments were to occur, they could have a material adverse effect on Ocuphire's sales.

Ocuphire's ability to enforce its patent rights depends on its ability to detect infringement. It is difficult to detect infringers who do not advertise the components that are used in their products. Moreover, it may be difficult or impossible to obtain evidence of infringement in a competitor's or potential competitor's product. Any litigation to enforce or defend Ocuphire's patent rights, if any, even if Ocuphire were to prevail, could be costly and time-consuming and would divert the attention of management and key personnel from Ocuphire's business operations. Ocuphire may not prevail in any lawsuits that it initiates and the damages or other remedies awarded if it were to prevail may not be commercially meaningful.

In addition, proceedings to enforce or defend Ocuphire's patents could put its patents at risk of being invalidated, held unenforceable, or interpreted narrowly. Such proceedings could also provoke third parties to assert claims against Ocuphire, including that some or all of the claims in one or more of Ocuphire's patents are invalid or otherwise unenforceable. If, in any proceeding, a court invalidated or found unenforceable Ocuphire's patents covering its product candidates, Ocuphire's financial position and results of operations would be adversely impacted. In addition, if a court found that valid, enforceable patents held by third parties covered Ocuphire's product candidates, its financial position and results of operations would also be adversely impacted.

The degree of future protection for Ocuphire's proprietary rights is uncertain, and Ocuphire cannot ensure that:

- any of Ocuphire's patents, or any of its pending patent applications, if issued, will include claims having a scope sufficient to protect its product candidates;
- any of its pending patent applications will result in issued patents;
- Ocuphire will be able to successfully commercialize its product candidates, if approved, before its relevant patents expire;
- Ocuphire was the first to make the inventions covered by each of its patents and pending patent applications;
- Ocuphire was the first to file patent applications for these inventions;
- others will not develop similar or alternative technologies that do not infringe Ocuphire's patents;
- any of Ocuphire's patents will be valid and enforceable;
- any patents issued to Ocuphire will provide a basis for an exclusive market for its commercially viable products, will provide Ocuphire with any competitive advantages or will not be challenged by third parties;
- Ocuphire will develop additional proprietary technologies or product candidates that are separately patentable; or
- that Ocuphire's commercial activities or products will not infringe upon the patents of others.

Patents have a limited lifespan. The natural expiration of a patent is generally 20 years after its effective filing date. Various extensions may be available; however, the life of a patent, and the protection it affords, is limited. Given the extensive period of time between patent filing and regulatory approval for a product candidate, the time during which Ocuphire can market a product candidate under patent protection is limited, and Ocuphire's patent may expire before it obtains such approval. Without patent protection for its product candidates, it may be vulnerable to competition from generic versions of its product candidates, which may affect the profitability of its product candidates.

If Ocuphire does not obtain protection under the Hatch-Waxman Act and similar foreign legislation by extending the patent terms and obtaining data exclusivity for its product candidate, its business may be materially harmed.

Depending upon the timing, duration of regulatory review, and date of FDA marketing approval of its APX3330 or other product candidates, if any, one of such U.S. patents may be eligible for patent term restoration under the Drug Price Competition and Patent Term Restoration Act of 1984, referred to as the Hatch-Waxman Act. The Hatch-Waxman Act provides for a patent restoration term, or patent term extension, of up to five years as compensation for the time the product is under FDA regulatory review. The duration of patent term extension is calculated based on the time spent in the regulatory review process. In the future, Ocuphire may plan to seek patent term extension for one or more of its patents related to its APX3330 or other product candidates. However, Ocuphire may not be granted an extension because of, for example, failing to apply within the applicable deadline, expiration of relevant patents prior to obtaining approval, or otherwise failing to satisfy applicable requirements. Moreover, the applicable time period or the scope of patent protection afforded could be shorter or less than what Ocuphire requests. If Ocuphire is unable to obtain patent term extension or the term of any such extension is less than it requests, Ocuphire's revenue could be reduced, possibly materially.

Changes in U.S. patent law could diminish the value of patents in general, thereby impairing Ocuphire's ability to protect its product candidates.

In 2011, the United States enacted wide-ranging patent reform legislation with the America Invents Act ("AIA").

An important change introduced by the AIA is that, as of March 16, 2013, the United States transitioned to a "first-to-file" system for deciding which party should be granted a patent when two or more patent applications are filed by different parties claiming the same invention. A third party that files a patent application in the USPTO after that date but before Ocuphire could therefore be awarded a patent covering an invention of ours even if Ocuphire had made the invention before it was made by the third party. This will require Ocuphire to be cognizant going forward of the time from invention to filing of a patent application, but circumstances could prevent Ocuphire from promptly filing patent applications on its inventions.

Among some of the other changes introduced by the AIA are changes that limit where a patentee may file a patent infringement suit and providing opportunities for third parties to challenge any issued patent in the USPTO. This applies to all of Ocuphire's U.S. patents, even those issued before March 16, 2013. Because of a lower evidentiary standard in USPTO proceedings compared to the evidentiary standard in U.S. federal courts necessary to invalidate a patent claim, a third party could potentially provide evidence in a USPTO proceeding sufficient for the USPTO to hold a claim invalid even though the same evidence would be insufficient to invalidate the claim if first presented in a district court action. Accordingly, a third party may attempt to use the USPTO procedures to invalidate Ocuphire's patent claims that would not have been invalidated if first challenged by the third party as a defendant in a district court action. The AIA and its implementation could increase the uncertainties and costs surrounding the prosecution of Ocuphire's patent applications and the enforcement or defense of Ocuphire's issued patents.

Additionally, the U.S. Supreme Court's holdings in several patent cases in recent years, such as *Association for Molecular Pathology v. Myriad Genetics, Inc.* (Myriad I), *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, and *Alice Corporation Pty. Ltd. v. CLS Bank International*, have narrowed the scope of patent protection available in certain circumstances or weakened the rights of patent owners in certain situations. In addition to increasing uncertainty about Ocuphire's ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents, once obtained. Depending on decisions by the U.S. Congress, the federal courts, and the USPTO, the laws and regulations governing patents could change in unpredictable ways that would weaken Ocuphire's ability to obtain new patents or to enforce Ocuphire's existing patents and patents that it might obtain in the future.

Ocuphire may not be able to protect or practice its intellectual property rights throughout the world.

In jurisdictions where Ocuphire has not obtained patent protection, competitors may use its intellectual property to develop their own products and further, may export otherwise infringing products to territories where Ocuphire has patent protection, but where it is more difficult to enforce a patent as compared to the United States. Competitor products may compete with Ocuphire's product candidates in jurisdictions where it does not have issued or granted patents or where its issued or granted patent claims or other intellectual property rights are not sufficient to prevent competitor activities in these jurisdictions. The legal systems of certain countries, particularly certain developing countries, make it difficult to enforce patents and such countries may not recognize other types of intellectual property protection, particularly that relating to pharmaceuticals. This could make it difficult for Ocuphire to prevent the infringement of its patents or marketing of competing products in violation of its proprietary rights generally in certain jurisdictions. Proceedings to enforce Ocuphire's patent rights in foreign jurisdictions could result in substantial cost and divert its efforts and attention from other aspects of its business.

The laws of some jurisdictions do not protect intellectual property rights to the same extent as the laws in the United States, and many companies have encountered significant difficulties in protecting and defending such rights in such jurisdictions. If Ocuphire, or any future licensor, encounters difficulties in protecting, or is otherwise precluded from effectively protecting, the intellectual property rights important for its business in such jurisdictions, the value of these rights may be diminished and Ocuphire may face additional competition from others in those jurisdictions. Many countries have compulsory licensing laws under which a patent owner may be compelled to grant licenses to third parties. In addition, many countries limit the enforceability of patents against government agencies or government contractors. In these countries, the patent owner may have limited remedies, which could materially diminish the value of such patent. If Ocuphire, or any licensor, is forced to grant a license to third parties with respect to any patents relevant to its business, Ocuphire's competitive position in the relevant jurisdiction may be impaired and its business and results of operations may be adversely affected.

Ocuphire may become involved in lawsuits to protect or enforce its patents and other intellectual property rights, which could be expensive, time consuming, and unsuccessful.

Competitors may infringe Ocuphire's patents, the patents of its licensing partners, or other intellectual property rights. To counter infringement or unauthorized use, Ocuphire may be required to file infringement claims, which can be expensive and time consuming. In addition, in an infringement proceeding, a court may decide that an Ocuphire patent is invalid or unenforceable, or may refuse to stop the other party from using the technology on the grounds that Ocuphire's patents do not cover the technology in question. An adverse result in any litigation proceeding could put one or more of Ocuphire's patents at risk of being invalidated or interpreted narrowly. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of Ocuphire's confidential information could be compromised by disclosure during this type of litigation. Moreover, there can be no assurance that Ocuphire will have sufficient financial or other resources to file and pursue such infringement claims, which typically last for years before they are concluded.

Litigation proceedings may fail and, even if successful, may be costly and a distraction to Ocuphire's management and other employees. Ocuphire may not be able to prevent, alone or with its collaborators, misappropriation of its proprietary rights, particularly in countries where the laws may not protect those rights as fully as in the United States.

In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of Ocuphire common stock.

Third parties may initiate legal proceedings alleging that Ocuphire is infringing their intellectual property rights, the outcome of which would be uncertain and could have an adverse effect on the success of Ocuphire's business.

Ocuphire's commercial success depends upon its ability and the ability of its collaborators to develop, manufacture, market and sell its product candidates and use its proprietary technologies without infringing the proprietary rights and intellectual property of third parties. The biotechnology and pharmaceutical industries are characterized by extensive litigation regarding patents and other intellectual property rights. Ocuphire may in the future become party to, or threatened with, adversarial proceedings or litigation regarding intellectual property rights with respect to its medicines and technology, including interference or derivation proceedings, post-grant reviews, *inter partes* reviews, or other procedures before the USPTO or other similar procedures in foreign jurisdictions. Third parties may assert infringement claims against Ocuphire based on existing patents or patents that may be granted in the future. If Ocuphire is found to infringe a third party's intellectual property rights, it could be required to obtain a license from such third party to continue developing and marketing its medicines and technology. However, Ocuphire may not be able to obtain any required license on commercially reasonable terms or at all. Even if Ocuphire were able to obtain a license, it could be non-exclusive, thereby giving its competitors and other third parties access to the same technologies licensed to it. Ocuphire could be forced, including by court order, to cease developing and commercializing the infringing technology or medicine. In addition, Ocuphire could be held liable for substantial monetary damages, potentially including treble damages and attorneys' fees, if found to have willfully infringed. A finding of infringement could prevent Ocuphire from commercializing a product candidate or force it to cease some of its business operations, which could harm Ocuphire's business. Alternatively, Ocuphire may need to redesign its infringing products, which may be impossible or require substantial time and monetary expenditure. Claims that Ocuphire has misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on its business.

The cost to Ocuphire of any litigation or other proceeding relating to patent or other proprietary rights, even if resolved in its favor, could be substantial and may result in substantial costs and distraction to Ocuphire's management and other employees. Some of Ocuphire's competitors may be able to sustain the costs of complex patent litigation more effectively than Ocuphire can because they have substantially greater resources. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could delay Ocuphire's research and development efforts and limit its ability to continue its operations.

Ocuphire may be subject to damages resulting from claims that its employees or Ocuphire has wrongfully used or disclosed alleged trade secrets of their former employers.

Ocuphire's employees and consultants have been previously employed at other biotechnology or pharmaceutical companies, including its competitors or potential competitors. Although Ocuphire is not aware of any claims currently pending against it, Ocuphire may be subject to claims that these employees or Ocuphire has inadvertently or otherwise used or disclosed trade secrets or other proprietary information or intellectual property of the former employers of its employees. Litigation may be necessary to defend against these claims. Even if Ocuphire is successful in defending against these claims, litigation could result in substantial costs and be a distraction to management. If Ocuphire fails in defending such claims, in addition to paying money claims, it may lose valuable intellectual property rights or personnel. A loss of key personnel or their work product could detract from Ocuphire's ability to develop or commercialize its product candidates.

If Ocuphire is not able to adequately prevent disclosure of trade secrets and other proprietary information, the value of any product it may pursue could be significantly diminished.

Ocuphire may rely upon trade secrets, know-how, and continuing technological innovation to develop and maintain its competitive position. However, trade secrets are difficult to protect. Ocuphire relies in part on confidentiality agreements with its employees, consultants, outside scientific collaborators, sponsored researchers, contract manufacturers, vendors, and other advisors to protect its trade secrets and other proprietary information. These agreements may not effectively prevent disclosure of confidential information and may not provide an adequate remedy in the event of unauthorized disclosure of confidential information. In addition, Ocuphire cannot guarantee that it has executed these agreements with each party that may have or has had access to trade secrets.

If a party breaches an agreement and discloses Ocuphire's proprietary information, including its trade secrets, Ocuphire may not be able to obtain adequate remedies for such breaches. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive, and time consuming, and the outcome is unpredictable. In addition, some courts in and outside of the United States are less willing or unwilling to protect trade secrets. If any of Ocuphire's trade secrets were to be lawfully obtained or independently developed by a competitor, Ocuphire would have no right to prevent them, or those to whom they disclose such trade secrets, from using that technology or information to compete with it. If any of Ocuphire's trade secrets were to be disclosed to, or independently developed by, a competitor or other third party, Ocuphire's competitive position would be harmed.

Obtaining and maintaining Ocuphire's trademark protection depends on approval from the USPTO and other foreign government agencies, and third parties may challenge, infringe, or otherwise weaken Ocuphire's trademark rights.

Ocuphire has obtained registration of the "Nyxol" trademark in the United States. It has not yet registered trademarks for any other product candidates in any jurisdiction. If Ocuphire does not secure and maintain registrations for its trademarks, it may encounter more difficulty in enforcing them against third parties than it otherwise would, which could affect its business. When Ocuphire files trademark applications for a product candidate, those applications may not be allowed for registration, and registered trademarks may not be obtained, maintained, or enforced. During trademark registration proceedings in the United States and foreign jurisdictions, Ocuphire may receive rejections. Ocuphire is given an opportunity to respond to those rejections, but may not be able to overcome such rejections. In addition, the USPTO and comparable agencies in many foreign jurisdictions allow third parties opportunities to oppose pending trademark applications and to seek to cancel registered trademarks. Opposition or cancellation proceedings may be filed against Ocuphire's trademarks and its trademarks may not survive such proceedings.

In addition, any proprietary name Ocuphire proposes to use with a future product candidate in the United States must be approved by the FDA, regardless of whether Ocuphire has registered it, or applied to register it, as a trademark. The FDA typically conducts a review of proposed drug names, including an evaluation of potential for confusion with other drug names. If the FDA objects to any proposed proprietary drug name for any product candidate, Ocuphire may be required to expend significant additional resources in an effort to identify a suitable substitute proprietary drug name that would qualify under applicable trademark laws, not infringe the existing rights of third parties, and be acceptable to the FDA.

If Ocuphire registers any of its trademarks, its trademarks or trade names may be challenged, infringed, circumvented, declared generic, or determined to infringe on other marks. Ocuphire may not be able to protect its rights to these trademarks and trade names or may be forced to stop using these names, which Ocuphire needs for name recognition by potential partners or customers in its markets of interest. If Ocuphire is unable to establish name recognition based on its trademarks and trade names, Ocuphire may not be able to compete effectively, and its business may be adversely affected.

Obtaining and maintaining Ocuphire's patent protection depends on compliance with various procedural, document submission, fee payment, and other requirements imposed by governmental agencies, and its patent protection could be reduced or eliminated for noncompliance with these requirements.

The USPTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment or other provisions during the patent application process. In addition, periodic maintenance and annuity fees on any issued patent are due to be paid to the USPTO and foreign patent agencies in several stages over the lifetime of the patent. While an inadvertent lapse can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, Ocuphire's competitors might be able to enter the market, which would have an adverse effect on Ocuphire's business.

Ocuphire depends on intellectual property sublicensed from Apexian Pharmaceuticals, Inc. (“Apexian”) for its APX3330 product candidate under development and its additional pipeline candidates, and the termination of, or reduction or loss of rights under, this sublicense would harm Ocuphire’s business.

Ocuphire entered into a sublicense agreement with Apexian (as amended, the “Apexian Sublicense Agreement”) to in-license patents and other intellectual property relating to the APX3330 product candidate and second-generation product candidates owned by Apexian, and intellectual property that Apexian in-licensed from Eisai Co., Ltd. (“Eisai”) including certain study reports, manufacturing and analytical records, data, know-how, technical and other proprietary information relating to APX3330. The rights granted under the Apexian Sublicense Agreement are subject to various milestone payment, royalty, insurance or other obligations on Ocuphire, and may be revocable under certain circumstances including if Ocuphire ceases to do business, fails to make the payments due thereunder, commits a material breach of the agreement that is not cured within a certain time period after receiving written notice or fails to meet certain specified development and commercial timelines. Termination of the Apexian Sublicense Agreement may result in Ocuphire having to negotiate a new or reinstated agreement, which may not be available to Ocuphire on equally favorable terms, or at all, which may mean Ocuphire is unable to develop or commercialize APX3330 and second-generation assets.

Ocuphire does not have total control over the preparation, filing, prosecution and maintenance of patents and patent applications covering the technology that it licenses under the Apexian Sublicense Agreement. Under the Sublicense Agreement, Indiana University Research and Technology Corp. (“IURTC”), the owner of the patents licensed to Apexian and sublicensed to Ocuphire, maintains the right to control all prosecution and maintenance of such patents. Therefore, Ocuphire cannot always be certain that these patents and patent applications will be prepared, filed, prosecuted and maintained in a manner consistent with the best interests of Ocuphire’s business. Although Ocuphire has a right to have its comments considered in connection with, and has agreed to bear the costs of, the prosecution and maintenance of the licensed patents, if IURTC fails to prosecute and maintain such patents, or loses rights to those patents or patent applications as a result of its control of the prosecution activities, the rights Ocuphire has licensed may be reduced or eliminated, and Ocuphire’s right to develop and commercialize any of its product candidates that are the subject of such licensed rights could be adversely affected.

Further, if Apexian breaches its license agreement with IURTC and fails to cure such breach within a 60-day cure period, IURTC may terminate such license agreement with Apexian, in which case, Ocuphire’s license shall also terminate and Ocuphire will lose all rights under the license agreement with Apexian. While the Apexian Sublicense Agreement provides that Apexian must cooperate with Ocuphire to remedy and cure Apexian’s breach of the license agreement with IURTC in order to prevent the termination of such license agreement, Ocuphire cannot guarantee that such efforts will be successful in preventing the termination of the license agreement between Apexian and IURTC. Similarly, if Apexian breaches its license agreement with Eisai and fails to cure such breach within a 60-day cure period, Eisai may terminate such license agreement with Apexian, in which case, Ocuphire’s sublicense rights under such license shall also terminate. While Ocuphire does not have any material obligations under the license agreement between Eisai and Apexian, Apexian has certain confidentiality and payment obligations that, if not met, could result in breach of the Eisai license agreement.

Under Apexian’s license agreement with IURTC, any act or omission by Ocuphire that would be a breach of the license agreement with IURTC if imputed to Apexian is deemed to be a breach by Apexian of such license agreement and cause for termination, including, in particular, any breach by Ocuphire of its payment, reporting, audit, and indemnification obligations.

The Apexian Sublicense Agreement obligates Ocuphire to make certain milestone payments.

Ocuphire is obligated to pay certain milestone payments to Apexian pursuant to the Apexian Sublicense Agreement. These milestone payments include (i) payments for specified developmental and regulatory milestones totaling up to \$11 million in the aggregate and (ii) payments for specified sales milestones of up to \$20 million in the aggregate.

Because certain of the milestone payments payable by Ocuphire are due upon certain events related to the development and regulatory approval of its product candidates, Ocuphire may be required to make such payments prior to the time at which it is able to generate revenue, if any, from sales any of its product candidates, if approved. There can be no assurance that Ocuphire will have the funds necessary to make such payments, or be able to raise such funds when needed, on terms acceptable to Ocuphire, or at all. Furthermore, if Ocuphire is forced to raise additional funds, it may be required to delay, limit, reduce or terminate its product development or future commercialization efforts, or grant rights to develop and market product candidates that it would otherwise develop and market themselves. If Ocuphire is unable to raise additional funds or maintain sufficient liquidity to make its payment obligations if and when they become due, it may be in material breach of its license and acquisition agreements and its counterparties may seek legal action or remedies against Ocuphire, which would harm its business, financial condition, results of operations and prospects.

Ocuphire may enter into collaborations, in-licensing arrangements, joint ventures, strategic alliances or partnerships with third parties that may not result in the development of commercially viable products or the generation of significant future revenues.

Ocuphire may enter into certain license or other collaboration agreements in the future. Such agreements may impose various diligence, milestone payment, royalty, insurance or other obligations on Ocuphire. If Ocuphire fails to comply with such obligations, Ocuphire's licensor or collaboration partners may have the right to terminate the relevant agreement, in which event Ocuphire would not be able to develop or market the products covered by such licensed intellectual property. Moreover, disputes may arise regarding intellectual property subject to a licensing agreement, including:

- the scope of rights granted under the license agreement and other interpretation-related issues;
- the extent to which Ocuphire's product candidates, technology and processes infringe on intellectual property of the licensor that is not subject to the licensing agreement;
- the sublicensing of patent and other rights under Ocuphire's collaborative development relationships;
- Ocuphire's diligence obligations under the license agreement and what activities satisfy those diligence obligations;
- the inventorship and ownership of inventions and know-how resulting from the joint creation or use of intellectual property; and
- the priority of invention of patented technology.

In addition, the agreements under which intellectual property or technology is licensed from third parties are complex, and certain provisions in such agreements may be susceptible to multiple interpretations. The resolution of any contract interpretation disagreement that may arise could narrow what Ocuphire believes to be the scope of Ocuphire's rights to the relevant intellectual property or technology, or increase what Ocuphire believes to be Ocuphire's financial or other obligations under the relevant agreement, either of which could have a material adverse effect on Ocuphire's business, financial condition, results of operations, and prospects. Moreover, if disputes over intellectual property that Ocuphire has licensed prevent or impair Ocuphire's ability to maintain Ocuphire's licensing arrangements on commercially acceptable terms, Ocuphire may be unable to successfully develop and commercialize the affected product candidates, which could have a material adverse effect on Ocuphire's business, financial conditions, results of operations, and prospects.

In addition, Ocuphire cannot be certain that the preparation, filing, prosecution and maintenance activities by any future licensors have been or will be conducted in compliance with applicable laws and regulations or will result in valid and enforceable patents and other intellectual property rights.

Risks Related to Ocuphire’s Employee Matters and Managing Growth

Ocuphire is dependent on its key personnel, and if it is not successful in attracting and retaining highly qualified personnel, it may not be able to successfully implement its business strategy.

Ocuphire is highly dependent on its management, scientific, and medical personnel, including Mina Sooch, its President, Chief Executive Officer and Board Vice Chair. Ocuphire has entered into employment agreements with its executive officers, but any employee may terminate his or her employment with Ocuphire. The loss of the services of any of Ocuphire’s executive officers, other key employees or consultants, or other scientific and medical advisors in the foreseeable future might impede the achievement of Ocuphire’s research, development, and commercialization objectives. Ocuphire relies on consultants and advisors, including scientific and clinical advisors, to assist it in formulating its development and commercialization strategy. Ocuphire’s consultants and advisors may be employed by employers other than Ocuphire and may have commitments under consulting or advisory contracts with other entities that may limit their availability to Ocuphire. Recruiting and retaining qualified scientific personnel and business and commercial personnel will also be critical to Ocuphire’s success. Ocuphire may not be able to attract and retain these personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. Ocuphire also experiences competition for the hiring of scientific personnel from universities and research institutions. Failure to succeed in clinical trials may also make it more challenging to recruit and retain qualified scientific personnel.

Ocuphire will need to develop and expand its company and may encounter difficulties in managing this development and expansion, which could disrupt its operations.

As of March 1, 2022, Ocuphire had nine full-time employees, and Ocuphire expects to increase its number of employees and the scope of its operations as it furthers the clinical development of its product candidates and becomes a public company. To manage its anticipated development and expansion, Ocuphire must continue to implement and improve its managerial, operational, and financial systems, expand its facilities, and continue to recruit and train additional qualified personnel. Also, Ocuphire’s management may need to divert a disproportionate amount of its attention away from its day-to-day activities and devote a substantial amount of time to managing these development activities. Due to its limited resources, Ocuphire may not be able to effectively manage the expansion of its operations or recruit and train additional qualified personnel. This may result in weaknesses in Ocuphire’s infrastructure, and give rise to operational mistakes, loss of business opportunities, loss of employees, or reduced productivity among remaining employees. The physical expansion of Ocuphire’s operations may lead to significant costs and may divert financial resources from other projects, such as the development of product candidates. If Ocuphire’s management is unable to effectively manage its expected development and expansion, its expenses may increase more than expected, its ability to generate or increase its revenue could be reduced and it may not be able to implement its business strategy. Ocuphire’s future financial performance and its ability to commercialize product candidates, if approved, and compete effectively will depend, in part, on its ability to effectively manage the future development and expansion of Ocuphire.

A variety of risks associated with operating internationally for Ocuphire and its collaborators could adversely affect its business.

In addition to its U.S. operations, Ocuphire may pursue international operations in the future and would face risks associated with such global operations, including possible unfavorable regulatory, pricing and reimbursement, legal, political, tax, and labor conditions, which could harm its business. Ocuphire plans to conduct clinical trials outside of the United States. Ocuphire is subject to numerous risks associated with international business activities, including:

- compliance with differing or unexpected regulatory requirements for its product candidates;
- different medical practices and customs affecting acceptance of its product candidates, if approved, or any other approved product in the marketplace;
- language barriers;
- the interpretation of contractual provisions governed by foreign law in the event of a contract dispute;
- difficulties in staffing and managing foreign operations, and an inability to control commercial or other activities where it is relying on third parties;
- workforce uncertainty in countries where labor unrest is more common than in the United States;

- potential liability under the Foreign Corrupt Practice Act of 1977 or comparable foreign regulations;
- production shortages resulting from any events affecting raw material supply or manufacturing capability abroad;
- foreign government taxes, regulations, and permit requirements;
- U.S. and foreign government tariffs, trade restrictions, price and exchange controls, and other regulatory requirements;
- economic weakness, including inflation, natural disasters, war, events of terrorism, or political instability in particular foreign countries;
- fluctuations in currency exchange rates, which could result in increased operating expenses and reduced revenues;
- compliance with tax, employment, immigration, and labor laws, regulations, and restrictions for employees living or traveling abroad;
- changes in diplomatic and trade relationships; and
- challenges in enforcing its contractual and intellectual property rights, especially in those foreign countries that do not respect and protect intellectual property rights to the same extent as the United States.

The COVID-19 pandemic has and could continue to adversely impact Ocuphire's business, financial condition, cash flows, liquidity, and result in stock price volatility,

The COVID-19 pandemic has caused, and continues to cause, a significant adverse effect on the level of economic activity around the world. In response to the COVID-19 pandemic, the governments of many countries, states, cities and other geographic regions have taken preventative or protective actions. The actions taken by governments, businesses and individuals in response to the pandemic have resulted in, and are expected to continue to result in, a curtailment of business activities (including changes in demand for a broad variety of goods and services), labor shortages, disruptions in supply, manufacturing and logistics, economic uncertainty and weakness, and volatility in the financial markets, both in the United States and abroad. Ocuphire has experienced a few disruptions in its manufacturing, supply chain, research and development operations, regulatory process, and financial position. During 2020 and 2021, these disruptions included manufacturing and analytical lab operations (e.g., shipment of active pharmaceutical ingredient supply from Italy and India), clinical trial operations and recruitment, and difficulties in obtaining more favorable financing terms.

The extent to which the COVID-19 pandemic continues to impact the Company's operations and financial condition will depend on future developments that are highly uncertain and cannot be predicted, including new government actions or restrictions, new information that may emerge concerning the severity of COVID-19, the longevity of COVID-19 and its variants and the impact of COVID-19 on economic activity. The COVID-19 pandemic has impacted the global economy creating certain macroeconomic conditions that make this a particularly challenging business environment for us, including global supply chain instability, inflationary cost increases and labor shortages. To the extent the COVID-19 pandemic materially adversely affects the Company's business and financial results, it may also have the effect of significantly heightening many of the other risks associated with the Company's business, results of operations, financial condition, cash flows, liquidity and stock price, including in ways that we cannot predict.

Ocuphire's business and operations would suffer in the event of system failures or unplanned events.

Despite the implementation of security measures, Ocuphire's internal computer systems and those of its current and future contractors and consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war, and telecommunications and electrical failures. In March 2021, we were the victim of a business email compromise. This fraud did not cause any losses to Ocuphire. If another such event were to occur and cause interruptions in its operations, it could result in a material disruption of Ocuphire's development programs and its business operations. For example, the loss of clinical trial data from completed or future clinical trials could result in delays in Ocuphire's regulatory approval efforts and significantly increase Ocuphire's costs to recover or reproduce the data. To the extent that any disruption or security breach were to result in a loss of, or damage to, Ocuphire's data or applications, or inappropriate disclosure of confidential or proprietary information, Ocuphire could incur liability and the further development and commercialization of its product candidates could be delayed. We may be required to expend significant resources, fundamentally change our business activities and practices, or modify our operations, including our clinical trial activities, or information technology in an effort to protect against security breaches and to mitigate, detect and remediate actual or potential vulnerabilities.

Furthermore, any unplanned event, such as flood, fire, explosion, tornadoes, earthquake, extreme weather condition, medical epidemics, power shortage, telecommunications failure, other natural or manmade accidents or incidents, or pandemics, including the ongoing COVID-19 pandemic, that result in Ocuphire being unable to fully utilize the facilities, may have an adverse effect on Ocuphire's ability to operate its business, particularly on a daily basis, and have significant negative consequences on its financial and operating conditions. Loss of access to these facilities may result in increased costs, delays in the development of its product candidates, or interruption of its business operations.

Ocuphire's insurance policies are expensive and protect only from some business risk, which leaves Ocuphire exposed to significant uninsured liabilities.

Ocuphire does not carry insurance for all categories of risks that its business may encounter, and insurance coverage is becoming increasingly expensive. Ocuphire does not know if it will be able to maintain existing insurance with adequate levels of coverage, and any liability insurance coverage it acquires in the future may not be sufficient to reimburse the company for any expenses or losses it may suffer. If Ocuphire obtains marketing approval for any product candidates that it may develop, Ocuphire intends to acquire insurance coverage to include the sale of commercial products, but it may be unable to obtain such insurance on commercially reasonable terms or in adequate amounts. Required coverage limits for such insurances are difficult to predict and may not be sufficient. If potential losses exceed Ocuphire's insurance coverage, its financial condition would be adversely affected. In the event of contamination or injury, Ocuphire could be held liable for damages or be penalized with fines in an amount exceeding its resources. Clinical trials or regulatory approvals for any of its product candidates could be suspended, which could adversely affect Ocuphire's results of operations and business, including by preventing or limiting the development and commercialization of any product candidates that the company or its collaborators may develop.

In addition, as a public company, it may be more difficult or more costly for us to obtain certain types of insurance, including directors' and officers' liability insurance, and we may be forced to accept reduced policy limits and coverage or incur substantially higher costs to obtain the same or similar coverage. The impact of these events could also make it more difficult for us to attract and retain qualified personnel to serve on our board of directors, our board committees or as executive officers.

Risks Related to Ownership of Ocuphire Common Stock

Ocuphire does not anticipate paying any cash dividends in the foreseeable future.

The current expectation is that Ocuphire will retain its future earnings, if any, to fund the development and growth of its business. As a result, capital appreciation, if any, of its common stock will be investors' sole source of gain, if any, for the foreseeable future.

If Ocuphire fails to comply with the continued listing standards of the Nasdaq Capital Market, Ocuphire common stock could be delisted. If it is delisted, the liquidity of Ocuphire's common stock would be impacted.

The continued listing of Ocuphire common stock on Nasdaq is contingent on Ocuphire's continued compliance with a number of listing standards. There is no assurance that Ocuphire will remain in compliance with these standards. Delisting from Nasdaq would adversely affect Ocuphire's ability to raise additional financing through the public or private sale of equity securities, significantly affect the ability of investors to trade Ocuphire's securities and negatively affect the value and liquidity of Ocuphire's common stock. Delisting also could limit Ocuphire's strategic alternatives and attractiveness to potential counterparties and have other negative results, including the potential loss of employee confidence, the loss of institutional investors or interest in business development opportunities.

In addition, if our common stock is delisted from the Nasdaq Capital Market and the trading price remains below \$5.00 per share, trading in our common stock might also become subject to the requirements of certain rules promulgated under the Exchange Act, which require additional disclosure by broker-dealers in connection with any trade involving a stock defined as a "penny stock" (generally, any equity security not listed on a national securities exchange or quoted on Nasdaq that has a market price of less than \$5.00 per share, subject to certain exceptions).

The market price of Ocuphire common stock may fluctuate significantly.

The market price of Ocuphire common stock may fluctuate significantly in response to factors, some of which are beyond Ocuphire's control, such as:

- the announcement of new products or product enhancements by Ocuphire or its competitors;
- changes in Ocuphire's relationships with its licensors or other strategic partners;
- developments concerning intellectual property rights and regulatory approvals;
- variations in Ocuphire's and Ocuphire's competitors' results of operations;
- substantial sales of shares of our common stock due to the release of lock-up agreements;
- the announcement of clinical trial results;
- the announcement of potentially dilutive financings;
- changes in earnings estimates or recommendations by securities analysts;
- changes in the structure of healthcare payment systems; and
- developments and market conditions in the pharmaceutical and biotechnology industries, including due to the COVID-19 pandemic.

Further, the stock market, in general, and the market for biotechnology companies, in particular, have experienced extreme price and volume fluctuations. Continued market fluctuations could result in extreme volatility in the price of Ocuphire's common stock, which may be unrelated or disproportionate to Ocuphire's operating performance and which could cause a decline in the value of Ocuphire's common stock.

Ocuphire may be subject to securities litigation, which is expensive and could divert management attention.

The market price of Ocuphire common stock may be volatile, and in the past companies that have experienced volatility in the market price of their stock have been subject to securities class action litigation. Ocuphire may be the target of this type of litigation in the future. Securities litigation against Ocuphire could result in substantial costs and direct Ocuphire management's attention from other business concerns, which could seriously harm Ocuphire's business.

ITEM 1B. UNRESOLVED STAFF COMMENTS

Not applicable.

ITEM 2. PROPERTIES

Ocuphire's headquarters is currently located in Farmington Hills, Michigan, and consists of approximately 1,600 square feet of leased office space under a lease that expires on December 31, 2022. Ocuphire may extend its current space or require additional space and facilities as its business expands, and it believes that suitable additional and alternative spaces will be available in the future on commercially reasonable terms.

ITEM 3. LEGAL PROCEEDINGS

From time to time, we are subject to litigation and claims arising in the ordinary course of business. Although the results of litigation and claims cannot be predicted with certainty, as of the date of this filing, we do not believe we are party to any claim or litigation, the outcome of which, if determined adversely to us, would individually or in the aggregate be reasonably expected to have a material adverse effect on our business or financial condition. Regardless of the outcome, litigation can have an adverse impact on us because of defense and settlement costs, diversion of management resources and other factors.

ITEM 4. MINE SAFETY DISCLOSURES

Not applicable.

PART II

ITEM 5. MARKET FOR REGISTRANT’S COMMON EQUITY, RELATED STOCKHOLDER MATTERS AND ISSUER PURCHASES OF EQUITY SECURITIES

Market Information

Our shares of common stock trade on the Nasdaq Capital Market under the symbol “OCUP”.

Holders

As of March 23, 2022, there were approximately 85 holders of record of our common stock. The number of holders of record is based on the actual number of holders registered on the books of our transfer agent and does not reflect holders of shares in “street name” or persons, partnerships, associations, corporations, or other entities identified in security position listings maintained by depository trust companies.

Dividend Policy

We have not paid any cash dividends on our common stock since our inception and do not anticipate paying any cash dividends in the foreseeable future. We plan to retain our earnings, if any, to provide funds for the expansion of our business.

Recent Sales of Unregistered Securities

All unregistered sales of securities have been previously reported on Form 10-Q.

ITEM 6. [RESERVED]

ITEM 7. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

You should read the following discussion and analysis of Ocuphire's financial condition and results of operations together with Ocuphire's financial statements and the related notes included elsewhere in this annual report. Some of the information contained in this discussion and analysis or set forth elsewhere in this annual report, including information with respect to Ocuphire's plans and strategy for Ocuphire's business and related financing, includes forward-looking statements that involve risks and uncertainties. As a result of many factors, including those factors set forth in the "Risk Factors" section of this annual report, Ocuphire's actual results could differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.

Overview

Ocuphire is a clinical-stage ophthalmic biopharmaceutical company focused on developing and commercializing therapies for the treatment of refractive and retinal eye disorders. Ocuphire's pipeline currently includes two small molecule product candidates targeting several of such indications.

Its lead product candidate, Nyxol[®] Eye Drops ("Nyxol"), is a once-daily eye drop formulation of phentolamine mesylate designed to reduce pupil diameter and improve visual acuity. As a result, Nyxol can potentially be used for the treatment of multiple indications such as reversal of pharmacologically-induced mydriasis ("RM") (dilation of the pupil), presbyopia (age-related blurry near vision) and dim light or night vision disturbances ("NVD") (halos and glares). Ocuphire's management believes these multiple indications potentially represent a significant market opportunity. Nyxol has been studied in a total of 9 clinical trials (3 Phase 1, 5 Phase 2 and 1 Phase 3) in a total of over 560 patients (with over 330 Nyxol-treated) and has demonstrated promising clinical data for use in the multiple ophthalmic indications mentioned above. Ocuphire reported positive top-line data from the first Phase 3 trial (MIRA-2) for RM, completed enrollment in a 2nd Phase 3 RM trial (MIRA-3) in February 2022, and completed enrollment on a pediatric safety study (MIRA-4) for RM in March 2022. Ocuphire also reported positive top-line data from a Phase 2 trial of Nyxol for treatment of presbyopia, both alone and with low-dose pilocarpine (pilocarpine hydrochloride 0.4% ophthalmic solution, "LDP") as adjunctive therapy. Ocuphire announced completion of enrollment of its NVD Phase 3 trial (LYNX-1) in January 2022. Ocuphire expects to report top-line results from the MIRA-3 RM Phase 3 study by end of the first quarter of 2022, followed by the LYNX-1 NVD Phase 3 study and the MIRA-4 RM pediatric study in the second quarter of 2022. Assuming successful and timely completion of the RM trials, Ocuphire anticipates submitting a new drug application ("NDA") to the U.S. Food and Drug Administration ("FDA") in late 2022 under the 505(b)(2) pathway for its drug led combination product. Ocuphire has started pre-commercialization planning and activities in anticipation of a successful RM approval.

Ocuphire's second product candidate, APX3330, is a twice-a-day oral tablet designed to target multiple pathways relevant to retinal and choroidal (the vascular layer of the eye) diseases such as diabetic retinopathy ("DR") and diabetic macular edema ("DME") which, if left untreated, can result in permanent visual acuity loss and eventual blindness. DR is a disease resulting from diabetes in which chronically elevated blood sugar levels cause progressive damage to blood vessels in the retina. DME is a severe form of DR which involves leakage of protein and fluid into the macula, the central portion of the retina, causing swelling and vascular damage. Prior to Ocuphire's in-licensing of the product candidate, APX3330 had been studied by other sponsors in a total of 11 clinical trials (6 Phase 1 and 5 Phase 2) in a total of over 420 healthy volunteers or patients (with over 340 APX3330-treated) for inflammatory and oncology indications, and had demonstrated evidence of tolerability, pharmacokinetics, durability, and target engagement. Ocuphire has also in-licensed APX2009 and APX2014, which are second-generation product candidates and analogs of APX3330. Ocuphire initiated a Phase 2 trial for APX3330 in April 2021 for the treatment of patients with DR, including moderately severe non-proliferative DR ("NPDR") and mild proliferative DR ("PDR"), as well as patients with DME without loss of central vision. In January 2022, Ocuphire reported masked safety data from the ongoing Phase 2 trial in DR/DME on 68 patients enrolled at the time. These safety data are consistent with safety data from the prior 11 clinical trials with total exposure experience of over 5000 subject days with 600 mg daily dose of APX3330. Ocuphire also reported enrollment completion of 103 patients in the ZETA-1 trial in March 2022, and expects to report top-line results from the ZETA-1 DR/DME Phase 2b study in the second half of 2022.

As part of its strategy, Ocuphire will continue to explore opportunities to acquire additional ophthalmic assets and seek strategic partners for late-stage development, regulatory preparation, and commercialization of drugs in key global markets.

Merger with Rexahn

On November 5, 2020, Rexahn Pharmaceuticals, Inc., or Rexahn, now known as Ocuphire Pharma, Inc., completed its reverse merger or, the “Merger”, with what was then known as “Ocuphire Pharma, Inc.,” or “Private Ocuphire”, in accordance with the terms of the Agreement and Plan of Merger and Reorganization dated as of June 17, 2020, as amended on June 29, 2020 (“Merger Agreement”). Rexahn’s shares of common stock listed on The Nasdaq Capital Market, previously trading through the close of business on November 5, 2020 under the ticker symbol “REXN,” commenced trading on The Nasdaq Capital Market, under the ticker symbol “OCUP,” on November 6, 2020.

Immediately following the Merger, Private Ocuphire became a wholly-owned subsidiary of Rexahn. Upon consummation of the Merger, Rexahn adopted the business plan of Private Ocuphire.

Although Rexahn was the legal acquirer and issued shares of its common stock to effect the Merger with Ocuphire, Ocuphire was considered the accounting acquirer. In accordance with the accounting guidance under Accounting Standards Update (“ASU”) 2017-01, the Merger was accounted for as an asset acquisition. Accordingly, the assets and liabilities of Rexahn were recorded as of the closing of the Merger at the purchase price of the accounting acquirer, Ocuphire. Ocuphire allocated the total purchase price among the individual assets acquired on a fair value basis or carrying value as appropriate. A final determination of these estimated fair values was based on the actual net tangible assets of Rexahn that existed as of the date of the completion of the transaction. As of the completion of the Merger, the net assets of Rexahn were recorded at their acquisition-date relative fair values in the consolidated financial statements of Ocuphire and the reported operating results prior to the Merger are those of Private Ocuphire.

Pursuant to the Merger Agreement, the number of shares of common stock issued to Private Ocuphire’s stockholders for each share of Ocuphire’s common stock outstanding immediately prior to the Merger was calculated using an exchange ratio (“Exchange Ratio”) of 1.0565 shares of Common Stock for each share of Private Ocuphire common stock.

Strategic Outlook

As part of its strategy, Ocuphire will continue to explore opportunities to acquire additional ophthalmic assets and to seek strategic partners for late-stage development, regulatory preparation and commercialization in key global markets. To date, Ocuphire’s primary activities have been conducting research and development activities, planning clinical trials, performing business and financial planning, recruiting personnel and raising capital. Ocuphire does not have any products approved for sale and has not generated any significant amounts of revenue. Ocuphire does not expect to generate significant revenues until, and unless, the FDA or other regulatory authorities approve Nyxol or APX3330 and Ocuphire successfully commercializes its product candidates. Until such time, if ever, as Ocuphire can generate substantial product revenue, Ocuphire expects to finance its cash needs through a combination of equity and debt financings as well as collaborations, strategic alliances and licensing arrangements. Through December 31, 2021, Ocuphire has funded its operations primarily through equity financings that totaled \$49.6 million in gross proceeds, of which \$21.15 million was received in connection with the Merger, net cash at Rexahn, a minor amount of license fee payments earned under license agreements related to Rexahn’s RX-3117 drug compound, and through the issuance of convertible notes in private placements that totaled \$8.5 million in gross proceeds. Ocuphire’s net losses were \$56.7 million and \$24.6 million for the years ended December 31, 2021 and 2020, respectively. As of December 31, 2021, Ocuphire had an accumulated deficit of \$89.4 million. Ocuphire anticipates that its expenses will increase substantially as it:

- continues clinical trials for Nyxol, APX3330 and for any other product candidate in its future pipeline;

- continues preclinical studies for Nyxol, APX3330 and for any other product candidate in its future pipeline;
- develops additional product candidates that it identifies, in-licenses or acquires;
- seeks regulatory approvals for any product candidates that successfully complete clinical trials;
- contracts to manufacture its product candidates;
- maintains, expands and protects its intellectual property portfolio;
- hires additional staff, including clinical, scientific, operational and financial personnel, to execute its business plan;
- adds operational, financial and management information systems and personnel, including personnel to support its product development and potential future commercialization efforts;
- continues to operate as a public company; and
- establishes on its own or with partners, a sales, marketing and distribution infrastructure to commercialize any products for which Ocuphire may obtain regulatory approval;

Ocuphire's net losses may fluctuate significantly from quarter-to quarter and year-to year, depending on the timing of its preclinical studies, clinical trials and its expenditures on other research and development activities as well as level of license fee payments received under license agreements in connection with the former Rexahn drug compounds.

Recent Developments

Clinical and CMC Milestones

In November 2021, clinical data on Nyxol and APX3330 was featured in poster sessions as presentations at the American Academy of Ophthalmology (AAO) 2021 annual meeting.

On January 5, 2022, it was announced that enrollment was complete in LYNX-1, a Phase 3 clinical trial evaluating the safety and efficacy of Nyxol eye drops for the treatment of NVD in 145 subjects.

On January 31, 2022, Ocuphire hosted a virtual investor R&D Day for the investment community. It featured six ophthalmic Key Opinion Leaders (KOLs) from refractive surgery, optometry and retina practice areas who shared their thoughts on three large unmet indications addressed by Ocuphire's two late-stage clinical drug assets. New masked safety data were presented that the Phase 2 ZETA-1 clinical trial demonstrated a favorable safety profile consistent with prior studies for the first-in-class APX3330 oral drug with additional exposure data in diabetic patients with retinal disease. In addition, new data from the Phase 2 VEGA-1 clinical trial were presented that show that Nyxol alone had statistically significant improvement in efficacy and long durability compared to placebo at 12 hours post-dosing supporting future clinical development as a single daily drop. A recording of the R&D Day is available under the News and Events section of Ocuphire's website.

On February 8, 2022, it was announced that enrollment was complete in MIRA-3, the second Phase 3 FDA registration trial evaluating the safety and efficacy of Nyxol eye drops to reverse pharmacologically-induced mydriasis (RM) in 368 subjects.

On March 8, 2022, it was announced that enrollment was complete in the MIRA-4 trial evaluating the safety and efficacy of Nyxol eye drops for RM in 23 pediatric subjects.

On March 16, 2022, it was announced that enrollment was complete in the ZETA-1 trial evaluating the safety and efficacy of oral APX3330 in 103 DR/DME subjects.

Regulatory Update

On February 14, 2022, Ocuphire completed a Type-C meeting with the FDA from which it obtained guidance regarding the design of pivotal studies for Nyxol both as a single agent and with LDP as adjunct eye drops for the treatment of presbyopia. In addition, the FDA provided clarification of CMC and other data requirements for filing an NDA to seek approvals of Nyxol.

COVID-19

As a result of the COVID-19 pandemic, Ocuphire has experienced, and will likely continue to experience, delays and disruptions in our clinical trials, as well as interruptions in our manufacturing and analytical lab operations, global supply chain and shipping, and clinical development operations.

Ocuphire's plans for further testing or clinical trials may be further impacted by the continuing effects of COVID-19. The global outbreak of COVID-19 continues to rapidly evolve. The extent to which the COVID-19 pandemic may further impact our business and clinical trials will depend on future developments, which are highly uncertain and cannot be predicted with confidence, such as the effect of the pandemic on our suppliers and distributors and the global supply chain, the ultimate geographic spread of the disease, the duration of the outbreak, travel restrictions and social distancing in the U.S. and other countries, business closures or business disruptions and the effectiveness of actions taken in the U.S. and other countries to contain and treat the disease. The COVID-19 pandemic may also continue to impact our business as a result of employee illness, school closures, and other community response measures.

The COVID-19 pandemic may also impact our ability to secure additional financing. Although Ocuphire cannot estimate the length or gravity of the impact of the COVID-19 outbreak at this time, if the pandemic continues, it may have a material adverse effect on the Company's results of future operations, financial position, and liquidity in for fiscal year 2022 and beyond.

See "Risk Factors—Risks Related to Our Business—The COVID-19 pandemic has and could continue to adversely impact Ocuphire's business, financial condition, cash flows, liquidity, and result in stock price volatility."

Financial Operations Overview

Collaborations Revenue

Collaborations revenue to date was derived from fees earned from license agreements with BioSense Global LLC ("BioSense") and Processa Pharmaceuticals, Inc. ("Processa") in connection with the Rexahn RX-3117 drug compound. We anticipate that we may earn additional revenues stemming from additional milestone and royalty payments from this or other license agreements related to Rexahn's legacy drug compounds; however, the attainment of milestones or level of sales required to earn royalty payments is highly uncertain for the reasons explained below.

To date, outside of the limited collaborations revenue referenced above, Ocuphire does not expect to generate significant revenue unless or until it obtains regulatory approval of and commercializes Nyxol or APX3330. If Ocuphire fails to complete the development of Nyxol, APX3330, or any other product candidate it may pursue in the future, in a timely manner, or fails to obtain regulatory approval, Ocuphire's ability to generate significant revenue would be compromised.

General and Administrative Expenses

General and administrative expenses consist primarily of personnel-related costs, including salaries, benefits and stock-based compensation costs, for personnel in functions not directly associated with research and administrative activities. Other significant costs include insurance coverage for directors and officers and other property and liability exposures, legal fees relating to intellectual property and corporate matters, professional fees for accounting and tax services, and other services provided by business consultants and legal settlements. Ocuphire anticipates that its general and administrative expenses will significantly increase in the future to support its continued research and development activities and costs associated with operating as a public company. These increases will include increased costs related to the hiring of additional personnel and fees for legal and professional services as well as other public-company related costs.

Research and Development Expenses

To date, Ocuphire's research and development expenses have related primarily to the clinical stage development of Nyxol and APX3330. Research and development expenses consist of costs incurred in performing research and development activities, including compensation and benefits for research and development employees and costs for consultants, costs associated with preclinical studies and clinical trials, regulatory activities, manufacturing activities to support clinical activities, license fees, nonlegal patent costs, fees paid to external service providers that conduct certain research and development, and an allocation of overhead expenses. Research and development costs are expensed as incurred and costs incurred by third parties are expensed as the contracted work is performed. Ocuphire accrues for costs incurred as the services are being provided by monitoring the status of the study or project, and the invoices received from its external service providers. Ocuphire adjusts its accrual as actual costs become known. Research and development activities are central to Ocuphire's business model.

Ocuphire expects that Nyxol and APX3330 will have higher development costs during their later stages of clinical development, as compared to costs incurred during their earlier stages of development, primarily due to the increased size and duration of the later-stage clinical trials. Ocuphire expects its research and development expenses to significantly increase over the next several years. However, it is difficult for Ocuphire to determine with certainty the duration, costs and timing to complete its current or future preclinical programs and clinical trials of Nyxol, APX3330, and other product candidates. The duration, costs and timing of clinical trials and development of Nyxol, APX3330 and other product candidates will depend on a variety of factors that include, but are not limited to, the following:

- per patient trial costs;
- the number of patients that participate in the trials;
- the number of sites included in the trials;
- the countries in which the trials are conducted;
- the length of time required to enroll eligible patients;
- the number of doses that patients receive;
- the drop-out or discontinuation rates of patients;
- potential additional safety monitoring or other studies requested by regulatory agencies;
- the duration of patient follow-up;
- the phase of development of the product candidate;
- arrangements with contract research organizations and other service providers; and
- the efficacy and safety profile of the product candidates.

Acquired In-Process Research and Development Expenses

Ocuphire includes costs to acquire or in-license product candidates as acquired in-process research and development expenses. These costs are immediately expensed provided that the payments do not also represent processes or activities that would constitute a "business" as defined under accounting standards generally accepted in the United States of America ("U.S. GAAP") or provided that the product candidate has not achieved regulatory approval for marketing and, absent obtaining such approval, has no alternative future use. Royalties owed on future sales of any licensed product will be expensed in the period the related revenues are recognized. The costs associated with the Merger and the Apexian Sublicense Agreement were recorded as acquired in-process research and development expenses ("IPR&D").

Interest Expense

Interest expense consists of interest costs related largely to interest on principal and to amortization of debt discount attributed to the Ocuphire convertible notes while these instruments were outstanding. The Ocuphire convertible notes had an annual interest rate of 8%. This category also includes interest on principal related to a short-term loan (related to financing an insurance policy) having an annual interest rate of 5.5%.

Fair Value Change in Warrant Liabilities and Premium Conversion Derivatives

The fair value change in warrant liabilities and premium conversion derivatives includes the change in the fair value of the warrant liabilities and the premium conversion derivatives during the period the premium conversion derivatives and warrant liabilities are outstanding.

Gain on Note Extinguishment

Gain on note extinguishment includes the gain associated with modifications made to the Ocuphire convertible notes that are accounted for as note extinguishments.

Other (Expense) Income, net

Other (expense) income, net reflected in this line item includes payments made by us in connection with the Contingent Value Rights Agreement (the “CVR Agreement”) with former Rexahn shareholders. In addition, Other (expense) income, net includes interest earned from cash and cash equivalent investments, realized and unrealized gains (losses) from equity investments and reimbursements in connection with grants and other sources.

Provision for Income Taxes

Provision for income taxes consists of federal and state income taxes in the United States, as well as deferred income taxes and changes in related valuation allowance reflecting the net tax effects of temporary differences between the carrying amounts of assets and liabilities for financial reporting purposes and the amounts used for income tax purposes. Currently, there is no provision for income taxes, as Ocuphire has incurred operating losses to date, and a full valuation allowance has been provided on the net deferred tax assets as of December 31, 2021 and 2020.

Results of Operations

The following table summarizes Ocuphire's operating results for the periods indicated (in thousands):

	For the Year Ended December 31,		
	2021	2020	Change
Collaborations revenue	\$ 589	\$ —	\$ 589
Operating expenses:			
General and administrative	8,121	2,818	5,303
Research and development	15,173	6,648	8,525
Acquired in-process research and development	—	10,502	(10,502)
Total operating expenses	23,294	19,968	3,326
Loss from operations	(22,705)	(19,968)	(2,737)
Interest expense	(2)	(6,847)	6,845
Fair value change in derivative and warrant liabilities	(33,829)	(1,486)	(32,343)
Gain on note extinguishment	—	3,672	(3,672)
Other (expense) income, net	(157)	9	(166)
Loss before income taxes	(56,693)	(24,620)	(32,073)
Provision for income taxes	—	—	—
Net loss	\$ (56,693)	\$ (24,620)	\$ (32,073)

Comparison of Years Ended December 31, 2021 and 2020

Collaborations Revenue

Collaborations revenue was \$0.6 million for the year ended December 31, 2021. Revenue during 2021 was derived from the collaboration and license agreements with Processa and BioSense related to certain technology transfers in connection with the Rexahn RX-3117 drug compound, a legacy asset not under development by Ocuphire. There was no collaborations revenue recognized during the prior year period.

General and Administrative

General and administrative expenses for the year ended December 31, 2021 were \$8.1 million compared to \$2.8 million for the year ended December 31, 2020. The \$5.3 million increase was primarily attributable to administrative employee headcount in the amount of \$0.8 million, stock-based compensation of \$0.4 million, insurance of \$0.9 million, legal costs of \$0.5 million, non-cash settlement costs of \$1.6 million with certain investors, costs associated with operating as a public company subsequent to the reverse merger of \$0.8 million, and professional services and other operating costs of \$0.3 million on a net basis. General and administrative expenses included \$1.1 million and \$0.7 million in stock-based compensation expense during the years ended December 31, 2021, and 2020, respectively.

Research and Development

Research and development expenses for the year ended December 31, 2021 were \$15.2 million compared to \$6.6 million for the year ended December 31, 2020. The \$8.5 million increase was primarily attributable to clinical trials of \$4.6 million, manufacturing activities to support clinical advancement of Nyxol and APX3330 of \$1.9 million, consulting services of \$1.1 million as well as regulatory and other research and development efforts of \$0.9 million on a net basis. Research and development expenses also included \$0.8 million in stock-based compensation expense during each of the years ended December 31, 2021 and 2020.

Acquired In-Process Research and Development Expenses

On January 21, 2020, Ocuphire entered into a sublicense agreement with Apexian for continued research and development and potential commercialization of its lead product, APX3330. Ocuphire issued 843,751 shares of its common stock to Apexian related to the Apexian Sublicense Agreement. The fair value of the common stock issued to Apexian was \$2.1 million and was recorded as IPR&D expense during the year ended December 31, 2022. In addition, research and development projects of Rexahn which were in-process at the Merger date were expensed as IPR&D and amounted to \$8.4 million. Current accounting standards require that the fair value of IPR&D with no alternative future use be charged to expense on the acquisition date. There were no IPR&D costs during the comparable current year period.

Interest Expense

Interest expense for the year ended December 31, 2021 of \$2,000 was attributable to a short-term loan (related to financing an insurance policy). Interest expense for the year ended December 31, 2020 was \$6.8 million (of which \$6.1 million was non-cash) and was primarily attributable to the amount by which the fair value of the Series A Warrants issued in connection with the Pre-Merger Financing exceeded proceeds, or \$4.7 million, as the Series A Warrants are classified as warrant liabilities. In addition, cash financing costs attributed to the Series A warrants in the amount of \$0.7 million also increased interest cost year-over-year. Lastly, interest on principal and amortization of debt discounts, in the aggregate of \$1.5 million, in connection with the Ocuphire convertible notes compromised the balance of interest expense during the year ended December 31, 2020.

Fair Value Change in Derivative and Warrant Liabilities

The fair value change in derivative and warrant liabilities was an expense of \$33.8 million for the year ended December 31, 2021 compared to an expense of \$1.5 million for the year ended December 31, 2020. The \$32.3 million change was due primarily to the issuance of the Series A warrants in connection with the Pre-Merger Financing and to the fluctuations in Ocuphire's common stock fair value and the number of potential shares of common stock issuable upon conversion of the underlying Ocuphire warrant liabilities and convertible notes that were outstanding during the relevant periods.

Gain on Note Extinguishment

Non-cash gain on note extinguishment for the year ended December 31, 2020 was \$3.7 million as a result of both the Note Conversion Agreement (as defined and further described below) of \$1.3 million and the conversion of the Ocuphire convertible notes in connection with the Merger. The Note Conversion Agreement was deemed to be a substantial modification to the Ocuphire convertible notes (as defined below), and as such, we recorded the modification as a note extinguishment. In addition, given that the Ocuphire convertible notes contained embedded derivatives, the conversion of the Ocuphire convertible notes into equity upon close of the Merger was also treated as a note extinguishment of \$2.4 million. There were no Ocuphire convertible notes outstanding during the current year period.

Other (Expense) Income, net

During the year ended December 31, 2021, Ocuphire had other expense of \$91,000 stemming from payments due in connection with the CVR Agreement and \$70,000 stemming principally from net unrealized losses from our short-term investments. Other expense during the year ended December 31, 2020 was negligible.

Other income during the year ended December 31, 2021 and 2020 was \$4,000 and \$9,000, respectively. Other income consisted primarily of interest earnings on our cash and cash equivalent investments during the year ended December 31, 2021. During the year ended December 31, 2020, Ocuphire had other income from cash and cash equivalent investments and from a grant received from the U.S. Small Business Administration for economic relief stemming from the COVID-19 pandemic.

Liquidity and Capital Resources

Capital Resources

As of December 31, 2021, Ocuphire's principal sources of liquidity consisted of cash and cash equivalents of \$24.5 million. Ocuphire believes that its cash on hand at the end of 2021 will be sufficient to fund its operations into the second quarter of 2023. The Company's cash and cash equivalents are invested primarily in cash deposits at a large, long-standing financial institution.

Ocuphire has not generated any revenue and anticipates that it will continue to incur losses for the foreseeable future. Future capital requirements depend on many factors, including the need for the following:

- continued clinical trials and preclinical studies for Nyxol, APX 3330 and for any other product candidate in its future pipeline;

- developing additional product candidates that it identifies, in-licenses or acquires;
- seeking regulatory approvals for any product candidates that successfully complete clinical trials;
- contracts to manufacture its product candidates;
- establishing on its own or with partners, a sales, marketing and distribution infrastructure to commercialize any products for which it may obtain regulatory approval;
- maintaining, expanding and protecting its intellectual property portfolio;
- hiring additional staff, including clinical, scientific, operational and financial personnel, to execute its business plan;
- adding operational, financial and management information systems and personnel, including personnel to support its product development and potential future commercialization efforts; and
- operating as a public company.

Historical Capital Resources

Ocuphire's primary source of cash to fund its operations has been various equity offerings in the amount of \$50.0 million and the issuance of convertible notes in the amount of \$8.5 million, inclusive of the promissory notes exchanged for Ocuphire convertible notes.

Registered Direct Offering

On June 4, 2021, the Company entered into a placement agency agreement with A.G.P./Alliance Global Partners ("AGP"). Pursuant to the terms of the placement agency agreement, AGP on June 8, 2021, sold an aggregate of 3,076,923 shares of the Company's common stock and warrants to purchase 1,538,461 shares of the Company's common stock (the "RDO Warrants") at an offering price of \$4.875 per share and 0.50 RDO Warrants, for gross proceeds of \$15.0 million, before deducting AGP's fees and related offering expenses in the amount of \$1.1 million. The purchase agreement contains customary representations, warranties and agreements by the Company, customary conditions to closing, indemnification obligations of the Company, other obligations of the parties and termination provisions.

The RDO Warrants have an exercise price of \$6.09 per share, are exercisable upon the initial issuance date of June 8, 2021, and will expire five years following the initial exercise date. Subject to limited exceptions, a holder of a RDO Warrant will not have the right to exercise any portion of its RDO Warrants if the holder, together with its affiliates, would beneficially own in excess of 4.99% (or, at the election of a holder prior to the date of issuance, 9.99%) of the number of shares of common stock outstanding immediately after giving effect to such exercise; provided, however, that upon prior notice to the Company, the holder may increase or decrease the beneficial ownership limitation, provided further that in no event shall the beneficial ownership limitation exceed 9.99%. As of December 31, 2021, 1,538,461 RDO Warrants were still outstanding.

The offering of the Securities was made pursuant to the Company's effective shelf registration statement on Form S-3.

At-The-Market Program

On February 4, 2021, Ocuphire filed a Form S-3 shelf registration under the Securities Act which was declared effective by the SEC on February 12, 2021 (the “2021 Shelf”) under which the Company may offer and sell, from time to time in its sole discretion, securities having an aggregate offering price of up to \$125 million. In connection with the 2021 Shelf, on March 11, 2021, Ocuphire entered into a Sales Agreement with JonesTrading Institutional Services LLC (“JonesTrading”) under which the Company may offer and sell, from time to time at its sole discretion, to or through JonesTrading, acting as agent and/or principal, shares of its common stock having an aggregate offering price of up to \$40 million (the “2021 ATM”). During the year ended December 31, 2021, 2,778,890 shares of common stock were sold under the 2021 ATM for gross proceeds in the amount of \$13.5 million before deducting issuance expenses in the amount of \$0.4 million.

Pre-Merger Financing

Securities Purchase Agreement

On June 17, 2020, Ocuphire, Rexahn and certain investors entered into a Securities Purchase Agreement, which was amended and restated in its entirety on June 29, 2020 (as amended and restated, the “Securities Purchase Agreement”). Pursuant to the Securities Purchase Agreement, the investors invested a total of \$21.15 million in cash, including \$300,000 invested by directors of Private Ocuphire and one director of Rexahn, upon closing of the Merger (the “Pre-Merger Financing”). Pursuant to the Pre-Merger Financing, (i) Ocuphire issued and sold to the investors shares of Private Ocuphire common stock (the “Initial Shares”) which converted pursuant to the exchange ratio in the Merger into an aggregate of 1,249,996 shares (the “Converted Initial Shares”) of common stock, (ii) Ocuphire deposited into escrow, for the benefit of the Investors, additional shares of Private Ocuphire common stock (the “Additional Shares”) which converted pursuant to the exchange ratio in the Merger into an aggregate of 3,749,992 shares of common stock (the “Converted Additional Shares”), which Converted Additional Shares were delivered (or became deliverable) to the investors on November 19, 2020, and (iii) the Company agreed to issue to each investor on the tenth trading day following the consummation of the Merger (x) Series A Warrants representing the right to acquire shares of common stock equal to the sum of (A) the Converted Initial Shares purchased by the investor, (B) the Converted Additional Shares delivered or deliverable to the investor, without giving effect to any limitation on delivery contained in the Securities Purchase Agreement and (C) the initial number of shares of common stock, if any, underlying the Series B Warrants issued to the Investor and (y) additional warrants to purchase shares of common stock.

Waiver Agreements

Effective February 3, 2021, each investor that invested in the Pre-Merger Financing (each, a “Holder”) entered into a Waiver Agreement with the Company (collectively, the “Waiver Agreements”). Pursuant to the Waiver Agreements, the Holders and the Company agreed to waive certain rights, finalize the exercise price and number of Series A Warrants and Series B Warrants, eliminate certain financing restrictions, extend the term of certain leak-out agreements, and, in the case of certain Holders, grant certain registration rights for the shares underlying the warrants.

The Waiver Agreements provide for the permanent waiver of the full ratchet anti-dilution provisions, contained in the Series A Warrants (as certain of the anti-dilution provisions had previously caused liability accounting treatment for the Series A Warrants). Upon the effective date of the Waiver Agreement, the Series A Warrants were reclassified to equity.

Pursuant to the Waiver Agreements, the number of shares underlying all of the Series B Warrants was fixed to 1,708,334 in the aggregate with respect to all Holders.

Series A Warrants

The Series A Warrants were issued on November 19, 2020 at an initial exercise price of \$4.4795 per share, were immediately exercisable upon issuance and have a term of five years from the date of issuance. The Series A Warrants are exercisable for 5,665,838 shares of common stock in the aggregate (without giving effect to any limitation on exercise contained therein). As of December 31, 2021, 5,665,838 Series A Warrants were still outstanding.

At issuance, the Series A Warrants contained certain provisions that could have resulted in a downward adjustment of the initial exercise price and an upward adjustment in the number of shares underlying the warrants if Ocuphire were to have issued or sold, or made an agreement to issue or sell, any shares of common stock for a price lower than the exercise price then in effect. Pursuant to the terms of the Waiver Agreements, these provisions are no longer in effect.

Series B Warrants

The Series B Warrants have an exercise price of \$0.0001, were exercisable upon issuance and will expire on the day following the later to occur of (i) the Reservation Date (as defined therein), and (ii) the date on which the investor's Series B Warrants have been exercised in full (without giving effect to any limitation on exercise contained therein) and no shares remain issuable thereunder. The Series B Warrants were initially exercisable for 665,836 shares of Common Stock in the aggregate (without giving effect to any limitation on exercise contained therein) and ultimately became exercisable for 1,708,334 shares of Common Stock upon execution of the Waiver Agreements. As of December 31, 2021, 78,700 Series B Warrants were still outstanding.

At issuance, the Series B Warrants contained certain provisions that could have resulted in the issuance of additional Series B Warrants depending on the dollar volume-weighted average prices of a share of Common Stock during a 45-trading day Reset Period. Pursuant to the terms of the Waiver Agreements, those provisions are no longer in effect.

Ocuphire Convertible Notes

From May 2018 through March 2020, Ocuphire issued convertible notes (the "Ocuphire convertible notes") for aggregate gross proceeds of \$8.5 million, inclusive of the promissory notes exchanged for Ocuphire convertible notes. The final closing of the Ocuphire convertible notes occurred on March 10, 2020. The Ocuphire convertible notes had an interest rate of 8% per annum. On November 4, 2020, all of Ocuphire's outstanding notes were converted into 977,128 shares of Ocuphire common stock as adjusted for the Exchange Ratio in connection with the completion of the Merger.

The original Convertible Note Purchase Agreement (the "Note Purchase Agreement") was dated May 25, 2018. Under the original terms of the Note Purchase Agreement, the Ocuphire convertible notes were payable on demand on July 31, 2019 unless converted earlier pursuant to their terms. Such conversion would automatically occur if Ocuphire (i) completed an initial public offering ("IPO"), (ii) completed a change in control ("CIC"), (iii) completed a sale and issuance of its capital stock resulting in gross proceeds to Ocuphire of at least \$5.0 million ("Qualified Financing"), or (iv) completed a reverse merger transaction ("Reverse Merger"), each a "Conversion Event". Upon a Conversion Event, the Ocuphire convertible notes would have automatically converted into the following:

- *Qualified Financing or IPO:* An amount of shares of Ocuphire common stock equal to 135% of the Note Value *divided by* the per share price of Ocuphire common stock issued to purchasers in the Qualified Financing or IPO.
- *CIC:* An amount of shares of Ocuphire common stock equal to 200% of the Note Value *divided by* the per share price of Ocuphire common stock based on the valuation of such CIC.
- *Reverse Merger:* Either (i) shares of Ocuphire common stock issued in the Reverse Merger or (ii) equity securities of the Reverse Merger counterparty, in an amount equal to 135% of the Note Value *divided by* the per share price at which such shares were issued to either stockholders of Ocuphire or stockholders of the Reverse Merger counterparty.

The Note Purchase Agreement was amended and restated on January 22, 2019 (the "Amended and Restated Mezz Note Purchase Agreement"). Under the Amended and Restated Mezz Note Purchase Agreement, the demand date of the Ocuphire convertible notes was extended to December 31, 2019 and the conversion provisions under the Ocuphire convertible notes were restated such that, upon a Conversion Event, the Ocuphire convertible notes would have automatically converted into the following:

- *IPO*: An amount of shares of Ocuphire common stock equal to the greater of: (i) 150% of the Note Value *divided by* the per share price of Ocuphire common stock issued to purchasers in the IPO, and (ii) 100% of the Note Value *divided by* the per share price of \$10.37.
- *CIC*: An amount of shares of Ocuphire common stock equal to the greater of: (i) 200% of the Note Value *divided by* the per share price of Ocuphire common stock based on the valuation of such CIC, and (ii) 100% of the Note Value *divided by* the per share price of \$10.37.
- *Qualified Financing*: An amount of shares of Ocuphire common stock equal to 150% of the Note Value *divided by* the per share price of Ocuphire common stock issued to purchasers in the Qualified Financing.
- *Reverse Merger*: Either shares of Ocuphire common stock issued in the Reverse Merger or equity securities of the Reverse Merger counterparty, in an amount equal to the greater of: (i) 150% of the Note Value *divided by* the per share price at which such shares were issued to either stockholders of Ocuphire or stockholders of the Reverse Merger counterparty, and (ii) 100% Note Value *divided by* the per share price of \$10.37.

The Amended and Restated Mezz Note Purchase Agreement was further amended on November 20, 2019 (the “First Amendment”). The terms under the First Amendment reflect the current terms in effect for the Ocuphire convertible notes as of the date of this Annual Report, except as further amended by the Note Conversion Agreement (defined below). The First Amendment extended the demand date of the Ocuphire convertible notes from December 31, 2019 to September 30, 2020, and changed the basis of interest from a 360-day year, 30-day month basis to a 365-day year basis. In addition, the First Amendment increased the automatic conversion factor applied to the Note Value to 175% in the event of an IPO, Qualified Financing or Reverse Merger and removed the fixed conversion option provision of \$10.37 per share in the event of an IPO, CIC or Reverse Merger.

On June 8, 2020, holders of the Ocuphire convertible notes entered into the Note Conversion Agreement with Ocuphire (the “Note Conversion Agreement”). The Note Conversion Agreement provided that prior to the consummation of the merger, following the Rexahn special meeting, all of the Ocuphire convertible notes would automatically convert into an amount of shares of Ocuphire common stock equal to 175% of the Note Value divided by the Fully Diluted Shares. “Fully Diluted Shares” for this purpose means as of the Conversion Date the sum of the following: (1) all of the issued outstanding shares of Ocuphire common stock; and (2) the aggregate number of shares of Ocuphire common stock reserved for issuance under all outstanding options or other awards under equity incentive plans of Ocuphire in effect as of the date of conversion.

The Note Conversion Agreement further provided that upon the issuance of shares of Ocuphire common stock in the conversion, each convertible note would be cancelled and extinguished without the need for surrender of such notes and all obligations of Ocuphire, including any obligations for payment of principal and interest on the convertible notes, would be unconditionally and irrevocably discharged.

Cash Flows

The following table summarizes Ocuphire’s cash flows for the periods indicated (in thousands):

	For the Year Ended	
	December 31,	
	2021	2020
Net cash used in operating activities	\$ (19,370)	\$ (6,797)
Net cash (used in) provided by investing activities	(100)	539
Net cash provided by financing activities	27,605	21,120
Net increase in cash and cash equivalents	<u>\$ 8,135</u>	<u>\$ 14,862</u>

Cash Flow from Operating Activities

For the year ended December 31, 2021, cash used in operating activities of \$19.4 million was attributable to a net loss of \$56.7 million, partially offset by \$37.1 million in non-cash operating expenses and a net change of \$0.2 million in Ocuphire's net operating assets and liabilities. The non-cash expenses consisted largely of stock-based compensation of \$1.9 million, fair value change in warrant liabilities in the amount of \$33.8 million, a share settlement with certain investors in the amount of \$1.6 million and non-cash impact from the receipt of common stock stemming from the fulfillment of revenue milestones (\$0.2) million. The change in operating assets and liabilities was primarily attributable to an overall net increase in Ocuphire's accounts payable offset in part by both an increase in prepaid expenses and a decrease in accrued expenses associated with the fluctuations of Ocuphire's operating expenses.

For the year ended December 31, 2020, cash used in operating activities of \$6.8 million was attributable to a net loss of \$24.6 million, partially offset by \$16.7 million in non-cash operating expenses and a net change of \$1.1 million in Ocuphire's net operating assets and liabilities. The non-cash expenses consisted of IPR&D in the amount \$10.5 million, day-one interest attributed to the issuance of Series A Warrants in the amount of \$4.7 million, stock-based compensation of \$1.5 million, non-cash interest and discount amortization related to the Ocuphire convertible notes of \$1.5 million, a fair value change in derivative and warrant liabilities in the amount of \$1.5 million, a reclassification of issuance costs to financing activities in the amount of \$0.7 million and depreciation expense of \$8,000, offset by a non-cash gain on note extinguishment of \$3.7 million. The change in operating assets and liabilities was primarily attributable to an overall net increase in Ocuphire's accrued liabilities and accounts payable offset in part by an increase in prepaid expenses associated with the fluctuations of Ocuphire's operating expenses and in connection with transaction costs attributed to the Merger.

Cash Flow from Investing Activities

During the years ended December 31, 2021 and 2020, net cash (used in) provided by investing activities was \$(0.1) million and \$0.5 million, respectively. Investing activities during the current year period related to the payment of the remaining transaction costs associated with the Merger. During the prior year period ended December 31, 2020, investing activities consisted of cash acquired, net of transaction costs paid, in connection with the Merger.

Cash Flow from Financing Activities

Net cash provided by financing activities during the year ended December 31, 2021 was \$27.6 million relating principally to proceeds received in connection with both the Registered Direct Offering and 2021 ATM, net of issuance costs, in the amount of \$27.0 million. Proceeds, net of payments, received in connection with a short-term loan in the amount of \$0.5 million and the exercise of stock options in the amount of \$0.1 million comprised the balance of financing activities during the period.

Net cash provided by financing activities during the year ended December 31, 2020 was \$21.1 million, consisting primarily of net proceeds as a result of the Pre-Merger Financing in the amount of \$19.4 million and from the issuance of the Ocuphire convertible notes in the amount of \$2.2 million, offset in part by the cash settlement of Rexahn warrants post-Merger in the amount of \$0.5 million.

Liquidity and Capital Resource Requirements

Ocuphire has no current source of revenue to sustain its present activities, and Ocuphire does not expect to generate revenue until, and unless, the FDA or other regulatory authorities approve Nyxol or APX3330 and it successfully commercializes its product candidates. Until such time, if ever, as Ocuphire can generate substantial product revenue, it expects to finance its cash needs through a combination of equity and debt financings as well as collaborations, strategic alliances and licensing arrangements. Ocuphire does not have any committed external source of funds. To the extent that Ocuphire raises additional capital through the sale of equity or convertible debt securities, the ownership interest of Ocuphire's stockholders will be diluted, and the terms of these securities may include liquidation, warrants, or other preferences that adversely affect your rights as a common stockholder. Debt financing, if available, may involve agreements that include covenants limiting or restricting Ocuphire's ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends. If Ocuphire raises additional funds through collaborations, strategic alliances or licensing arrangements with pharmaceutical partners, Ocuphire may have to relinquish valuable rights to its technologies, future revenue streams or grant licenses on terms that may not be favorable to Ocuphire. If Ocuphire is unable to raise additional funds through equity or debt financings or through collaborations, strategic alliances or licensing arrangements when needed, Ocuphire may be required to delay, limit, reduce or terminate its product development, future commercialization efforts, or grant rights to develop and market its product candidates that Ocuphire would otherwise prefer to develop and market itself.

Future Capital Requirements

Ocuphire's independent registered public accounting firm included an explanatory paragraph in its report on Ocuphire's financial statements as of and for the years ended December 31, 2021 and 2020, noting the existence of substantial doubt about its ability to continue as a going concern. This uncertainty arose from management's review of Ocuphire's results of operations and financial condition and its conclusion that, based on Ocuphire's operating plans, Ocuphire did not have sufficient existing working capital to sustain operations substantially beyond twelve months following the date of this filing. To continue to fund operations, Ocuphire will need to raise capital. Ocuphire may obtain additional financing in the future through the issuance of common stock, through other equity or debt financings or through collaborations or partnerships with other companies. Ocuphire may not be able to raise additional capital on terms acceptable to it, or at all, and any failure to raise capital as and when needed could compromise Ocuphire's ability to execute on its business plan.

The development of Nyxol and APX3330 is subject to numerous uncertainties, and Ocuphire has based these estimates on assumptions that may prove to be substantially different than what Ocuphire currently anticipates and could result in cash resources being used sooner than what Ocuphire currently expects. Additionally, the process of advancing early-stage product candidates and testing product candidates in clinical trials is costly, and the timing of progress in these clinical trials is uncertain. Ocuphire's ability to successfully transition to profitability will be dependent upon achieving a level of product sales adequate to support its cost structure. Ocuphire cannot give any assurance that it will ever be profitable or generate positive cash flow from operating activities.

Contractual Obligations and Commitments

Facility Lease

Ocuphire leases a facility under a non-cancellable operating lease that commenced on June 8, 2019 and expires on December 31, 2022, as amended, for a base rent in the amount of \$3,000 per month.

Apexian Sublicense Agreement

On January 21, 2020, Ocuphire entered into the Apexian Sublicense Agreement, pursuant to which it obtained exclusive worldwide patent and other intellectual property rights that constitute a Ref-1 Inhibitor program relating to therapeutic applications to treat disorders related to ophthalmic and diabetes mellitus conditions. The lead compound in the Ref-1 Inhibitor program is APX3330, which Ocuphire intends to develop as an oral tablet therapeutic to treat DR and diabetic macular edema, and potentially wAMD.

In connection with the Apexian Sublicense Agreement, Ocuphire issued 843,751 shares of Private Ocuphire common stock to Apexian and certain of Apexian's affiliates. The share issuance transaction was recorded in the amount of \$2.1 million as IPR&D expense for the year ended December 31, 2020 based on the fair market value of the common shares issued since no processes or activities that would constitute a "business" were acquired and none of the rights and underlying assets acquired had alternative future uses or reached a stage of technological feasibility. Ocuphire also reimbursed Apexian \$0.4 million of Ref-1 Inhibitor program costs during 2020.

Ocuphire agreed to make one-time milestone payments under the Apexian Sublicense Agreement for each of the first ophthalmic indication and the first diabetes mellitus indication. These milestone payments include (i) payments for specified developmental and regulatory milestones (including completion of the first Phase 2 trial and the first Phase 3 pivotal trial in the United States, and filing and achieving regulatory approval from the FDA for the first New Drug Application for a compound) totaling up to \$11 million in the aggregate and (ii) payments for specified sales milestones of up to \$20 million in the aggregate, each of which net sales milestone payments is payable once, upon the first achievement of such milestone.

Lastly, Ocuphire also agreed to make royalty payments equal to a single-digit percentage of its net sales of products covered by the patents under the Apexian Sublicense Agreement. None of the milestone or royalty payments were triggered as of the date of this Annual Report.

Other Commitments

In the course of normal operations, Ocuphire entered into cancellable purchase commitments with its suppliers for various key research, clinical and manufacturing services. The purchase commitments covered by these arrangements are subject to change based on Ocuphire's research and development efforts.

Other Funding Requirements

As noted above, certain of our cash requirements relate to the funding of our ongoing research and development of Nyxol and APX3330, inclusive of any potential milestone and royalty obligations under our intellectual property licenses. See "Part I, Item 1— Business—Nyxol and APX3330 Clinical Experience Summaries —Ocuphire Clinical Development Plan —Future Planned Nyxol Trials—Potential Clinical Plans for APX3330—Future In-Licensing and Acquisition Opportunities—Manufacturing—Apexian Sublicense Agreement— Review and Approval of Drugs in the United States" in our Annual Report for a discussion of design, development, pre-clinical and clinical activities that we may conduct in the future, including expected cash expenditures required for some of those activities, to the extent we are able to estimate such costs.

Our other cash requirements within the next twelve months include accounts payable, accrued expenses, purchase commitments and other current liabilities. Our other cash requirements greater than twelve months from various contractual obligations and commitments may include operating leases and contractual agreements with third-party service providers for clinical research, product development, manufacturing, supplies, payroll, equipment maintenance, and audits for periods into calendar year 2023. Refer to Note 3 – Commitments and Contingencies included in "Part II, Item 8 – Financial Statements and Supplementary Data" in this Annual Report for further detail of our lease obligation and license agreements with regard to the timing of expected future payments.

We expect to satisfy our short-term and long-term obligations through cash on hand and from future equity and debt financings until we generate an adequate level of revenue from commercial sales to cover expenses, if ever.

Critical Accounting Policies and Estimates

Ocuphire's financial statements are prepared in accordance with U.S. GAAP. These accounting principles require Ocuphire to make estimates and judgments that can affect the reported amounts of assets and liabilities as of the date of the financial statements as well as the reported amounts of revenue and expense during the periods presented. Ocuphire believes that the estimates and judgments upon which it relies are reasonably based upon information available to Ocuphire at the time that it makes these estimates and judgments. To the extent that there are material differences between these estimates and actual results, Ocuphire's financial results will be affected. The accounting policies that reflect Ocuphire's more significant estimates and judgments and which it believes are the most critical to aid in fully understanding and evaluating its reported financial results are described below.

Our significant accounting policies are discussed in Note 1 — Company Description and Summary of Significant Accounting Policies, included in "Part II, Item 8 – Financial Statements and Supplementary Data" of this Annual Report. We believe that the following accounting policies and estimates are the most critical to aid in fully understanding and evaluating our reported financial results. These estimates require our most difficult, subjective, or complex judgments because they relate to matters that are inherently uncertain. We have reviewed these critical accounting policies and estimates and related disclosures with the Audit Committee of our Board of Directors. We have not made any material changes to date, nor do we believe there is a reasonable likelihood of a material future change to the accounting methodologies for the areas described below.

Collaborations Revenue

We account for collaborations revenue in accordance with the provisions of the Financial Accounting Standards Board (“FASB”) Accounting Standards Codification (“ASC”) 606, *Revenue from Contracts with Customers*. The guidance provides a unified model to determine how revenue is recognized. We have entered into license agreements which have revenue recognition implications. For discussion about the determination of collaborations revenue, see Note 10 — Collaboration and License Agreements included in “Part II, Item 8 – Financial Statements and Supplementary Data” of this Annual Report. To date, we have not had, nor do we expect to have in the future, significant variable consideration adjustments related to our collaborations revenue.

Warrant Liabilities

Following the Merger, Ocuphire issued the Series A Warrants in connection with the Pre-Merger Financing, and assumed Rexahn warrants issued prior to the Merger. Ocuphire accounts for these warrants as a liability at fair value as long as certain provisions precluding equity accounting treatment are present. Upon the execution of the Waiver Agreements described in Note 9 — Stockholders’ Equity (Deficit) included in “Part II, Item 8 – Financial Statements and Supplementary Data” of this Annual Report, the Series A Warrants were no longer subject to cash settlement or indexation provisions precluding equity classification, and as a result, not subject to fair value remeasurement. Ocuphire will continue to adjust the Rexahn warrant liability for changes in fair value until the earlier of the exercise, expiration, or until such time that cash settlement or indexation provisions are no longer in effect for the Rexahn warrants. We do not expect that the fluctuations in fair value attributed to the Rexahn warrant liability will be significant.

Share-based Compensation

Ocuphire accounts for share-based compensation in accordance with the provisions of ASC 718, Compensation — Stock Compensation. Accordingly, compensation costs related to equity instruments granted are recognized at the grant date fair value which is not subject to remeasurement. We record equity instrument forfeitures when they occur. For discussions about the application of grant date fair value associated with our share-based compensation, see Note 9 — Share-based Compensation included in “Part II, Item 8 – Financial Statements and Supplementary Data” of this Annual Report.

Income Tax Assets and Liabilities

Currently, there is no provision for income taxes, as we have incurred operating losses to date, and a full valuation allowance has been provided on our net deferred tax assets. For additional information, see Note 12 — Income Taxes included in “Part II, Item 8 – Financial Statements and Supplementary Data” of this Annual Report.

Contingencies

We are subject to numerous contingencies arising in the ordinary course of business, including obligations related to certain license agreements. For additional information, see Note 3 — Commitments and Contingencies included in “Part II, Item 8 – Financial Statements and Supplementary Data” of this Annual Report.

Recent Accounting Pronouncements

From time to time the FASB, or other standard-setting bodies, issue new accounting pronouncements. Where applicable, Ocuphire adopts these new standards according to the specified effective dates. Unless otherwise disclosed in the notes to the financial statements appearing in this annual report, Ocuphire believes that the impact of any recently issued standard(s) that are not yet effective will not have a material impact on its financial position or results of operations upon adoption. See Note 1, “Company Description and Summary of Significant Accounting Policies,” in the notes to Ocuphire’s financial statements for a more in-depth discussion of recently issued accounting standard(s).

ITEM 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

Not applicable.

ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

The information required by this item is included in this Annual Report beginning on page F-1 and is incorporated herein by reference.

ITEM 9. CHANGES IN AND DISAGREEMENTS WITH ACCOUNTANTS ON ACCOUNTING AND FINANCIAL DISCLOSURE

None.

ITEM 9A. CONTROLS AND PROCEDURES

Evaluation of Disclosure Controls and Procedures

As required by Rule 13a-15(b) of the Securities Exchange Act of 1934, as amended, or the Exchange Act, under the direction of the Chief Executive Officer and the principal financial officer, we have evaluated our disclosure controls and procedures as of the end of the period covered by this Annual Report. Based on this evaluation, our Chief Executive Officer and principal financial officer have concluded that our disclosure controls and procedures were effective as of the end of the period covered by this Annual Report.

Management's Annual Report on Internal Control over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting to provide reasonable assurance regarding the reliability of our financial reporting and the preparation of financial statements for external purposes in accordance with U.S. generally accepted accounting principles. Internal control over financial reporting includes those policies and procedures that: (i) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of our assets; (ii) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with U.S. generally accepted accounting principles, and that our receipts and expenditures are being made only in accordance with authorizations of our management and Board; and (iii) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use or disposition of our assets that could have a material effect on the financial statements.

Our management, including our Chief Executive Officer and principal financial officer, recognizes that our internal control over financial reporting cannot prevent or detect all errors and all fraud. A control system, no matter how well designed and operated, can provide only reasonable, not absolute, assurance that the control system's objectives will be met. The design of a control system must reflect the fact that there are resource constraints, and the benefits of controls must be considered relative to their costs. Further, because of the inherent limitations in all control systems, no evaluation of controls can provide absolute assurance that misstatements due to error or fraud will not occur or that all control issues and instances of fraud, if any, have been detected. The design of any system of controls is based in part on certain assumptions about the likelihood of future events, and there can be no assurance that any design will succeed in achieving its stated goals under all potential future conditions.

Management, with the participation of the Chief Executive Officer and principal financial officer, assessed our internal control over financial reporting as of December 31, 2021, the end of our fiscal year. Management based its assessment on criteria established in Internal Control—Integrated Framework (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission. Based on that evaluation, management has concluded that the Company's internal control over financial reporting was effective as of December 31, 2021.

Changes in Internal Control over Financial Reporting

There were no changes in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) that occurred during the quarter ended December 31, 2021 which have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

ITEM 9B. OTHER INFORMATION

None.

ITEM 9C. DISCLOSURE REGARDING FOREIGN JURISDICTIONS THAT PREVENT INSPECTIONS

Not applicable.

PART III

We will file a definitive Proxy Statement for our 2022 Annual Meeting of Stockholders (the “2022 Proxy Statement”) with the SEC, pursuant to Regulation 14A, not later than 120 days after the end of our fiscal year. Accordingly, certain information required by Part III has been omitted under General Instruction G(3) to Form 10-K. Only those sections of the 2022 Proxy Statement that specifically address the items set forth herein are incorporated by reference.

ITEM 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE

The information required by Item 10 is hereby incorporated by reference to the sections of the 2022 Proxy Statement under the captions “Board and Committee Information” and “Proposal No. 1 – Election of Directors,” “Executive Officers”.

ITEM 11. EXECUTIVE COMPENSATION

The information required by Item 11 is hereby incorporated by reference to the sections of the 2022 Proxy Statement under the captions “Executive Compensation” and “Proposal No. 1 – Election of Directors – Non-Employee Director Compensation.”

ITEM 12. SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT AND RELATED STOCKHOLDER MATTERS

The information required by Item 12 is hereby incorporated by reference to the sections of the 2022 Proxy Statement under the captions “Security Ownership of Certain Beneficial Owners and Management” and “Securities Authorized for Issuance under Equity Compensation Plans.”

ITEM 13. CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS, AND DIRECTOR INDEPENDENCE

The information required by Item 13 is hereby incorporated by reference to the sections of the 2022 Proxy Statement under the captions “Certain Relationships and Related-Party Transactions” and “Board and Committee Information.”

ITEM 14. PRINCIPAL ACCOUNTANT FEES AND SERVICES

The information required by Item 14 is hereby incorporated by reference to the sections of the 2022 Proxy Statement under the caption “Proposal No. 2 – Ratification of Independent Registered Public Accounting Firm.”

PART IV

The following documents are filed as a part of this Annual Report on Form 10-K:

- (a) Financial Statements: The financial statements filed as part of this report are listed in Part II, Item 8.
- (b) Financial Statement Schedules: The schedules are either not applicable or the required information is presented in the consolidated financial statements or notes thereto.
- (c) Exhibits: The following exhibits are incorporated by reference or filed as part of this Annual Report on Form 10-K:

ITEM 15. EXHIBITS, FINANCIAL STATEMENT SCHEDULES

EXHIBIT NUMBER	DESCRIPTION OF DOCUMENT
2.1+	Agreement and Plan of Merger, dated as of June 17, 2020, by and among the Registrant, Razor Merger Sub, Inc. and Ocuphire Pharma, Inc. (incorporated by reference to Exhibit 2.1 to the Registrant’s Current Report on Form 8-K, filed on June 19, 2020)..
2.2	First Amendment to Agreement and Plan of Merger and Reorganization, dated as of June 29, 2020, by and among Rexahn, Merger Sub and Ocuphire (incorporated by reference to Exhibit 2.1 to the Registrant’s Current Report on Form 8-K , filed on July 1, 2020).
3.1	Amended and Restated Certificate of Incorporation of the Registrant (incorporated by reference to Appendix G to the Registrant’s Definitive Proxy Statement on Schedule 14A, filed on April 29, 2005).
3.2	Certificate of Amendment of Amended and Restated Certificate of Incorporation of the Registrant (incorporated by reference to Exhibit 3.1 to the Registrant’s Current Report on Form 8-K, filed on May 5, 2017).
3.3	Certificate of Amendment of Amended and Restated Certificate of Incorporation of the Registrant (incorporated by reference to Exhibit 3.1 to the Registrant’s Current Report on Form 8-K, filed on August 30, 2018).
3.4	Certificate of Amendment of Amended and Restated Certificate of Incorporation of the Registrant (incorporated by reference to Exhibit 3.1 to the Registrant’s Current Report on Form 8-K, filed on April 12, 2019).
3.5	Certificate of Amendment of Amended and Restated Certificate of Incorporation (incorporated by reference to Exhibit 3.1 to the Registrant’s Current Report on Form 8-K, filed on November 6, 2020).
3.6	Certificate of Amendment of Amended and Restated Certificate of Incorporation (incorporated by reference to Exhibit 3.2 to the Registrant’s Current Report on Form 8-K, filed on November 6, 2020).
3.7	Second Amended and Restated Bylaws of the Registrant (incorporated by reference to Exhibit 3.3 to the Registrant’s Current Report on Form 8-K, filed on November 6, 2020).
4.1	Specimen Certificate for the Registrant’s Common Stock, par value \$.0001 per share (incorporated by reference to Exhibit 4.3 to the Registrant’s Registration Statement on Form S-8 (File No. 333-129294), filed on October 28, 2005).
4.2	Form of Common Stock Purchase Warrant (incorporated by reference to Exhibit 4.1 to the Registrant’s Current Report on Form 8-K, filed on November 6, 2015).
4.3	Form of Common Stock Purchase Warrant (incorporated by reference to Exhibit 4.1 to the Registrant’s Current Report on Form 8-K, filed on February 26, 2016).
4.4	Form of Common Stock Purchase Warrant (incorporated by reference to Exhibit 4.1 to the Registrant’s Current Report on Form 8-K, filed on September 14, 2016).

4.5	Form of Common Stock Purchase Warrant (incorporated by reference to Exhibit 4.1 to the Registrant's Current Report on Form 8-K, filed on June 7, 2017).
4.6	Form of Common Stock Purchase Warrant (incorporated by reference to Exhibit 4.1 to the Registrant's Current Report on Form 8-K, filed on October 13, 2017).
4.7	Form of Common Stock Purchase Warrant (incorporated by reference to Exhibit 4.1 to the Registrant's Current Report on Form 8-K, filed on October 19, 2018).
4.8	Form of Common Stock Purchase Warrant (incorporated by reference to Exhibit 4.1 to the Registrant's Current Report on Form 8-K, filed on January 25, 2019).
4.9	Stockholders Agreement, dated as of April 10, 2018, among Ocuphire Pharma, Inc. and Stockholders as defined therein (incorporated by reference to Exhibit 4.9 to the Registrant's Registration Statement on Form S-4 (File No. 333-239702), filed on September 30, 2020).
4.10	Form of Series A/B Warrants (incorporated by reference to Exhibit 4.1 to the Registrant's Current Report on Form 8-K, filed on July 1, 2020).
4.11	Description of Securities (incorporated by reference to Exhibit 4.11 to the Registrant's Annual Report on Form 10-K, filed on March 11, 2021).
4.12	Form of Warrant to purchase shares of common stock (incorporated by reference to Exhibit 4.1 to the Registrant's Current Report on Form 8-K/A, filed on June 7, 2021).
10.1*++	Amended and Restated Employment Agreement by and among the Company and Mina Sooch, effective as of November 5, 2020 (incorporated by reference to Exhibit 10.27 to the Registrant's Registration Statement on Form S-4 (File No. 333-239702), filed on September 30, 2020).
10.2*	Amended and Restated Employment Agreement by and among the Company and Bernhard Hoffmann, effective as of November 5, 2020 (incorporated by reference to Exhibit 10.29 to the Registrant's Registration Statement on Form S-4 (File No. 333-239702), filed on September 30, 2020).
10.3*	Form of Indemnification Agreement (incorporated by reference to Exhibit 10.30 to the Registrant's Registration Statement on Form S-4 (File No. 333-239702), filed on September 30, 2020).
10.4++	Sublicense Agreement, dated as of January 21, 2020, by and between Ocuphire Pharma, Inc. and Apexian Pharmaceuticals, Inc (incorporated by reference to Exhibit 10.31 to the Registrant's Registration Statement on Form S-4 (File No. 333-239702), filed on September 30, 2020).
10.4.1	First Amendment to Sublicense Agreement, dated as of June 4, 2020, by and between Apexian Pharmaceuticals, Inc. and Ocuphire Pharma, Inc (incorporated by reference to Exhibit 10.32 to the Registrant's Registration Statement on Form S-4 (File No. 333-239702), filed on September 30, 2020).
10.5	Lease Agreement, dated as of May 19, 2019, by and between Ocuphire Pharma, Inc. and Duke & Duke, LP (incorporated by reference to Exhibit 10.33 to the Registrant's Registration Statement on Form S-4 (File No. 333-239702), filed on September 30, 2020).
10.5.1	First Amendment to Lease Agreement, dated as of October 29, 2019, by and between Ocuphire Pharma, Inc. and Duke & Duke, LP (incorporated by reference to Exhibit 10.34 to the Registrant's Registration Statement on Form S-4 (File No. 333-239702), filed on September 30, 2020).
10.5.2	Second Lease Amendment, dated as of November 17, 2020, by and between the Company and Duke & Duke (incorporated by reference to Exhibit 10.43 to the Registrant's Annual Report on Form 10-K, filed on March 11, 2021)
10.5.3	Third Lease Amendment, dated as of September 9, 2021, by and between the Company and Duke & Duke. (incorporated by reference to Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q, filed on November 12, 2021)
10.6*	Ocuphire Pharma, Inc. 2018 Equity Incentive Plan, dated as of April 9, 2018 (incorporated by reference to Exhibit 10.35 to the Registrant's Registration Statement on Form S-4 (File No. 333-239702), filed on September 30, 2020).
10.6.1*	First Amendment to 2018 Equity Incentive Plan, dated as of December 23, 2019 (incorporated by reference to Exhibit 10.36 to the Registrant's Registration Statement on Form S-4 (File No. 333-239702), filed on September 30, 2020).
10.6.2*	Form of Option Agreement issuable under the Ocuphire Pharma, Inc. 2018 Equity Incentive Plan (incorporated by reference to Exhibit 10.37 to the Registrant's Registration Statement on Form S-4 (File No. 333-239702), filed on September 30, 2020).

10.7*	Ocuphire Pharma, Inc. 2020 Equity Incentive Plan (incorporated by reference to Exhibit 10.38 to the Registrant’s Registration Statement on Form S-4 (File No. 333-239702), filed on September 30, 2020).
10.8	Contingent Value Rights Agreement, dated as of November 5, 2020, by and among the Company, Shareholder Representative Services LLC and the Olde Monmouth Stock Transfer Co., Inc. (incorporated by reference to Exhibit 10.4 to the Registrant’s Current Report on Form 8-K, filed on November 6, 2020).
10.9*	Ocuphire Pharma, Inc. 2021 Inducement Plan (incorporated by reference to Exhibit 10.41 to the Registrant’s Annual Report on Form 10-K, filed on March 11, 2021)
10.10*	Employment Agreement dated November 11, 2020, by and between the Company and Amy Rabourn (incorporated by reference to Exhibit 10.42 to the Registrant’s Annual Report on Form 10-K, filed on March 11, 2021)
10.11	Capital on Demand™ Sales Agreement, dated March 11, 2021 between the Company and JonesTrading Institutional Services LLC (incorporated by reference to Exhibit 1.1 to the Registrant’s Current Report on Form 8-K, filed on March 11, 2021).
10.12	Form of Securities Purchase Agreement, dated as of June 4, 2021, by and among Ocuphire Pharma, Inc. and the purchasers identified on the signature pages thereto (incorporated by reference to Exhibit 10.1 to the Registrant’s Current Report on Form 8-K/A, filed on June 7, 2021).
10.13	Processa License Agreement dated June 16, 2021 (incorporated by reference to Exhibit 10.1 to the Registrant’s Current Report on Form 8-K, filed on June 23, 2021).
21.1	Subsidiaries of the Registrant
23.1	Consent of Ernst & Young, LLP.
31.1	Certification of Principal Executive Officer pursuant to Rules 13a-14(a) and 15d-14(a) promulgated under the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002
31.2	Certification of Principal Financial Officer pursuant to Rules 13a-14(a) and 15d-14(a) promulgated under the Securities Exchange Act of 1934, as adopted pursuant to section 302 of the Sarbanes-Oxley Act of 2002
32.1	Certification of Principal Executive Officer and Principal Financial Officer pursuant to Rules 13a-14(b) and 15d-14(b) promulgated under the Securities Exchange Act of 1934 and 18 U.S.C. Section 1350, as adopted pursuant to section 906 of The Sarbanes-Oxley Act of 2002
101.INS	Inline XBRL Instance Document (the instance document does not appear in the Interactive Data File because its XBRL tags are embedded within the Inline XBRL document).
101.SCH	Inline XBRL Taxonomy Extension Schema Document
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document
101.LAB	Inline XBRL Taxonomy Extension Label Linkbase Document
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document
104	Cover Page Interactive Data File (formatted as inline XBRL and contained in Exhibit 101)

* Indicates management contract or compensatory plan.

+ Certain schedules and exhibits have been omitted pursuant to Item 601(b)(2) of Regulation S-K. A copy of any omitted schedule and/or exhibit will be furnished to the SEC upon request.

++ Portions of this exhibit have been omitted in compliance with Item 601 of Regulation S-K.

ITEM 16. FORM 10-K SUMMARY

None

ITEM 8. CONSOLIDATED FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

INDEX TO FINANCIAL STATEMENTS

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Report of Independent Registered Public Accounting Firm

To the Board of Directors and Stockholders
Ocuphire Pharma, Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Ocuphire Pharma, Inc. (the Company) as of December 31, 2021 and 2020, the related consolidated statements of comprehensive loss, changes in stockholders' equity (deficit) and cash flows for each of the two years in the period ended December 31, 2021, and the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2021 and 2020, and the results of its operations and its cash flows for each of the two years in the period ended December 31, 2021, in conformity with U.S. generally accepted accounting principles.

The Company's Ability to Continue as a Going Concern

The accompanying consolidated financial statements have been prepared assuming that the Company will continue as a going concern. As discussed in Note 1 to the financial statements, the Company has suffered recurring losses from operations, has negative cash flow from operations, and has stated that substantial doubt exists about the Company's ability to continue as a going concern. Management's evaluation of the events and conditions and management's plans regarding these matters are also described in Note 1. The consolidated financial statements do not include any adjustments that might result from the outcome of this uncertainty.

Basis for Opinion

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits, we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

Critical Audit Matter

The critical audit matter communicated below is a matter arising from the current period audit of the financial statements that were communicated or required to be communicated to the audit committee and that: (1) relates to accounts or disclosures that are material to the financial statements and (2) involved our especially challenging, subjective or complex judgments. The communication of the critical audit matter does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matter below, providing a separate opinion on the critical audit matter or on the accounts or disclosures to which it relates.

Accounting for Warrants

*Description of
the Matter*

As discussed in Notes 1 and 9 to the consolidated financial statements, in connection with the merger transaction, the Company issued Series A and Series B warrants (collectively, the Warrants) to purchase additional common stock on November 19, 2020 (the Warrant Closing Date). As of the Warrant Closing Date and December 31, 2020, the Series A warrants were determined to be liability classified instruments and the Series B warrants were determined to be equity classified instruments. On February 3, 2021, the Company entered into Waiver Agreements which, among other things, modified certain features of the Warrants. Upon the effective date of the Waiver Agreements, the Series A warrants were reclassified to equity.

Auditing the accounting conclusions related to the Warrants was challenging because of the complex provisions affecting valuation and classification and required extensive audit effort. The accounting for the Warrants involved an assessment of the particular features of each type of warrant, and the impact of those features on the accounting and classification of the Warrants.

*How we
Addressed the
Matter in Our
Audit*

To test the accounting and determine proper classification of the Warrants, our audit procedures included, among others, inspecting the agreements and evaluating the completeness and accuracy of the Company's technical accounting analyses, application of the relevant accounting guidance and review of legal interpretation from counsel. Our audit procedures also included the involvement of subject matter resources to assist in evaluating management's conclusion on the interpretation and application of the relevant accounting literature.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2018.

Detroit, Michigan
March 24, 2022

Ocuphire Pharma, Inc.
Consolidated Balance Sheets
(in thousands, except share amounts and par value)

	As of December 31,	
	2021	2020
Assets		
Current assets:		
Cash and cash equivalents	\$ 24,534	\$ 16,399
Prepays and other current assets	1,314	1,269
Short-term investments	219	—
Total current assets	26,067	17,668
Property and equipment, net	10	14
Total assets	\$ 26,077	\$ 17,682
Liabilities and stockholders' equity (deficit)		
Current liabilities:		
Accounts payable	\$ 1,584	\$ 1,214
Accrued expenses	1,733	1,971
Short-term loan	538	—
Total current liabilities	3,855	3,185
Warrant liabilities	—	27,964
Total liabilities	3,855	31,149
Commitments and contingencies (Note 3 and Note 9)		
Stockholders' equity (deficit)		
Preferred stock, par value \$0.0001; 10,000,000 shares authorized as of December 31, 2021 and 2020; no shares issued and outstanding at December 31, 2021 and 2020.	—	—
Common stock, par value \$0.0001; 75,000,000 shares authorized as of December 31, 2021 and 2020; 18,845,828 and 10,882,495 shares issued and outstanding at December 31, 2021 and 2020, respectively.	2	1
Additional paid-in capital	111,588	19,207
Accumulated deficit	(89,368)	(32,675)
Total stockholders' equity (deficit)	22,222	(13,467)
Total liabilities and stockholders' equity (deficit)	\$ 26,077	\$ 17,682

See accompanying notes.

Ocuphire Pharma, Inc.
Consolidated Statements of Comprehensive Loss
(in thousands, except share and per share amounts)

	For the Year Ended December 31,	
	2021	2020
Collaborations revenue	\$ 589	\$ —
Operating expenses:		
General and administrative	8,121	2,818
Research and development	15,173	6,648
Acquired in-process research and development	—	10,502
Total operating expenses	23,294	19,968
Loss from operations	(22,705)	(19,968)
Interest expense	(2)	(6,847)
Fair value change in derivative and warrant liabilities	(33,829)	(1,486)
Gain on note extinguishment	—	3,672
Other (expense) income, net	(157)	9
Loss before income taxes	(56,693)	(24,620)
Benefit (provision) for income taxes	—	—
Net loss	(56,693)	(24,620)
Other comprehensive loss, net of tax	—	—
Comprehensive loss	\$ (56,693)	\$ (24,620)
Net loss per share:		
Basic and diluted (Note 11)	\$ (3.82)	\$ (5.28)
Number of shares used in per share calculations:		
Basic and diluted	14,852,745	4,661,110

See accompanying notes.

Ocuphire Pharma, Inc.
Consolidated Statements of Changes in Stockholders' Equity (Deficit)
(in thousands, except share amounts)

	Common Stock		Additional Paid-In Capital	Accumulated Deficit	Total Stockholders' Equity (Deficit)
	Shares	Amount			
Balance at December 31, 2019	2,852,485	\$ —	\$ 495	\$ (8,055)	\$ (7,560)
Issuance of common stock in exchange for in-process research and development	891,422	—	2,126	—	2,126
Gain on note extinguishment	—	—	971	—	971
Conversion of convertible notes into common stock upon close of the merger	977,128	—	6,953	—	6,953
Issuance of common stock and warrants in connection with pre-merger financing	4,999,988	1	(1)	—	—
Issuance costs attributed to pre-merger financing	—	—	(1,080)	—	(1,080)
Issuance of common stock, warrants and options to former Rexahn stockholders and effect of asset acquisition	1,120,800	—	8,115	—	8,115
Share-based compensation	—	—	1,506	—	1,506
Reclassification of Rexahn warrants from liability to equity	—	—	64	—	64
Exercise of stock options	40,672	—	58	—	58
Net and comprehensive loss	—	—	—	(24,620)	(24,620)
Balance at December 31, 2020	10,882,495	1	19,207	(32,675)	(13,467)
Reclassification of Series A warrant liability to equity	—	—	61,793	—	61,793
Issuance of common stock and warrants in connection with registered direct offering	3,076,923	1	14,999	—	15,000
Issuance of common stock in connection with the at-the-market program	2,778,890	—	13,491	—	13,491
Issuance of common stock in connection with settlement with investors	350,000	—	1,614	—	1,614
Issuance costs	—	—	(1,517)	—	(1,517)
Exercise of Series B warrants	1,629,634	—	—	—	—
Share-based compensation	54,444	—	1,914	—	1,914
Exercise of stock options	73,442	—	87	—	87
Net and comprehensive loss	—	—	—	(56,693)	(56,693)
Balance at December 31, 2021	<u>18,845,828</u>	<u>\$ 2</u>	<u>\$ 111,588</u>	<u>\$ (89,368)</u>	<u>\$ 22,222</u>

See accompanying notes.

Ocuphire Pharma, Inc.
Consolidated Statements of Cash Flows
(in thousands)

	For the Year Ended December 31,	
	2021	2020
Operating activities		
Net loss	\$ (56,693)	\$ (24,620)
Adjustments to reconcile net loss to net cash used in operating activities:		
Share-based compensation	1,914	1,506
Depreciation	4	8
Non-cash acquired in-process research and development	—	10,502
Gain on note extinguishment	—	(3,672)
Non-cash interest on convertible notes	—	492
Non-cash interest on convertible notes – related party	—	51
Non-cash discount amortization on convertible notes	—	873
Non-cash discount amortization on convertible notes – related party	—	71
Fair value change in derivative and warrant liabilities	33,829	1,486
Non-cash interest attributed to Series A warrant issuance	—	4,671
Issuance costs attributed to Series A warrants	—	689
Non-cash share settlement with investors	1,614	—
Receipt of investments related to license agreement	(289)	—
Unrealized loss from short-term investments	70	—
Change in assets and liabilities:		
Prepaid expenses and other assets	(45)	(906)
Accounts payable	381	792
Accrued expenses	(155)	1,260
Net cash used in operating activities	<u>(19,370)</u>	<u>(6,797)</u>
Investing activities		
Cash acquired in connection with asset acquisition	—	2,014
Transaction costs in connection with asset acquisition	(100)	(1,475)
Net cash (used in) provided by investing activities	<u>(100)</u>	<u>539</u>
Financing activities		
Proceeds from pre-merger financing	—	21,150
Proceeds from issuance of common stock	28,491	—
Proceeds from issuance of convertible notes	—	2,197
Issuance costs attributed to pre-merger financing	—	(1,769)
Issuance costs attributed to common stock and convertible notes	(1,511)	(10)
Proceeds from short-term loan	646	—
Payment made on short-term loan principal	(108)	—
Settlement of Rexahn warrants	—	(506)
Exercise of stock options	87	58
Net cash provided by financing activities	<u>27,605</u>	<u>21,120</u>
Net increase in cash and cash equivalents	8,135	14,862
Cash and cash equivalents at beginning of period	16,399	1,537
Cash and cash equivalents at end of period	<u>\$ 24,534</u>	<u>\$ 16,399</u>
<i>Supplemental disclosure of cash flow information:</i>		
Cash paid for income taxes	\$ —	\$ —
Cash paid for interest	\$ 2	\$ —
<i>Supplemental non-cash financing transactions:</i>		
Non-cash reclassification of Series A warrant liability to equity	\$ 61,793	\$ —
Non-cash conversion of convertible notes to common stock	\$ —	\$ 9,365
Common stock and warrants issued in connection with the asset acquisition	\$ —	\$ 8,883
Unpaid transaction costs in connection with asset acquisition	\$ —	\$ 100
Net assets assumed in connection with asset acquisition	\$ —	\$ 68
Bifurcation and modification of premium conversion derivative related to convertible notes	\$ —	\$ 831
Unpaid issuance costs	\$ 6	\$ —

See accompanying notes.

Ocuphire Pharma, Inc.
Notes to Consolidated Financial Statements

1. Company Description and Summary of Significant Accounting Policies

Nature of Business

Ocuphire is a clinical-stage ophthalmic biopharmaceutical company focused on developing and commercializing therapies for the treatment of refractive and retinal eye disorders. Ocuphire's pipeline currently includes two small molecule product candidates targeting several of such indications. The Company's lead product candidate, Nyxol® Eye Drops ("Nyxol"), is a once-daily eye drop formulation of phentolamine mesylate designed to reduce pupil diameter and improve visual acuity. The Company's second product candidate, APX3330, is a twice-a-day oral tablet designed to target multiple pathways relevant to retinal and choroidal (the vascular layer of the eye) diseases such as diabetic retinopathy ("DR") and diabetic macular edema ("DME") which, if left untreated, can result in permanent visual acuity loss and eventual blindness. The Company has also in-licensed APX2009 and APX2014, which are second-generation product candidates and analogs of APX3330.

The Company has sustained operating losses since inception and expects such losses to continue indefinitely until a sustained revenue source is realized. Management plans to continue financing the Company's operations primarily through additional issuances of the Company's equity and debt securities. If adequate funds are not available, the Company may be required to delay, reduce the scope of, or eliminate part or all of its research and development programs.

Reverse Merger with Rexahn

On June 17, 2020, Ocuphire, Rexahn Pharmaceuticals, Inc. ("Rexahn"), Razor Merger Sub, Inc., a Delaware corporation and wholly-owned subsidiary of Rexahn ("Merger Sub"), entered into an Agreement and Plan of Merger and Reorganization, as amended on June 29, 2020 (as amended, the "Merger Agreement"), pursuant to which, among other things, and subject to the satisfaction or waiver of certain conditions set forth in the Merger Agreement, Merger Sub would merge with and into Ocuphire, with Ocuphire continuing as a wholly-owned subsidiary of Rexahn and the surviving corporation of the merger (the "Merger"). The Merger closed on November 5, 2020. Upon completion of the Merger, Rexahn changed its name to Ocuphire Pharma, Inc. and changed its ticker symbol on the Nasdaq Capital Market to "OCUP".

The Company's headquarters is located in Farmington Hills, Michigan.

COVID-19

As a result of the COVID-19 pandemic, the Company has experienced, and will likely continue to experience, delays and disruptions in our clinical trials, as well as interruptions in our manufacturing, supply chain, shipping and research and development operations.

The Company's plans for further testing or clinical trials may be further impacted by the continuing effects of COVID-19. The global outbreak of COVID-19 continues to evolve. The extent to which the COVID-19 pandemic may further impact our business and clinical trials will depend on future developments, which are highly uncertain and cannot be predicted with confidence, such as the effect of the pandemic on our suppliers and distributors and the global supply chain, the ultimate geographic spread of the disease, the duration of the outbreak, travel restrictions and social distancing in the U.S. and other countries, business closures or business disruptions and the effectiveness of actions taken in the U.S. and other countries to contain and treat the disease. The COVID-19 pandemic may also continue to impact our business as a result of employee illness, school closures, and other community response measures.

The COVID-19 pandemic may also impact the Company's ability to secure additional financing. Although the Company cannot estimate the length or gravity of the impact of the COVID-19 outbreak at this time, if the pandemic continues, it may have a material adverse effect on the Company's results of future operations, financial position, and liquidity in for fiscal year 2022 and beyond.

Ocuphire Pharma, Inc.
Notes to Consolidated Financial Statements

Basis of Presentation

The accompanying financial statements have been prepared in accordance with accounting standards generally accepted in the United States of America (“GAAP”).

All of the share and per share amounts presented were adjusted, on a retroactive basis, to reflect the exchange of the shares of Ocuphire pre-Merger (“Private Ocuphire”) into 1.0565 shares of the Company (the “Exchange Ratio”), except for par value and share authorizations of Private Ocuphire for periods presented prior to the Merger.

On December 31, 2021, the Company merged its wholly owned subsidiary, OcuSub Inc, with and into the Company, with the Company remaining as the surviving entity. The merger of the Company’s wholly owned subsidiary did not have a financial impact to the periods presented. Upon close of this merger, the Company did not have any remaining entities that required consolidation for financial statement reporting purposes.

Going Concern

The Company’s ability to continue operating as a going concern is contingent upon, among other things, its ability to secure additional financing and to achieve and maintain profitable operations. The Company plans to issue additional equity instruments and possibly debt to finance operating and working capital requirements. While the Company expects to obtain the additional financing that is needed, there is no assurance that the Company will be successful in obtaining the necessary funding for future operations. These factors raise substantial doubt as to the Company’s ability to continue as a going concern. The consolidated financial statements do not include any adjustments that might result from the outcome of these uncertainties.

Common Stock Valuation

Prior to the close of the Merger, due to the absence of an active market for the Private Ocuphire’s common stock, the Company utilized methodologies in accordance with the framework of the American Institute of Certified Public Accountants’ Technical Practice Aid, *Valuation of Privately-Held Company Equity Securities Issued as Compensation*, to estimate the fair value of Private Ocuphire common stock. The valuation methodology included estimates and assumptions that required the Company’s judgment. These estimates and assumptions included a number of objective and subjective factors, including external market conditions affecting the biotechnology industry sector, and the likelihood of achieving a liquidity event, such as an initial public offering (“IPO”), reverse merger or sale. Significant changes to the key assumptions used in the valuations resulted in different fair values of common stock at each valuation date.

For the valuation of equity awards granted in October 2020 and September 2020, the Company used a contemporaneous third-party valuation of \$8.76 and \$7.89 per share, respectively. For the valuation of equity awards granted in April 2020 and June 2020, the Company applied a straight-line calculation using the contemporaneous third-party valuations of \$1.74 per share as of March 31, 2020 and \$9.54 per share as of June 18, 2020 to determine the fair value of Private Ocuphire common stock. Using the benefit of hindsight, the Company determined that the straight-line calculation would provide the most reasonable conclusion for the valuation of the Company’s common stock on these interim dates between valuations because the Company did not identify any single event or series of events that occurred during this interim period that would have caused a material change in fair value. Based on this calculation, the Company assessed the fair value of its common stock for awards granted in April 2020 and June 2020 at \$2.33 and \$8.65 per share, respectively.

Ocuphire Pharma, Inc.
Notes to Consolidated Financial Statements

Use of Estimates

The preparation of consolidated financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the amounts reported in the consolidated financial statements and accompanying notes. Actual results could differ from those estimates.

Segment Information

Operating segments are components of an enterprise for which separate financial information is available and is evaluated regularly by the Company's chief operating decision maker in deciding how to allocate resources and assessing performance. The Company's chief operating decision maker is its Chief Executive Officer. The Company's Chief Executive Officer views the Company's operations and manages its business in one operating segment, which is the business of development and commercialization of products related to vision performance and health. Accordingly, the Company has a single reporting segment.

Cash and Cash Equivalents

The Company considers all highly liquid investments with an original maturity of 90 days or less at the time of deposit to be cash equivalents.

Concentration of Credit Risk

Financial instruments that potentially subject the Company to a concentration of credit risk consist of cash and cash equivalents. The Company's cash is held by two long-standing financial institutions in the United States. Amounts on deposit may at times exceed federally insured limits. Management believes that the financial institutions are financially sound, and accordingly, minimal credit risk exists with respect to the financial institutions. As of December 31, 2021, the Company had deposits that exceeded federally insured amounts by approximately \$24.0 million.

Short-term Investments

The Company determines the appropriate classification of its investments in debt and equity securities at the time of purchase and are recorded on a settlement date basis. The Company's investments are comprised of equity securities, which in accordance with the fair value hierarchy described below are recorded at fair value using Level I inputs on the consolidated balance sheets. Subsequent changes in fair values are recorded in other (expense) income, net on the consolidated statements of comprehensive loss. The Company classifies investments available to fund current operations as current assets on its consolidated balance sheets. The Company did not recognize any impairments on its investments to date through December 31, 2021.

Revenue Recognition

The Company follows the provisions of Accounting Standards Codification ("ASC") 606, *Revenue from Contracts with Customers*. The guidance provides a five-step model to determine how revenue is recognized. The Company has entered into license agreements which have revenue recognition implications. (See Note 10 – Collaboration License Agreements.)

In determining the appropriate amount of revenue to be recognized, the Company performs the following steps: (i) identification of the contracts with a customer; (ii) determination of the performance obligations in the contract; (iii) measurement of the transaction price, including potential constraints on variable consideration; (iv) allocation of the transaction price to the performance obligations based on estimated stand-alone selling prices; and (v) recognition of revenue when (or as) the Company satisfies a performance obligation.

A performance obligation is a promise in a contract to transfer a distinct good or service to the customer and is the unit of account in ASC 606. Performance obligations may include license rights, development services, and services associated with regulatory submission and approval processes. Significant management judgment is required to determine the level of effort required under an arrangement and the period over which the Company expects to complete its performance obligations under the arrangement. If the Company cannot reasonably estimate when its performance obligations are either completed or become inconsequential, then revenue recognition is deferred until the Company can reasonably make such estimates. Revenue is then recognized over the remaining estimated period of performance using the cumulative catch-up method.

Ocuphire Pharma, Inc.
Notes to Consolidated Financial Statements

As part of the accounting for these arrangements, the Company must develop assumptions that require judgment to determine the stand-alone selling price of each performance obligation identified in the contract. The Company uses key assumptions to determine the stand-alone selling price, which may include forecasted revenues, development timelines, reimbursement rates for personnel costs, discount rates and probabilities of technical and regulatory success. The Company allocates the total transaction price to each performance obligation based on the estimated relative standalone selling prices of the promised goods or service underlying each performance obligation.

Licenses of intellectual property: If the license to the Company's intellectual property is determined to be distinct from the other performance obligations identified in the arrangement, the Company recognizes revenues from non-refundable, up-front fees allocated to the license when the license is transferred to the customer, and the customer can use and benefit from the license. For licenses that are bundled with other promises, the Company utilizes judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue from non-refundable, up-front fees. The Company evaluates the measure of progress each reporting period and, if necessary, adjusts the measure of performance and related revenue recognition.

Milestone payments: At the inception of each arrangement that includes milestone payments, the Company evaluates whether the milestones are considered probable of being achieved and estimates the amount to be included in the transaction price using the most likely amount method. If it is probable that a significant revenue reversal would not occur, the value of the associated milestone (such as a regulatory submission) is included in the transaction price. Milestone payments that are not within the control of the Company, such as approvals from regulators, are not considered probable of being achieved until such contingency occurs (such as receipt of those approvals). When the Company's assessment of probability of achievement changes and variable consideration becomes probable, any additional estimated consideration is allocated to each performance obligation based on the estimated relative standalone selling prices of the promised goods or service underlying each performance obligation and recorded in collaborations revenue based upon when the customer obtains control of each element.

Royalties: For arrangements that include sales-based royalties, including milestone payments based on the level of sales, and the license is deemed to be the predominant item to which the royalties relate, the Company recognizes revenue at the later of (a) when the related sales occur, or (b) when the performance obligation to which some or all of the royalty has been allocated has been satisfied (or partially satisfied).

General and Administrative Expenses

General and administrative expenses ("G&A") consist primarily of personnel-related costs, including salaries and stock-based compensation costs, for personnel in functions not directly associated with research and development activities. Other significant costs include legal fees relating to intellectual property and corporate matters, professional fees for accounting and tax services, settlement costs with third parties and other services provided by business consultants.

Research and Development

Research and development expenses ("R&D") consist of costs incurred in performing research and development activities, including compensation for research and development employees and consultants, costs associated with preclinical studies and clinical trials, regulatory activities, manufacturing activities to support clinical activities, license fees, fees paid to external service providers that conduct certain research and development, and an allocation of R&D related overhead expenses.

Ocuphire Pharma, Inc.
Notes to Consolidated Financial Statements

Acquired In-Process Research and Development Expenses

The Company includes costs to acquire or in-license product candidates as acquired in-process research and development expenses (“IPR&D”). These costs are immediately expensed provided that the payments do not also represent processes or activities that would constitute a “business” as defined under GAAP or provided that the product candidate has not achieved regulatory approval for marketing, and absent obtaining such approval, has no alternative future use. Royalties owed on future sales of any licensed product will be expensed in the period the related revenues are recognized. See Note 8 – Apexian Sublicense Agreement.

Other (Expense) Income, net

Other (expense) income, net reflected in this line item includes payments made by the Company in connection with the Contingent Value Rights Agreement discussed further below with former Rexahn shareholders. In addition, Other (expense) income, net includes interest earned from cash and cash equivalent investments, realized and unrealized gains (losses) from equity investments and reimbursements in connection with grants and other sources.

Share-Based Compensation

The Company accounts for share-based compensation in accordance with the provisions of the Financial Accounting Standards Board (“FASB”) Accounting Standards Codification (“ASC 718”), *Compensation — Stock Compensation*. Accordingly, compensation costs related to equity instruments granted are recognized at the grant-date fair value. The Company records forfeitures when they occur. Share-based compensation arrangements to non-employees are accounted for in accordance with the applicable provisions of ASC 718.

Warrant Liabilities

The Company issued Series A Warrants in connection with the Pre-Merger Financing (see Note 9 – Pre-Merger Financing) and assumed Rexahn warrants issued prior to the Merger. The Company accounts for these warrants as a liability while outstanding at fair value during periods when certain provisions preclude equity accounting treatment for these instruments. Additionally, issuance costs associated with the warrants classified as liabilities are expensed as incurred and reflected as interest expense in the accompanying consolidated statements of comprehensive loss. The change in fair value of the warrant liabilities while outstanding were recognized as a component of the fair value change in derivative and warrant liabilities line item in the consolidated statements of comprehensive loss.

Premium Conversion Derivatives

The Company evaluates all conversion and redemption features contained in a debt instrument to determine if there are any embedded derivatives that require separation from the host debt instrument. An embedded derivative that requires separation is bifurcated from its host debt instrument and a corresponding discount to the host debt instrument is recorded. The discount is amortized and recorded to interest expense over the term of the host debt instrument using the straight-line method which approximates the effective interest method. The embedded derivative is accounted for separately on a fair market value basis while outstanding. The Company records the fair value changes of a separated embedded derivative at each reporting period in the fair value change in derivative and warrant liabilities line item in the accompanying consolidated statements of comprehensive loss. The Company determined that the redemption features under the convertible notes, while they were outstanding, qualified as embedded derivatives and were separated from their debt hosts.

Fair Value Measurements

The Company follows accounting guidance that emphasizes that fair value is a market-based measurement, not an entity-specific measurement. Fair value is defined as “the price that would be received to sell an asset or paid to transfer a liability in an orderly transaction between market participants at the measurement date.” Fair value measurements are defined on a three-level hierarchy:

- Level 1 inputs: Unadjusted quoted prices for identical assets or liabilities in active markets;
- Level 2 inputs: Quoted prices for similar assets and liabilities in active markets, quoted prices in markets that are not active, or inputs which are observable, whether directly or indirectly, for substantially the full term of the asset or liability; and
- Level 3 inputs: Unobservable inputs that reflect the Company’s own assumptions about the assumptions market participants would use in pricing the asset or liability in which there is little, if any, market activity for the asset or liability at the measurement date.

Ocuphire Pharma, Inc.
Notes to Consolidated Financial Statements

As of December 31, 2021 and 2020, the fair values of cash and cash equivalents, prepaid and other assets, accounts payable, accrued expenses and short-term loan approximated their carrying values because of the short-term nature of these assets or liabilities. The estimated fair value of the Company's convertible notes while outstanding were based on amortized cost which was deemed to approximate fair value. The fair value of the investments, while outstanding, were based on observable Level 1 inputs in the form of quoted market prices from a major stock exchange. The fair value of the warrant liabilities and premium conversion derivatives, while outstanding, were based on cash flow models discounted at current implied market rates evidenced in recent arms-length transactions representing expected returns by market participants for similar instruments and were based on Level 3 inputs. There were no transfers between fair value hierarchy levels during the years ended December 31, 2021 and 2020.

The fair value of financial instruments measured on a recurring basis is as follows (in thousands):

Description	As of December 31, 2021			
	Total	Level 1	Level 2	Level 3
Assets:				
Short-term investments	\$ 219	\$ 219	\$ —	\$ —
Total assets at fair value	<u>\$ 219</u>	<u>\$ 219</u>	<u>\$ —</u>	<u>\$ —</u>

Description	As of December 31, 2020			
	Total	Level 1	Level 2	Level 3
Liabilities:				
Warrant liabilities	\$ 27,964	\$ —	\$ —	\$ 27,964
Total liabilities at fair value	<u>\$ 27,964</u>	<u>\$ —</u>	<u>\$ —</u>	<u>\$ 27,964</u>

The following table provides a roll-forward of investments measured at fair value on a recurring basis using observable level 1 inputs for the year ended December 31, 2021 and 2020 (in thousands):

	<u>2021</u>	<u>2020</u>
Short-term investments		
Balance as of beginning of period	\$ —	\$ —
Receipt of investments related to license agreement	289	—
Unrealized loss	(70)	—
Balance as of end of period	<u>\$ 219</u>	<u>\$ —</u>

Ocuphire Pharma, Inc.
Notes to Consolidated Financial Statements

The following table provides a roll-forward of the warrant liabilities and premium conversion derivatives measured at fair value on a recurring basis using unobservable level 3 inputs for the years ended December 31, 2021 and 2020 (in thousands):

	<u>2021</u>	<u>2020</u>
Warrant liabilities		
Balance as of beginning of period	\$ 27,964	\$ —
Value assigned to warrants upon in connection with pre-merger financing	—	25,821
Issuance of warrants to former Rexahn stockholders classified as a liability	—	768
Cash settlement of warrant liabilities	—	(506)
Change in fair value of warrant liabilities	33,829	1,945
Reclassification of warrants from liability to equity	(61,793)	(64)
Balance as of end of period	<u>\$ —</u>	<u>\$ 27,964</u>
Premium conversion derivatives		
Balance as of beginning of period	\$ —	\$ 2,714
Value assigned to the underlying derivatives in connection with convertible notes	—	831
Revaluation due to convertible note extinguishment	—	(3,086)
Change in fair value of premium conversion derivatives	—	(459)
Balance as of end of period	<u>\$ —</u>	<u>\$ —</u>

There were no financial instruments measured on a non-recurring basis for any of the periods presented.

Income Taxes

The Company utilizes the liability method of accounting for income taxes as required by ASC 740, *Income Taxes*. Under this method, deferred tax assets and liabilities are determined based on differences between financial reporting and the tax basis of assets and liabilities and are measured using enacted tax rates and laws that will be in effect when the differences are expected to reverse. Currently, there is no provision for income taxes, as the Company has incurred operating losses to date, and a full valuation allowance has been provided on the net deferred tax assets.

Property and Equipment

Property and equipment, net is recorded at cost and reduced by accumulated depreciation. Depreciation expense is recognized over the estimated useful lives of the assets using the straight-line method. Equipment and furniture are depreciated over a five year estimated useful life. Tangible assets acquired for research and development activities which have alternative use are capitalized and depreciated over the useful life of the acquired asset. Estimated useful lives are periodically reviewed, and when appropriate, changes are made prospectively. When certain events or changes in operating conditions occur, asset lives may be adjusted and an impairment assessment may be performed on the recoverability of the carrying amounts. Maintenance and repairs are charged directly to expense as incurred.

Recent Accounting Pronouncements

In June 2016, the FASB issued Accounting Standards Update (“ASU”) 2016-13, “*Financial Instruments – Credit Losses*”. The ASU sets forth a “current expected credit loss” (“CECL”) model which requires the Company to measure all expected credit losses for financial instruments held at the reporting date based on historical experience, current conditions, and reasonable supportable forecasts. This replaces the existing incurred loss model and is applicable to the measurement of credit losses on financial assets measured at amortized cost and applies to some off-balance sheet credit exposures. The Company does not expect that the adoption of this ASU on January 1, 2023 will have a significant impact on its consolidated financial statements.

In August 2020, FASB issued ASU 2020-06, *Debt—Debt with Conversion and Other Options (Subtopic 470-20) and Derivatives and Hedging—Contracts in Entity’s Own Equity (Subtopic 815-40): Accounting for Convertible Instruments and Contracts in an Entity’s Own Equity*, which, among other things, provides guidance on how to account for contracts on an entity’s own equity. This ASU eliminates the beneficial conversion and cash conversion accounting models for convertible instruments. It also amends the accounting for certain contracts in an entity’s own equity that are currently accounted for as derivatives because of specific settlement provisions. In addition, this ASU modifies how particular convertible instruments and certain contracts that may be settled in cash or shares impact the diluted EPS computation. The amendments in this ASU are effective for public business entities that meet the definition of a Securities and Exchange Commission (“SEC”) filer, excluding entities eligible to be smaller reporting companies as defined by the SEC, for fiscal years beginning after December 15, 2021, including interim periods within those fiscal years. For all other entities, the amendments are effective for fiscal years beginning after December 15, 2023, including interim periods within those fiscal years. The Company is currently evaluating the impact of ASU 2020-06 on its consolidated financial statements.

Ocuphire Pharma, Inc.
Notes to Consolidated Financial Statements

In November 2021, the FASB issued ASU 2021-10, *Government Assistance (Topic 832) - Disclosures by Business Entities about Government Assistance*, to increase the transparency of government assistance including the disclosure of the types of assistance, an entity’s accounting for the assistance, and the effect of the assistance on an entity’s financial statements. The amendments in this ASU are effective for all entities within their scope for financial statements issued for annual periods beginning after December 15, 2021. The Company is currently evaluating the impact of the adoption of Topic 832.

2. Merger

On November 5, 2020, the Company completed its merger transaction with Rexahn in accordance with the terms of the Merger Agreement. Immediately after the Merger, there were approximately 7,091,878 shares of the Company’s common stock, par value \$0.0001 per share (the “Common Stock”) outstanding (not including 3,749,992 Additional Shares under the Securities Purchase Agreement that were held in escrow subject to final adjustment). The former stockholders and option holders of Private Ocuphire (including the Investors under the Securities Purchase Agreement) owned, or held rights to acquire, in the aggregate approximately 86.6% of the fully-diluted Common Stock, which for these purposes is defined as the outstanding Common Stock, plus outstanding options of the Company, and not including any Additional Shares (the “Fully-Diluted Common Stock”), with the former Rexahn stockholders immediately prior to the Merger owning approximately 13.4% of the Fully-Diluted Common Stock. Pursuant to the Merger Agreement, the number of shares of Common Stock issued to Private Ocuphire’s stockholders for each share of Ocuphire’s common stock outstanding immediately prior to the Merger was calculated using an Exchange Ratio of approximately 1.0565 shares of Common Stock for each share of Private Ocuphire common stock. Immediately following the Merger, the stockholders of Private Ocuphire owned approximately 86.6% of the outstanding common stock of the Company.

The transaction was accounted for as an asset acquisition in accordance with GAAP. Under this method of accounting, Private Ocuphire was deemed to be the accounting acquirer for financial reporting purposes. This determination was primarily based on the facts that, immediately following the Merger: (i) Private Ocuphire’s stockholders owned substantially all of the voting rights in the combined company, (ii) Private Ocuphire designated all, but one, of the members of the initial board of directors of the combined company, and (iii) Private Ocuphire’s senior management holds all key positions in the senior management of the combined company. As a result, as of the closing date of the Merger, the net assets of Rexahn were recorded at their acquisition-date relative fair values in the consolidated financial statements of the Company and the reported operating results prior to the Merger are those of Private Ocuphire.

The total purchase price paid in the Merger has been allocated to the net assets acquired and liabilities assumed based on their fair values as of the completion of the Merger. The following summarizes the purchase price paid in the Merger (in thousands, except share and per share amounts):

Number of shares of the combined organization owned by the Company’s Pre-Merger stockholders	1,120,800
Multiplied by the fair value per share of REXN’s common stock (1)	\$ 7.24
Fair value of common stock issued to affect the Merger	8,115
Fair value of warrants and options issued to affect the Merger	768
Transaction costs	1,575
Purchase price	<u>\$ 10,458</u>

(1) Based on the last reported sale price of the Rexahn’s common stock on the Nasdaq Capital Market on November 5, 2020, the closing date of the Merger, and gives effect to the Reverse Stock Split.

Ocuphire Pharma, Inc.
Notes to Consolidated Financial Statements

The allocation of the purchase price is as follows:

Cash acquired	\$ 2,014
Net assets assumed	68
IPR&D (2)	8,376
Purchase price	<u>\$ 10,458</u>

- (2) Represents the pre-Merger research and development projects of Rexahn which were in-process, but not yet completed, and which the Company may advance post-Merger. This includes the development of RX-3117, RX-0301 and RX-0047. Current accounting standards require that the fair value of IPR&D projects acquired in an asset acquisition with no alternative future use be allocated a portion of the consideration transferred and charged to expense on the acquisition date. The acquired assets did not have outputs or employees.

Contingent Value Rights Agreement

On November 5, 2020, in connection with the Merger, the Company, Shareholder Representatives Services LLC, as representative of the Rexahn stockholders prior to the Merger, and Olde Monmouth Stock Transfer Co., Inc., as the rights agent, entered into a Contingent Value Rights Agreement (the "CVR Agreement").

Pursuant to the Merger Agreement and the CVR Agreement, Rexahn stockholders of record as of immediately prior to the Effective Time received one contingent value right ("CVR") for each share of Rexahn Common Stock held.

Each CVR entitles such holders to receive, for each calendar quarter (each, a "CVR Payment Period") during the 15-year period after the Closing (the "CVR Term"), an amount equal to the following:

- 90% of all payments received by Rexahn or its affiliates during such CVR Payment Period from or on behalf of BioSense Global LLC ("BioSense") pursuant to that certain License and Assignment Agreement, dated as of February 25, 2019, by and between BioSense and Rexahn, as amended by Amendment No. 1, dated August 24, 2019, and as further amended by Amendment No. 2, dated March 10, 2020, minus certain permitted deductions;
- 90% of all payments received by Rexahn or its affiliates during such CVR Payment Period from or on behalf of Zhejiang HaiChang Biotechnology Co., Ltd. ("HaiChang") pursuant to that certain Exclusive License Agreement, dated as of February 8, 2020, by and between HaiChang and Rexahn, minus certain permitted deductions; and
- 75% of the sum of (i) all cash consideration paid by a third party to Rexahn or its affiliates during the applicable CVR Payment Period in connection with the grant, sale or transfer of rights to Rexahn's pre-Closing intellectual property (other than a grant, sale or transfer of rights involving a sale or disposition of the post-Merger combined company) that is entered into during the 10-year period after the Closing ("Parent IP Deal"), plus (ii) with respect to any non-cash consideration received by Rexahn or its affiliates from a third party during the applicable CVR Payment Period in connection with any Parent IP Deal, all amounts received by Rexahn and its affiliates for such non-cash consideration at the time such non-cash consideration is monetized by Rexahn or its affiliates, minus (iii) certain permitted deductions.

The CVRs are not transferable, except in certain limited circumstances, will not be certificated or evidenced by any instrument, will not accrue interest and will not be registered with the SEC or listed for trading on any exchange. The CVR Agreement will continue in effect until the later of the end of the CVR Term and the payment of all amounts payable thereunder. As of December 31, 2021, \$91,000 was paid under the CVR Agreement and was recorded in the other (expense) income, net line item in the condensed consolidated statements of comprehensive loss.

Ocuphire Pharma, Inc.
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As of the November 5, 2020, the Merger closing date, and December 31, 2021, no additional milestones under the license agreements subject to the CVR Agreement had been accrued as there were no potential milestones yet considered probable.

Former Rexahn Warrants and Stock Options

Following the closing of the Merger, 231,433 outstanding, unexercised Rexahn warrants to purchase Common Stock remained outstanding, the majority of which were subsequently repurchased according to the terms of the original warrant agreements. As of December 31, 2021, 66,538 of the Rexahn warrants remained outstanding with exercise prices ranging from \$38.40 to \$198.00 per share with an average remaining contractual life of 1.9 years. In addition, there were 993 outstanding, unexercised Rexahn stock options to purchase Common Stock upon close of the Merger of which 82 options were outstanding as of December 31, 2021 (see Note 7 – Share-based Compensation).

3. Commitments and Contingencies

Apexian Sublicense Agreement

On January 21, 2020, the Company entered into a sublicense agreement with Apexian Pharmaceuticals, Inc., pursuant to which it obtained exclusive worldwide patent and other intellectual property rights. In exchange for the patent and other intellectual rights, the Company agreed to certain milestone and royalty payments on future sales (See Note 8 — Apexian Sublicense Agreement). As of December 31, 2021, there was sufficient uncertainty with regard to both the outcome of the clinical trials and the ability to obtain sufficient funding to support any of the cash milestone payments under the sublicense agreement, and as such, no liabilities were recorded related to the sublicense agreement.

Facility Leases

In May 2019, the Company entered into a short-term non-cancellable facility lease (the “Lease”) for its operations and headquarters for a seven-month term beginning in June 2019. The Lease, as amended, has extended the term to December 31, 2022. Additionally, Ocuphire leased office space in Rockville, Maryland through June 30, 2021 previously occupied by Rexahn (the “Rexahn Lease”). The Lease and the Rexahn Lease qualified for the short-term lease exception under ASC 842, *Leases*. The monthly base rent, as amended, for the Lease is approximately \$3,000. The monthly base rent for the Rexahn Lease was \$13,000. The rent expense associated with the Lease and Rexahn Lease amounted to \$116,000 and \$54,000 during the years ended December 31, 2021 and 2020, respectively. Total expected rental payments under the Lease for the year ended December 31, 2022 are approximately \$36,000.

Issuance of Settlement Shares

On May 6, 2021, the Company issued 350,000 shares of common stock of the Company to three accredited investors pursuant to a settlement agreement, dated May 6, 2021, in exchange for a release of potential claims. The fair value of the share settlement of \$1,614,000 was based on the closing Ocuphire stock price for that day. The fair value of the share settlement was recorded in general and administrative expenses in the accompanying consolidated statements of comprehensive loss.

Other

In the ordinary course of business, from time to time, the Company may be subject to a broad range of claims and legal proceedings that relate to contractual allegations, patent infringement and other claims. In addition, the Company from time to time may be potentially committed to reimburse third parties for costs incurred associated with business development related transactions upon the achievement of certain milestones. The Company establishes accruals when applicable for matters and commitments which it believes losses are probable and can be reasonably estimated. To date, no loss contingency for such matters and potential commitments have been recorded. Although it is not possible to predict with certainty the outcome of these matters or potential commitments, the Company is of the opinion that the ultimate resolution of these matters and potential commitments will not have a material adverse effect on its results of operations or financial position.

Ocuphire Pharma, Inc.
Notes to Consolidated Financial Statements

4. Supplemental Balance Sheet Information

Prepaid and Other Assets

Prepaid and other assets consist of the following (in thousands):

	December 31,	
	2021	2020
Prepays	\$ 1,243	\$ 1,243
Other	71	26
Total prepaids and other assets	<u>\$ 1,314</u>	<u>\$ 1,269</u>

Property and Equipment, net

Property and equipment held for use by category are presented in the following table (in thousands):

	December 31,	
	2021	2020
Equipment	\$ 20	\$ 20
Furniture	5	5
Total property and equipment	25	25
Less accumulated depreciation	(15)	(11)
Property and equipment, net	<u>\$ 10</u>	<u>\$ 14</u>

Depreciation expense was \$4,000 and \$8,000 for the years ended December 31, 2021 and 2020, respectively.

Accrued Expenses

Accrued expenses consist of the following (in thousands):

	December 31,	
	2021	2020
R&D services and supplies	\$ 1,081	\$ 1,440
Payroll	488	320
Professional services	84	186
Other	80	25
Total	<u>\$ 1,733</u>	<u>\$ 1,971</u>

Short-Term Loan

The Company entered into an unsecured short-term loan (the “Loan”) agreement in the amount of \$0.6 million in November 2021 related to financing an insurance policy. The Loan is payable in six monthly installments of \$108,000 beginning in December 2021. The Loan has an annual interest rate of 5.5% per annum. Interest expense in the amount of \$2,000 was recognized in connection with the Loan during the year ended December 31, 2021.

5. Convertible Notes

The Company entered into a series of unsecured convertible note financings (the “Convertible Notes”) with certain investors beginning on May 25, 2018. The total issuance of Convertible Notes amounted to \$8.5 million (see Note 6 – Related Party Transactions). On November 4, 2020, all of Ocuphire’s outstanding Convertible Notes were converted into 977,128 shares of Ocuphire common stock as adjusted for the Exchange Ratio in connection with the completion of the Merger. The conversion was accounted for as a debt extinguishment given the bifurcation of the embedded premium conversion derivatives. The fair value of the newly issued common shares associated with the Convertible Notes conversion relative to the carrying value of the debt and fair value of premium conversion derivatives on the conversion date was \$2.7 million lower and was recorded largely as a gain on note extinguishment in the amount of \$2.4 million in the accompanying consolidated statements of comprehensive loss with the remaining portion of \$0.3 million differential being recorded as additional paid-in capital for the portion attributed to related parties.

Ocuphire Pharma, Inc.
Notes to Consolidated Financial Statements

Prior to the conversion of the Convertible Notes, the Company amended the Convertible Notes (the “Conversion Agreement”) on June 8, 2020. Under the Conversion Agreement, upon such date selected by the Company following Rexahn’s receipt of the required Rexahn stockholder vote and prior to the effectiveness of the Merger, each Convertible Note would automatically and without any action required by any purchaser or the Company be cancelled and, simultaneously with such cancellation, would convert into that number of fully paid and non-assessable shares of the Company’s common stock that was equal to 175% times the outstanding principal and accrued but unpaid interest (Note Value) divided by the conversion price (the “Conversion Price”), rounded to the nearest whole share. The Conversion Price had the meaning of the per share price resulting from the quotient of (1) \$100,000,000 less the aggregate amount of 175% times the Note Value of all of the Convertible Notes divided by (2) the fully diluted shares (the “Fully Diluted Shares”). Fully Diluted Shares had the meaning of: (1) all of the issued outstanding shares of the Company’s common stock; and (2) the aggregate number of shares of the Company’s common stock reserved for issuance under all outstanding options or other awards under equity incentive plans of the Company in effect as of such date of determination.

The addition of the new conversion feature under the Conversion Agreement represented a substantial modification to the Convertible Notes, and as such, the Company recorded the modification as a note extinguishment. On the modification date, the fair value of the Convertible Notes (inclusive of the embedded features) was \$1.3 million lower upon modification than the aggregate of the carrying value of the Convertible Notes and the fair value of the embedded features; the difference was recorded as a gain on note extinguishment in the accompanying consolidated statements of comprehensive loss for the year ended December 31, 2020.

Lastly, an increase to additional paid-in capital in the amount of \$1.0 million was recorded in connection with the Conversion Agreement to account for the excess of the Convertible Notes’ fair value over the aggregate value of outstanding note principal, accrued interest and fair value of the premium conversion derivatives upon execution of the Conversion Agreement.

The Convertible Notes accrued interest at a rate of 8% per annum, calculated on a 365-day year basis. Interest expense on principal during the year ended December 31, 2020 was \$0.5 million.

Previous to the Conversion Agreement, the outstanding principal of, and accrued interest on the Convertible Notes were payable on demand, in the absence of the Merger closing discussed above, at any time as of the first to occur of (i) September 30, 2020 or (ii) an event of default (each defined by the Convertible Notes as a Payoff Event). If, prior to a Payoff Event, the Company (i) completed an initial public offering (“IPO”), (ii) completed a change in control (“CIC”), (iii) completed a sale and issuance of its capital stock resulting in gross proceeds to the Company of at least \$5 million (“Qualified Financing”), or (iv) completed a reverse merger transaction (Reverse Merger), then the outstanding principal of, and accrued but unpaid interest on the Convertible Notes would have automatically converted upon the earliest of such events to occur as follows:

- **IPO:** The Convertible Notes would have automatically converted into the number of fully paid and non-assessable shares of the Company’s common stock equal to One Hundred and Seventy-Five Percent (175%) times Note Value divided by the per share price such shares were issued to purchasers of the Company’s equity securities in the IPO rounded to the nearest whole share.
- **CIC:** The Convertible Notes would have automatically converted prior to the effectiveness of such CIC into that number of fully paid and non-assessable shares of the Company’s common stock equal to Two Hundred Percent (200%) of the Note Value divided by the per share price of the Company’s common stock at which the Company’s common stock was valued in such CIC (after giving effect to such conversion). The Convertible Note holder would have been entitled to the same contractual rights and would have been bound by the same restrictions and obligations as the other stockholders of the Company in such CIC.
- **Qualified Financing:** The Convertible Notes would have automatically converted into that number of fully paid and non-assessable shares of the Company that were issued by the Company in the Qualified Financing, determined by dividing an amount equal to One Hundred and Seventy-Five Percent (175%) times the Note Value by the per share price such shares of the Company were issued to purchasers of the Company’s equity securities in the Qualified Financing, rounded to the nearest whole share. The Convertible Note holder would have been entitled to the same contractual rights and would have been bound by the same restrictions and obligations as the other purchasers of shares in the Qualified Financing. A Qualified Financing was defined as a sale and issuance of capital stock of the Company (or its successor) in a single transaction or series of related transactions resulting in gross proceeds to the Company of not less than \$5,000,000 (including new equity investment of at least \$1,000,000 plus the sum of the outstanding principal amount of the Convertible Notes being so converted under this provision).

Ocuphire Pharma, Inc.
Notes to Consolidated Financial Statements

- **Reverse Merger (excluding close of Merger with Rexahn):** The Convertible Notes would have automatically converted into that number of fully paid and non-assessable shares of the Combined Company whose shares were publicly traded in the United States or other jurisdiction following the completion of the Reverse Merger (the “Reverse Merger Parent”), determined by dividing an amount equal to One Hundred and Seventy-Five Percent (175%) times the Note Value divided by the per share price at which such shares were issued by the Reverse Merger Parent in such Reverse Merger, rounded to the nearest whole share. The Convertible Note holder would have been entitled to the same contractual rights and would have been bound by the same restrictions and obligations as the other stockholders of the Company in the Reverse Merger.

The Company was not permitted to prepay the Convertible Notes prior to a Payoff Event. The Convertible Notes contained default provisions, and when triggered, the holders of the Convertible Notes could have immediately accelerated payment of the Convertible Notes and the outstanding principal and interest would have become payable immediately. During a period of default, interest would have been assessed at a 12% per annum rate.

Redemption Features

The Company determined that all of the conversion provisions, except for the conversion provision upon Merger close, were redemption features that qualified as embedded derivatives. The qualifying embedded derivatives were collectively separated from their debt host upon the issuance of the Convertible Notes. The bifurcation of the embedded derivatives from the debt host resulted in a discount to the Convertible Notes in the amount of \$0.8 million during the year ended December 31, 2020. The embedded derivatives were accounted for separately on a fair market value basis. The fair value of the derivatives was \$2.7 million at December 31, 2020 and was included in the premium conversion derivatives line item on the accompanying consolidated balance sheets. There were no outstanding premium conversion derivatives as of December 31, 2021 given the conversion of the Convertible Notes. The Company recorded the fair value changes of the premium conversion derivatives while outstanding to fair value change in derivative and warrant liabilities in the accompanying consolidated statements of comprehensive loss which amounted to a benefit of \$0.5 million during the year ended December 31, 2020.

The Company recorded a discount to the Convertible Notes, attributed to both third party costs in connection with the note extinguishments and note issuance costs, of \$8,000 during the year ended December 31, 2020.

The note discounts were amortized to interest expense over the term of the Convertible Notes using the straight-line method which approximates the effective interest method and amounted to \$0.9 million during the year ended December 31, 2020.

6. Related Party Transactions

CVR Agreement

The Company entered into a CVR Agreement with the former Rexahn stockholders. See Note 2 – Merger.

Ocuphire Pharma, Inc.
Notes to Consolidated Financial Statements

Convertible Notes with Related Parties

The Company entered into Convertible Notes with certain investors beginning on May 25, 2018. Through December 31, 2021, Convertible Notes in the principal aggregate amount equal to \$0.7 million were issued to four board members and to two officers, one of which was also a board member of the Company. On November 4, 2020, all of Ocuphire's outstanding Convertible Notes were converted into Ocuphire common, see Note 5 – Convertible Notes.

Apexian Sublicense Agreement

On January 21, 2020, as amended on June 4, 2020, the Company entered into a sublicense agreement with Apexian Pharmaceuticals, Inc. (“Apexian”) and issued a total of 843,751 shares of common stock to Apexian and to certain affiliates of Apexian. See Note 8 – Apexian Sublicense Agreement.

Pre-Merger Financing

Five directors of Private Ocuphire and one director of Rexahn participated in the Pre-Merger Financing, investing an aggregate of \$300,000. Following the closing of the Merger, these directors received 17,729 Converted Initial Shares, 53,189 Converted Additional Shares, 80,366 Series A Warrants and 9,444 Series B Warrants. See Note 9 – Stockholders' Equity (Deficit).

Waiver Agreements

Six directors of the Company signed Waiver Agreements, waiving certain reset provisions financing restrictions. See Note 9 – Stockholders' Equity (Deficit).

7. Share-based Compensation

Share-based compensation expense was included in general and administrative and research and development costs as follows in the accompanying statements of comprehensive loss for the periods indicated below (in thousands):

	December 31,	
	2021	2020
General and administrative	\$ 1,116	\$ 675
Research and development	798	831
Total share-based compensation	<u>\$ 1,914</u>	<u>\$ 1,506</u>

*Ocuphire Stock Options**Inducement Plan*

On February 22, 2021, the Company adopted the Ocuphire Pharma, Inc. Inducement Plan (the “Plan”), pursuant to which the Company reserved 325,258 shares of its common stock to be used exclusively for grants of awards to individuals who were not previously employees or directors of the Company, as an inducement material to the individual's entry into employment with the Company within the meaning of Rule 5635(c)(4) of the Nasdaq Listing Rules.

2020 Equity Incentive Plan

The stockholders of the Company approved the 2020 Equity Incentive Plan (the “2020 Plan”) for share-based awards. The 2020 Plan became effective on November 5, 2020. Under the 2020 Plan, (i) 1,000,000 new shares of common stock are reserved for issuance and (ii) up to 70,325 additional shares of common stock may be issued, consisting of (A) shares that remain available for the issuance of awards under prior equity plans and (B) shares of common stock subject to outstanding stock options or other awards covered by prior equity plans that have been cancelled or expire on or after the date that the 2020 Plan became effective. The 2020 Plan permits the grant of incentive and nonstatutory stock options, appreciation rights, restricted stock, restricted stock units, performance stock and cash awards, and other share-based awards.

Ocuphire Pharma, Inc.
Notes to Consolidated Financial Statements

2018 Equity Incentive Plan

Prior to the 2020 Plan, the Company had adopted a 2018 Equity Incentive Plan (the “2018 Plan”) in April 2018 under which 1,175,000 shares of the Company’s common stock were reserved for issuance to employees, directors and consultants. Upon the effective date of the 2020 Plan, no additional shares were available for issuance under the 2018 Plan.

During the years ended December 31, 2021 and 2020, 420,300 and 830,167 stock options were granted to newly-hired officers, directors, employees and consultants (as adjusted for the Exchange Ratio), respectively, generally vesting over an immediate to forty-eight (48) month period. The Company recognized \$1.8 million and \$1.4 million in share-based compensation expense related to stock options during the years ended December 31, 2021 and 2020, respectively. During the years ended December 31, 2021 and 2020, 73,442 and 40,672 stock options were exercised, respectively, with an intrinsic value of \$345,000 and \$175,000, respectively. The following table summarizes the Company’s stock option plan activity:

	<u>Number of Options</u>	<u>Weighted Average Exercise Price</u>	<u>Weighted Average Remaining Contractual Term (years)</u>	<u>Aggregate Intrinsic Value(1) (in thousands)</u>
Outstanding at December 31, 2019	1,037,705	\$ 1.06	9.20	\$ 1,374
Granted	830,167	\$ 3.50	—	—
Exercised	(40,672)	\$ —	—	—
Forfeited/Cancelled	(43,002)	\$ —	—	—
Outstanding at December 31, 2020	<u>1,784,198</u>	<u>\$ 2.17</u>	<u>8.87</u>	<u>\$ 7,744</u>
Granted	420,300	\$ 5.72	—	—
Exercised	(73,442)	\$ —	—	—
Forfeited/Cancelled	(34,220)	\$ —	—	—
Outstanding at December 31, 2021	<u>2,096,836</u>	<u>\$ 2.97</u>	<u>8.20</u>	<u>\$ 2,795</u>
Vested and exercisable at December 31, 2021	<u>1,281,263</u>	<u>\$ 1.88</u>	<u>7.63</u>	<u>\$ 2,370</u>

(1) The aggregate intrinsic value is calculated as the difference between the exercise price of the underlying options and the fair value of our common stock as of December 31, 2021 and 2020 of \$3.73 and \$6.49 per share (as adjusted for the Exchange Ratio), respectively.

The weighted average fair value per share of options granted during the years ended December 31, 2021 and 2020 was \$4.36 and \$3.92, respectively. The Company measures the fair value of stock options with service-based and performance-based vesting criteria to employees, directors, consultants and directors on the date of grant using the Black-Scholes option pricing model. The Company does not have history to support a calculation of volatility and expected term. As such, the Company has used a weighted-average volatility considering the volatilities of several guideline companies.

For purposes of identifying similar entities, the Company considered characteristics such as industry, length of trading history, and stage of life cycle. The assumed dividend yield was based on the Company’s expectation of not paying dividends in the foreseeable future. The average expected life of the options was based on the contractual term for agreements that allow for exercise of vested options through the end of the contractual term upon termination of continuous service, and for all other agreements, was based on the mid-point between the vesting date and the end of the contractual term according to the “simplified method” as described in Staff Accounting Bulletin 110. The risk-free interest rate is determined by reference to implied yields available from U.S. Treasury securities with a remaining term equal to the expected life assumed at the date of grant. The Company records forfeitures when they occur.

Ocuphire Pharma, Inc.
Notes to Consolidated Financial Statements

The weighted-average assumptions used in the Black-Scholes option-pricing model are as follows during the years ended December 31, 2021 and 2020:

	<u>2021</u>	<u>2020</u>
Expected stock price volatility	98.1%	86.8%
Expected life of options (years)	5.8	7.2
Expected dividend yield	0%	0%
Risk free interest rate	0.9%	0.6%

During the years ended December 31, 2021 and 2020, 468,301 and 379,576 stock options vested (as adjusted for the Exchange Ratio), respectively. The weighted average fair value per share of options vesting during the years ended December 31, 2021 and 2020 was \$3.49 and \$2.77, respectively. During the years ended December 31, 2021 and 2020, 34,220 and 43,002 stock options were forfeited, respectively. As of December 31, 2021, 890,542 shares in the aggregate were available for future issuance under the 2020 Plan and Inducement Plan.

Unrecognized share-based compensation cost was \$2.4 million as of December 31, 2021. The unrecognized share-based expense is expected to be recognized over a weighted average period of 1.1 years.

Ocuphire Restricted Stock Awards

On November 11, 2020, the Company granted 40,000 restricted stock awards (“RSAs”) that vested on January 8, 2021. There were no RSAs granted during the years ended December 31, 2021.

The share-based compensation expense attributed to the RSAs during each of the years ended December 31, 2021 and 2020 was \$22,000 and \$0.1 million, respectively.

A summary of RSA activity is as follows for the years ended December 31, 2021 and 2020:

	<u>Number of Shares</u>
Non-vested at December 31, 2019	—
Granted	40,000
Vested	—
Non-vested at December 31, 2020	40,000
Granted	—
Vested	(40,000)
Non-vested at December 31, 2021	—

Common Stock Issued for Services

The Company granted stock for services in the amount of 21,414 common shares to two board members who elected to receive their board retainers in the form of stock for services performed during the year ended December 31, 2021. The share-based compensation related to these services amounted to \$108,000 during the year ended December 31, 2021.

Former Rexahn Options

Following the closing of the Merger, 123 unexercised and vested options to purchase Common Stock granted under the Rexahn Pharmaceuticals Stock Option Plan, as amended (the “Rexahn 2003 Plan”, and together with the Rexahn 2013 Plan, the “Prior Plans”) were outstanding. As of December 31, 2021, 82 of the former Rexahn options remained outstanding. During the year ended December 31, 2021, 41 of the former Rexahn options expired. The exercise price related to the outstanding options granted under the Prior Plans was \$182.40 per share with an average remaining contractual life of 0.5 years.

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8. Apexian Sublicense Agreement

On January 21, 2020, as amended on June 4, 2020, the Company entered into a sublicense agreement (the “Sublicense Agreement”) with Apexian, pursuant to which it obtained exclusive worldwide patent and other intellectual property rights that constitute a Ref-1 Inhibitor program relating to therapeutic applications to treat disorders related to ophthalmic and diabetes mellitus conditions. The lead compound in the Ref-1 Inhibitor program is APX3330, which the Company intends to develop as an oral pill therapeutic to treat diabetic retinopathy and diabetic macular edema initially, and potentially later to treat wet age-related macular degeneration.

In connection with the Sublicense Agreement, the Company issued a total of 843,751 shares of its common stock to Apexian and to certain affiliates of Apexian. The share issuance transaction was recorded in the amount of \$2.1 million as IPR&D expense for the year ended December 31, 2020 based on the fair market value of the common shares issued since no processes or activities that would constitute a “business” were acquired and none of the rights and underlying assets acquired had alternative future uses or reached a stage of technological feasibility. Additionally, in accordance with the Sublicense Agreement, the Company was required to pay any balance remaining related to \$0.4 million of Ref-1 Inhibitor program costs to Apexian following the Company’s listing on a major stock exchange. In December 2020, the Company paid the remaining Ref-1 Inhibitor program cost balance to Apexian in the amount of \$0.3 million following the close of the Merger. The Ref-1 Inhibitor program costs were recorded as research and development expenses in the accompanying statements of comprehensive loss.

The Company also agreed to make one-time milestone payments under the Sublicense Agreement for each of the first ophthalmic indication and the first diabetes mellitus indication for the Development and Regulatory milestones, and once for each of the Sales milestones. These milestone payments include (i) payments for specified developmental and regulatory milestones (including completion of the first Phase 2 trial and the first Phase 3 pivotal trial in the United States, and filing and achieving regulatory approval from the FDA for the first New Drug Application for a compound) totaling up to \$11 million in the aggregate and (ii) payments for specified sales milestones of up to \$20 million in the aggregate, which net sales milestone payments are payable once, upon the first achievement of such milestone. Lastly, the Company also agreed to make a royalty payment equal to a single-digit percentage of its net sales of products associated with the covered patents under the Sublicense Agreement. If it is not terminated pursuant to its terms, the Sublicense Agreement shall remain in effect until expiration of the last to expire of the covered patents.

None of the milestone or royalty payments, outside of the Ref-1 Inhibitor program cost reimbursement, were triggered or deemed probable as of December 31, 2021.

9. Stockholder Equity (Deficit)

At-The-Market Program

On February 4, 2021, Ocuphire filed a Form S-3 shelf registration under the Securities Act of 1933 which was declared effective by the SEC on February 12, 2021 (the “2021 Shelf”) under which the Company may offer and sell, from time to time in its sole discretion, securities having an aggregate offering price of up to \$125 million. In connection with the 2021 Shelf, on March 11, 2021, Ocuphire entered into a Sales Agreement with JonesTrading Institutional Services LLC (“JonesTrading”) under which the Company may offer and sell, from time to time at its sole discretion, to or through JonesTrading, acting as agent and/or principal, shares of its common stock having an aggregate offering price of up to \$40 million (the “2021 ATM”). During the year ended December 31, 2021, 2,778,890 common shares were sold under the 2021 ATM for gross proceeds in the amount of \$13.5 million before deducting issuance expenses, including the placement agent’s fees, legal and accounting expenses, in the amount of \$0.4 million.

Registered Direct Offering

On June 4, 2021, the Company entered into a placement agency agreement with A.G.P./Alliance Global Partners (“AGP”). Pursuant to the terms of the placement agency agreement, AGP on June 8, 2021 sold an aggregate of 3,076,923 shares of the Company’s common stock and warrants to purchase 1,538,461 shares of the Company’s common stock (the “RDO Warrants”) at an offering price of \$4.875 per one share and 0.50 RDO Warrants, for gross proceeds of \$15.0 million, before AGP’s fees and related offering expenses in the amount of \$1.1 million. The proceeds were allocated between the relative fair values of common stock and warrants at the sale date. The purchase agreement contains customary representations, warranties and agreements by the Company, customary conditions to closing, indemnification obligations of the Company, other obligations of the parties and termination provisions. The offering of the Securities (the “Registered Direct Offering”) was made pursuant to the Company’s 2021 Shelf.

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The RDO Warrants have an exercise price of \$6.09 per share, are exercisable from the initial issuance date of June 8, 2021, and will expire five years following the initial issuance date. The fair value of the RDO Warrants was determined to be \$6.4 million based on the Black-Scholes pricing model. Input assumptions used were as follows: a risk-free interest rate of 0.8%; expected volatility of 99.2%; expected life of 5 years; expected dividend yield of 0%; and the underlying fair market of the common stock. The RDO Warrants were classified in stockholders' equity (deficit) after considering indexation and settlement rules of ASC 480 and 815 that require that the number of issuable shares are fixed and determinable and other conditions required for equity treatment. As of December 31, 2021, 1,538,461 RDO Warrants were outstanding.

Subject to limited exceptions, a holder of a RDO Warrant will not have the right to exercise any portion of its RDO Warrants if the holder, together with its affiliates, would beneficially own in excess of 4.99% (or, at the election of a holder prior to the date of issuance, 9.99%) of the number of shares of the Company's common stock outstanding immediately after giving effect to such exercise; provided, however, that upon prior notice to the Company, the holder may increase or decrease the beneficial ownership limitation, provided further that in no event shall the beneficial ownership limitation exceed 9.99%.

Pre-Merger Financing

Waiver Agreements

Effective February 3, 2021, each investor that invested in the Pre-Merger Financing (as defined below) entered into a Waiver Agreement with the Company (collectively, the "Waiver Agreements"). Pursuant to the Waiver Agreements, the investors and the Company agreed to waive certain rights, finalize the exercise price and number of Series A Warrants and Series B Warrants, eliminate certain financing restrictions, extend the term of certain leak-out agreements, and, in the case of certain investors, grant certain registration rights for the shares underlying the warrants.

The Waiver Agreements provide for the elimination of the full ratchet anti-dilution provisions, contained in the Series A Warrants (as certain of the anti-dilution provisions had previously caused liability accounting treatment for the Series A Warrants). Upon the effective date of the Waiver Agreements, the Series A Warrants were reclassified to equity.

Pursuant to the Waiver Agreements, the number of shares underlying all of the Series B Warrants was fixed to 1,708,334 in the aggregate with respect to all investors, eliminating any future resets.

Securities Purchase Agreement

On June 17, 2020, Ocuphire, Rexahn and certain investors entered into a Securities Purchase Agreement, which was amended and restated in its entirety on June 29, 2020 (as amended and restated, the "Securities Purchase Agreement"). Pursuant to the Securities Purchase Agreement, the investors invested a total of \$21.15 million in cash, including \$300,000 invested by five directors of Private Ocuphire and one director of Rexahn, upon closing of the Merger (the "Pre-Merger Financing"). Pursuant to the Pre-Merger Financing, (i) Ocuphire issued and sold to the investors shares of Private Ocuphire common stock (the "Initial Shares") which converted pursuant to the exchange ratio in the Merger into an aggregate of approximately 1,249,996 shares (the "Converted Initial Shares") of common stock, (ii) Ocuphire deposited into escrow, for the benefit of the Investors, additional shares of Private Ocuphire common stock (the "Additional Shares") which converted pursuant to the exchange ratio in the Merger into an aggregate of approximately 3,749,992 shares of common stock (the "Converted Additional Shares"), which Converted Additional Shares were delivered (or became deliverable) to the investors on November 19, 2020, and (iii) the Company agreed to issue to each investor on the tenth trading day following the consummation of the Merger (x) Series A Warrants representing the right to acquire shares of common stock equal to the sum of (A) the Converted Initial Shares purchased by the investor, (B) the Converted Additional Shares delivered or deliverable to the investor, without giving effect to any limitation on delivery contained in the Securities Purchase Agreement and (C) the initial number of shares of common stock, if any, underlying the Series B Warrants issued to the Investor and (y) additional warrants to purchase shares of common stock.

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Series A Warrants

The Series A Warrants were issued on November 19, 2020 at an initial exercise price of \$4.4795 per share, were immediately exercisable upon issuance and have a term of five years from the date of issuance. The Series A Warrants are exercisable for 5,665,838 shares of common stock in the aggregate (without giving effect to any limitation on exercise contained therein) and were outstanding as of December 31, 2021.

The Series A Warrants provide that, until the second anniversary of the date on which all shares of common stock issued and issuable to the investors may be sold without restriction or limitation pursuant to Rule 144, if Ocuphire publicly announces, issues or sells, enters into a definitive, binding agreement pursuant to which Ocuphire is required to issue or sell or is deemed, pursuant to the provisions of the Series A Warrants, to have issued or sold, any shares of common stock for a price per share lower than the exercise price then in effect, subject to certain limited exceptions, then the exercise price of the Series A Warrants will be reduced to such lower price per share. Further, on each Reset Date (as defined below under Series B Warrants) the Series A Warrants will be adjusted downward (but not increased) such that the exercise price thereof becomes 120% of the Reset Price (as defined below), and the number of shares underlying the Series A Warrants will be increased (but not decreased) to the quotient of (a) (i) the exercise price in effect prior to such Reset (as defined below under Series B Warrants) multiplied by (ii) the number of shares underlying the Series A Warrants prior to the Reset divided by (b) the resulting exercise price. In addition, the exercise price and the number of shares of Common Stock issuable upon exercise of the Series A Warrants will also be subject to adjustment in the event of any stock splits, dividends or distributions or other similar transactions.

The Series A Warrants were initially accounted for and classified as liabilities upon close of the Merger through the date of the Waiver Agreements given that certain price reset provisions existed that cannot be used for a fair valuation under a fixed for fixed settlement scenario required for equity balance sheet classification. A Monte Carlo simulation model was used to estimate the aggregate fair value of the Series A Warrants. Input assumptions used were as follows: risk-free interest rate 0.4%; expected volatility of 83.6%; expected life of 5 years; and expected dividend yield zero percent. The underlying stock price used was the market price as quoted on Nasdaq as of November 19, 2020. The aggregate fair value of the Series A Warrants of \$25.8 million upon issuance was recorded as a long-term liability on the accompanying consolidated balance sheets. The amount by which the aggregate fair value of the Series A Warrants exceeded the \$21.15 million gross proceeds from the Pre-Merger Financing, or \$4.7 million, was recorded as day-one interest on the accompanying consolidated statements of comprehensive loss during the year ended December 31, 2020. The Company recorded the fair value change of the Series A Warrants in the amount of \$2.1 million to the fair value change in derivative and warrant liabilities line item on the accompanying consolidated statements of comprehensive loss for the year ended December 31, 2020.

Upon the February 3, 2021 effective date of the Waiver Agreements, the Series A Warrants were reclassified to equity. A final fair valuation of the Series A Warrants was performed utilizing a Black Scholes model to estimate the aggregate fair value of the Series A Warrants prior to being re-classified as equity. Input assumptions used were as follows: risk-free interest rate 0.4%; expected volatility of 86.6%; expected life of 4.8 years; and expected dividend yield zero percent. The underlying stock price used was the market price as quoted on Nasdaq as of February 3, 2021, the effective date of the Waiver Agreement. The fair value change of the Series A Warrants was \$33.8 million and was recorded to the fair value change in warrant liabilities and premium conversion derivatives line item on the accompanying consolidated statements of comprehensive loss for the year ended December 31, 2021. As a result of the reclassification to equity, the Series A Warrants are no longer subject to remeasurement.

Series B Warrants

The Series B Warrants have an exercise price of \$0.0001, were exercisable upon issuance and will expire on the day following the later to occur of (i) the Reservation Date (as defined therein), and (ii) the date on which the investor's Series B Warrants have been exercised in full (without giving effect to any limitation on exercise contained therein) and no shares remain issuable thereunder. The Series B Warrants are fixed and were exercisable for 1,708,334 shares of Common Stock, as of the effective date of the Waiver Agreement, in the aggregate (without giving effect to any limitation on exercise contained therein). In April 2021, investors exercised Series B Warrants for a total of 1,629,634 shares. As of December 31, 2021, 78,700 Series B warrants were outstanding.

Ocuphire Pharma, Inc.
Notes to Consolidated Financial Statements

Prior to the Waiver Agreements, the Series B warrants were initially exercisable for 665,836 shares of Common Stock in the aggregate (without giving effect to any limitation on exercise contained therein). Additionally, prior to the Waiver Agreement, the number of Series B were subject to adjustment whereby every ninth trading day up to and including the 45th trading day (each, a “Reset Date”) following (i) six months following the issuance date (the “Six Month Reset Date”) and (ii) if a Public Information Failure has occurred at any time following the Six Month Reset Date, the earlier to occur of (x) the date that such Public Information Failure is cured and no longer prevents the holder from selling all underlying securities pursuant to Rule 144 without restriction or limitation and (y) the earlier to occur of (I) the date all of the underlying securities may be sold without restriction or limitation pursuant to Rule 144 and without the requirement to be in compliance with Rule 144(c)(1) and (II) one year after the issuance date (each such date provided in the foregoing clauses (i), (ii) and (iii), an “End Reset Measuring Date”) (such 45 trading day period, the Reset Period and each such 45th trading day after an End Reset Measuring Date, an “End Reset Date”), the number of shares issuable upon exercise of each Investor’s Series B Warrants shall be increased (a “Reset”) to the number (if positive) obtained by subtracting (i) the sum of (a) the number of Converted Initial Shares issued to the investor and (b) the number of Converted Additional Shares delivered or deliverable to the investor as of the Warrant Closing Date, from (ii) the quotient determined by dividing (a) the pro rata portion of the Purchase Price paid by the Investor, by (b) the greater of (x) the arithmetic average of the five lowest dollar volume-weighted average prices of a share of Common Stock on Nasdaq during the applicable Reset Period immediately preceding the applicable Reset Date to date and (y) a floor price per share calculated based on a pre-money valuation (of the Combined Company, assuming for this purpose the pre-money issuance of the Converted Initial Shares and Converted Additional Shares) of \$10 million.

The Series B Warrants were accounted for and classified as equity on the accompanying consolidated balance sheets.

Other

In connection with the Pre-Merger Financing, the Company incurred issuance costs in the amount of \$1.8 million which included (i) a placement agent cash fee of \$1.6 million and (ii) legal and other fees of \$0.2 million. Issuance costs in the amount of \$0.7 million attributed to the Series A Warrants were recorded as interest expense on the accompanying consolidated statements of comprehensive loss for the year ended December 31, 2020 and \$1.1 million was recorded as an offset to additional paid-in capital.

10. Collaboration and License Agreements

BioSense License and Assignment Agreement

On March 10, 2020, pre-Merger, Rexahn entered into an amendment to its collaboration and license agreement, (as amended, the “BioSense License and Assignment Agreement”) with BioSense to advance the development and commercialization of RX-3117 for all human uses in the Republic of Singapore, China, Hong Kong, Macau, and Taiwan (the “BioSense Territory”). Under the terms of the BioSense License and Assignment Agreement, the Company (i) granted BioSense an exclusive license to develop and commercialize pharmaceutical products containing RX-3117 as a single agent for all human uses in the BioSense Territory and (ii) assigned and transferred all of the former Rexahn patents and patent applications related to RX-3117 in the BioSense Territory. The upfront payment consisted of an aggregate of \$1,650,000, of which \$1,550,000 was paid to Rexahn prior to the Merger. During the year ended December 31, 2021, the Company satisfied a performance obligation for the \$100,000 payment that was remaining and recorded this amount as collaboration revenue.

Ocuphire Pharma, Inc.
Notes to Consolidated Financial Statements

Under the BioSense License and Assignment Agreement, the Company is eligible to receive additional milestone payments in an aggregate of up to \$84,500,000 upon the achievement of development, regulatory and commercial goals and will also be eligible to receive tiered royalties at low double-digit rates on annual net sales in the BioSense Territory. The Company determined that none of the milestone payments under the BioSense License and Assignment Agreement were probable of payment as of December 31, 2021, and as a result, no revenue related to the milestones was recognized as the achievement of events entitling the Company to any milestone payments were highly susceptible to factors outside of the Company's control. Future sales-based royalties related to the exclusive license to develop RX-3117 will be recognized in the period the underlying sales transaction occurs.

Payments received under the BioSense License and Assignment Agreement are subject to the CVR Agreement described in Note 2 – Merger.

Processa License Agreement

On June 16, 2021, the Company entered into a license agreement (the "Processa License Agreement") with Processa Pharmaceuticals, Inc. ("Processa"), pursuant to which the Company has agreed to grant Processa an exclusive license to develop, manufacture and commercialize RX-3117 globally, excluding the BioSense Territory.

As consideration for the Processa License Agreement, the Company received an upfront payment in July 2021 consisting of 44,689 shares of Processa common stock with a fair value of \$289,000 (at the contract date) and a \$200,000 cash payment. The Company is restricted from selling the Processa common stock for a period of one year ending June 16, 2022. As additional consideration, Processa will make payments to the Company upon the achievement of certain development and regulatory milestones, which primarily consist of dosing a patient in pivotal trials or having a drug indication approved by a regulatory authority in the United States or another country. In addition, Processa will pay the Company mid-single-digit royalties based on annual sales under the license and will make one-time sales milestone payments based on the achievement during a calendar year of certain thresholds for annual sales. Processa is also required to give the Company 32% of any milestone payments received based on any sub-license agreement Processa may enter into with respect to the Processa License Agreement. The Company determined that none of the milestone payments under the Processa License Agreement were probable of payment as of December 31, 2021, and as a result, no revenue related to the milestones was recognized, as the achievement of events entitling the Company to any milestone payments were highly susceptible to factors outside of the Company's control.

Processa is required to use commercially reasonable efforts, at its sole cost and expense, to conduct development activities in one or more countries, including meeting specific diligence milestones that consist of: (i) first patient administered drug in a clinical trial of a licensed product prior to the three (3) year anniversary of the effective date; and (ii) first patient administered drug in a pivotal clinical trial of a licensed product or first patient administered drug in a clinical trial for a second indication of a licensed product prior to the five (5) year anniversary of the effective date. Either party may terminate the agreement in the event of a material breach of the agreement that has not been cured following written notice and a 120-day opportunity to cure such breach, and Processa may terminate the agreement for any reason upon 120 days prior written notice to Ocuphire.

As of December 31, 2021, the Company has fulfilled its performance obligations with respect to the upfront payment under the Processa License Agreement and has recognized the associated licensing revenue in connection with the payment.

Payments received under the Processa License Agreement will be subject to the CVR Agreement described in Note 2 – Merger.

11. Net loss per share

Basic loss per share of common stock is computed by dividing net loss by the weighted average number of shares of common stock outstanding during the period. Diluted earnings or loss per share of common stock is computed similarly to basic earnings or loss per share except the weighted average shares outstanding are increased to include additional shares from the assumed exercise of any common stock equivalents, if dilutive. The Company's warrants, convertible notes, restricted stock awards and stock options while outstanding are considered common stock equivalents for this purpose. Diluted earnings is computed utilizing the treasury method for the warrants, restricted stock and stock options. No incremental common stock equivalents were included in calculating diluted loss per share because such inclusion would be anti-dilutive given the net loss reported for the periods presented. The historical share and per share data for periods on or prior to the November 5, 2020 close of the Merger have been adjusted to give effect to the Exchange Ratio.

Ocuphire Pharma, Inc.
Notes to Consolidated Financial Statements

The following potential common shares were not considered in the computation of diluted net loss per share as their effect would have been anti-dilutive for the year end periods presented below:

	2021	2020
Series A, Series B and RDO warrants	7,282,999	6,331,674
Stock options	2,096,836	1,784,198
Restricted stock awards including pending issuances of stock for services	6,970	40,000
Former Rexahn warrants	66,538	66,538
Former Rexahn options	82	123

12. Income Taxes

The effective tax rate for the years ended December 31, 2021 and 2020 was zero percent.

A reconciliation of income tax computed at the statutory federal income tax rate to the provision (benefit) for income taxes included in the accompanying statements of comprehensive loss is as follows for the years ended December 31, 2021 and 2020:

	2021	2020
Income tax (benefit) provision at federal statutory rate	(21.0)%	(21.0)%
Valuation allowance	11.9	13.8
State income tax, net of federal benefit	(4.8)	(4.7)
Acquired in-process research and development expense	—	8.8
Warrants	15.3	7.6
Convertible notes	—	(3.3)
Stock options	(0.1)	(0.1)
Research and development	(1.1)	(1.1)
Other	(0.2)	—
Effective tax rate	—%	—%

Significant components of the Company's deferred tax assets and liabilities are summarized in the tables below as of December 31, 2021 and 2020:

	2021	2020
Deferred tax assets:		
Federal and state operating loss carryforwards	\$ 19,244	\$ 3,351
Acquired intangibles	547	547
Organizational costs	7	8
Other	18	—
Share-based compensation	811	466
Research and development	1,035	275
Subtotal	21,662	4,647
Valuation allowance	(21,662)	(4,647)
Total deferred tax assets, net of valuation allowance	—	—
Deferred tax liabilities:		
Total deferred tax liabilities	—	—
Net deferred tax assets	\$ —	\$ —

Ocuphire Pharma, Inc.
Notes to Consolidated Financial Statements

As of December 31, 2021 and 2020, the Company had gross deferred tax assets of approximately \$21.7 million and \$4.6 million, respectively. Realization of the deferred assets is primarily dependent upon future taxable income, if any, the amount and timing of which are uncertain. The Company has had significant pre-tax losses since its inception. The Company has not yet generated revenues and faces significant challenges to becoming profitable. Accordingly, the net deferred tax assets have been fully offset by a valuation allowance of \$21.7 million and \$4.6 million as of December 31, 2021 and 2020, respectively. U.S. net deferred tax assets will continue to require a valuation allowance until the Company can demonstrate their realizability through sustained profitability or another source of income.

As of December 31, 2021 and 2020, the tax effect of the Company's federal net operating loss carryforwards was approximately \$15.7 million and \$2.7 million, respectively. The Company had federal research credit carryforwards as of December 31, 2021 and 2020 of approximately \$1.0 million and \$0.3 million, respectively. The federal net operating loss carryforwards will not expire and the tax credit carryforwards will begin to expire in 2040 if not utilized. As of December 31, 2021 and 2020, the Company had state net operating loss carryforwards with a tax effect of approximately \$3.6 million and \$0.6 million, respectively. The Company did not have any state research credit carryforwards as of December 31, 2021 and 2020. The state net operating loss carryforwards will begin to expire in 2028.

Utilization of the net operating loss carryforwards and credits may be subject to a substantial annual limitation due to the ownership change limitations provided by Section 382 and Section 383 of the Internal Revenue Code of 1986, as amended, and similar state provisions. Generally, in addition to certain entity reorganizations, the limitation applies when one or more "5-percent shareholders" increase their ownership, in the aggregate, by more than 50 percentage points over a 3 year testing period, or beginning the day after the most recent ownership change, if shorter. The annual limitation may result in the expiration of net operating losses and credits before utilization. As a result of the Merger, the Company recorded deferred tax assets of \$10.3 million relating to net operating loss carryforwards which were fully offset by a valuation allowance. The \$10.3 million net deferred tax assets recorded in relation to the Merger did not include federal and state net operating loss carryforwards that were estimated to expire under Internal Revenue Code Sections 382 as a result of the Merger. The Company has not yet evaluated the impact of Section 382 and Section 383 on its remaining tax attributes that were generated by Ocuphire since the formation of the Company in 2018.

The Company recognizes interest and/or penalties related to uncertain tax positions in income tax expense. There were no uncertain tax positions as of December 31, 2021 and 2020, and as such, no interest or penalties were recorded to income tax expense.

The Company's corporate returns are subject to examination for the beginning with the 2018 tax year for both federal income tax purposes and for state income tax purposes in one state jurisdiction.

13. Subsequent Events

2020 Plan Evergreen Provision

Under the 2020 Plan, the shares reserved automatically increase on January 1 of each year, for a period of not more than ten years from the date the 2020 Plan is approved by the stockholders of the Company, commencing on January 1, 2021 and ending on (and including) January 1, 2030, by an amount equal to 5% of the shares of common stock outstanding as of December 31st of the preceding calendar year. Notwithstanding the foregoing, the Board of Directors may act prior to January 1st of a given year to provide that there will be no January 1 increase in the share reserve for such year or that the increase in the share reserve for such year will be a lesser number of shares of common stock than would otherwise occur pursuant to the preceding sentence. On January 1, 2022, 942,291 shares were added to the 2020 Plan as a result of the evergreen provision.

Ocuphire Pharma, Inc.
Notes to Consolidated Financial Statements

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

OCUPHIRE PHARMA, INC.

Dated: March 24, 2022

By: /s/ Mina Sooch
Mina Sooch
President, Chief Executive Officer and Director

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

By /s/ Mina Sooch Date: March 24, 2022
Mina Sooch
President, Chief Executive Officer and Director

By /s/ Amy Rabourn Date: March 24, 2022
Amy Rabourn
Vice President of Finance

By /s/ Sean Ainsworth Date: March 24, 2022
Sean Ainsworth
Director

By /s/ James S. Manuso Date: March 24, 2022
James S. Manuso
Director

By /s/ Cam Gallagher Date: March 24, 2022
Cam Gallagher
Director

By /s/ Jay Pepose Date: March 24, 2022
Jay Pepose
Director

By /s/ Richard J. Rodgers Date: March 24, 2022
Richard J. Rodgers
Director

By /s/ Susan K. Benton Date: March 24, 2022
Susan K. Benton
Director

LIST OF SUBSIDIARIES

Subsidiaries of Ocuphire Pharma, Inc.

Subsidiaries

Jurisdiction of Incorporation

None

Consent of Independent Registered Public Accounting Firm

We consent to the incorporation by reference in the Registration Statements on Form S-3 (No. 333-252715) and Form S-8 (No. 333-254923, 333-249978, 333-217627, 333-189240, and 333-129294) of Ocuphire Pharma, Inc., of our report dated March 24, 2022, relating to the consolidated financial statements of Ocuphire Pharma, Inc., included in this Annual Report (Form 10-K) of Ocuphire Pharma, Inc. for the year ended December 31, 2021.

/s/ Ernst & Young LLP

Detroit, MI
March 24, 2022

**CERTIFICATION PURSUANT TO RULE 13a-14(a) OR RULE 15d-14(a)
OF THE SECURITIES EXCHANGE ACT OF 1934, AS AMENDED**

I, Mina Sooch, certify that:

1. I have reviewed this Annual Report on Form 10-K of Ocuphire Pharma, Inc. (the “Company”);
2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;
3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;
4. The Registrants other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f) for the registrant and have:
 - (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;
 - (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;
 - (c) Evaluated the effectiveness of the registrant’s disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and
 - (d) Disclosed in this report any change in the registrant’s internal control over financial reporting that occurred during the registrant’s most recent fiscal quarter (the registrant’s fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant’s internal control over financial reporting; and
5. The registrant’s other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant’s auditors and the audit committee of the registrant’s board of directors (or persons performing the equivalent functions):
 - (a) all significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant’s ability to record, process, summarize and report financial information; and
 - (b) any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant’s internal control over financial reporting.

Date: March 24, 2022

/s/ Mina Sooch

Name: Mina Sooch

Title: Chief Executive Officer

(Principal Executive Officer)

**CERTIFICATION PURSUANT TO EXCHANGE ACT RULE 13a-14(a) OR 15d-14(a), AS ADOPTED
PURSUANT TO SECTION 302 OF THE SARBANES OXLEY ACT OF 2002**

I, Amy Rabourn, certify that:

1. I have reviewed this Annual Report on Form 10-K of Ocuphire Pharma, Inc. (the "Company");
2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;
3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;
4. The Registrants other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f) for the registrant and have:
 - (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;
 - (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;
 - (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and
 - (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and
5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):
 - (a) all significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and
 - (b) any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 24, 2022

/s/ Amy Rabourn

Name: Amy Rabourn
Title: Vice President of Finance
(Principal Financial Officer)

**CERTIFICATION PURSUANT TO SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002
(Subsections (a) and (b) of Section 1350, Chapter 63 of Title 18, United States Code)**

In connection with the Annual Report on Form 10-K for the year ended December 31, 2021 (the “Report”) of Ocuphire Pharma, Inc., a Delaware corporation (the “Company”) as filed with the Securities and Exchange Commission (the “Report”), Mina Sooch, as Chief Executive Officer of the Company, and Amy Rabourn, as Vice President of Finance of the Company, each hereby certifies, pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, 18 U.S.C. Section 1350), that to the best of her knowledge and belief:

- (1) The Report fully complies with the requirements of section 13(a) or 15(d) of the Securities Exchange Act of 1934 (15 U.S.C. 78m or 78o(d)); and
- (2) The information contained in the Report fairly presents, in all material respects, the financial condition and result of operations of the Company.

Date: March 24, 2022

/s/ Mina Sooch
Mina Sooch
Chief Executive Officer
(Principal Executive Officer)

/s/ Amy Rabourn
Amy Rabourn
Vice President of Finance
(Principal Financial Officer and
Principal Accounting Officer)
