ENCODE
IDEAS

Ocuphire Pharma, Inc. (OCUP)
INITIATION REPORT

November 9, 2020

HIGH CONVICTION INVESTMENT IDEA

Low Science / High Science, Low Risk / High Risk, Ocuphire has a little of everything, heading into a data-rich 2021.

Ocuphire is an ophthalmology focused drug development company with two mid/late stage drugs, Nyxol and APX3330, in their pipeline. Nyxol, their lead asset, is an ophthalmic formulation of a well-known API, that has been studied in 7 previous ophthalmology studies, and being developed under FDA's 505(b)2 pathway. Ocuphire is running three clinical studies with Nyxol in three unique front of the eye indications, all of which will report data in 2021. We believe Nyxol is a de-risked asset, with a high probability of success in one or more of these studies. Their second asset, APX3330, is an oral new chemical entity (NCE), previously studied in hepatitis and oncology, with a novel mechanism of action (MOA) that Ocuphire believes is well suited for targeting back of the eye diseases. The company will be initiating a Ph2 study with APX3330 in early 2021 and expects top-line data at the end of the year. We view APX3330 as a high risk / high reward asset that offers homerun optionality for Ocuphire investors. We like the cadence of clinical news that Ocuphire will generate in 2021, with the lower risk Nyxol trials reading out before the higher risk APX3330 data at the end of the year. Regardless, 2021 will be a data-rich year for Ocuphire, where clinical success from any of their four clinical trials can materially rerate the stock.

Nyxol

We would categorize Nyxol as a low-science, spec pharma product. An ophthalmic reformulation of an FDA-approved drug, with a well-known and validated MOA. Over the course of 7 previously run Ph1 and Ph2 studies, it is apparent Nyxol rapidly and consistently reduces pupil diameter, leading to an improvement in visual acuity. Throughout 2021, Ocuphire will complete three studies, two Ph3 and one Ph2, with Nyxol in indications where there are no FDA-approved drugs; reversal of mydriasis (RM), night vision disturbances (NVD), and presbyopia. Across the three indications being pursued by Ocuphire with Nyxol, we believe RM has the highest probability of clinical success, where the Ph3 endpoint of pupil diameter reduction is very achievable. Conveniently top-line Ph3 RM data will also be the first of the three studies to readout, likely 1Q21. The market opportunity for Nyxol in RM is modest, given the one-time dosing, whereas NVD and presbyopia are large chronic application markets. Ocuphire has earlier data for Nyxol in NVD that are suggestive of its efficacy, so we believe there is a good probability of clinical success in Ph3. Presbyopia, the biggest of the three indications, is arguably the highest risk of the Nyxol programs being pursued by Ocuphire, as there are no previous Nyxol data in this indication. However, we would highlight that Ocuphire is testing a combination of Nyxol with low-dose pilocarpine in its Ph2 presbyopia study, and that Abbvie/Allergan recently reported positive Ph3 data from two presbyopia studies with their 1.25% pilocarpine solution. Overall, we believe there is sound mechanistic, clinical, and commercial rationale for all three indications being pursued with Nyxol. In our opinion, there is a high probability Ocuphire delivers positive data in one or more of their three Nyxol studies in 2021.

APX3330

We would categorize APX3330 as a high-science product, an oral NCE, with a novel, albeit still unproven, MOA (ref-1 inhibition) for ophthalmology. In-licensed from Apexian (who had in-licensed from Eisai), APX3330 has been in >10 clinical studies by its previous owners, predominantly testing its potential efficacy in hepatitis and oncology. Ref-1 inhibition appears to have benefit upstream of blockbuster anti-VEGF drugs, Lucentis and Eylea, in the hypoxia pathway, as well as being upstream of steroids in the inflammatory pathway, giving APX3330 potential in back of the eye indications. Ocuphire will run a proof-of-concept Ph2 study with APX3330 in patients with diabetic macular edema (DME) or diabetic retinopathy (DR) in 2021. This is a high risk / high reward opportunity in our opinion. DME and DR are big markets, and an effective oral therapy, that can be used complementary to existing injectable blockbusters, Lucentis and Eylea, would be a homerun. Unlike Nyxol with its plethora of legacy ophthalmic data, with APX3330 investors need to make a bigger leap that the drug's MOA translates into clinical efficacy in DME and/or DR. Top-line data from this Ph2 study are expected YE21.

FINANCIAL SUMMARY TABLE

Symbol	OCUP
Exchange	NASDAQ
Current Price	$6.14
52 week High	$6.72
52 week Low	$5.98
O/S	~7.1mm*
Market Cap est	~60mm**
Average Volume (3M)	~67k
Cash	~$21.15mm*

*as of 11/06/2020

**please see the financial consideration section for our estitmate

KEY CATALYST DATES

1Q 2021	RM Ph3 MIRA-2 Data Release
2Q 2021	Presbyopia Ph2 VEGA-1 Data Release
3Q 2021	NVD Ph3 LYNX-1 Data Release
4Q 2021	DME / DR Ph2 ZETA-1 Data Release

KEY DISCLOSURES

The Encode Ideas, L.P. partners own stock in the covered company; Encode Ideas, L.P. is currently engaged by Ocuphire to provide research coverage and awareness. Encode Ideas, L.P. intends to continue transacting in the securities covered therein, and we may be long, short, or neutral thereafter.

Drug	Indication	PoC Data	Stage	Prob of Success	Market Size (U.S.)
Nyxol	RM	Ph2 MIRA-1	Entering Ph3	V. Good	$400mm
Nyxol	NVD	Ph2 SVN & 01a	Entering Ph3	Good	$2B
Nyxol + Pilo	Presbyopia	Arguably ORION-1	Entering Ph2	Good	>$10B
APX3330	DR/DME	None	Entering Ph2	Moderate	>$10B

Nyxol

Nyxol, is a once-daily eye drop formulation of phentolamine (0.75%) and mesylate salt (0.25%), referred to as both 1% Nyxol (active + salt) or 0.75% Nyxol (just active), designed to reduce pupil diameter and improve visual acuity. PM is a non selective alpha 1&2 adrenergic antagonist, and is the active ingredient in two FDA-approved drugs; (1) Regitine injectable for pre & post operative hypertension (2) Oraverse injectable for anaesthesia reversal after oral surgery. In 2021 Ocuphire will be running studies with Nyxol in 3 ophthalmic indications, none of which have any FDA-approved products yet; reversal of mydriasis (RM), night vision disturbances (NVD), and presbyopia. These indications are not traditional diseases, rather they are inconveniences that occur with our vision, predominantly due to aging. We would describe Nyxol as a drug of "convenience" or "lifestyle", as such, it is basically held to a different standard, at least by the patient (the customer), than a drug treating a true disease. Patients' willingness to pay out-of-pocket for the benefit and convenience of Nyxol will be highly correlated to not only the product's efficacy, but tolerability, ease-of-use, and price point. Fortunately Nyxol should check these convenience boxes, with mild transient eye redness as the only real side effect (easily managed by dosing before bed), convenient once-daily dosing, and low COGs, allowing for pricing flexibility. Finally, Nyxol's adoption benefit substantially from having a receptive prescribing audience with optometrists. Similar to how dermatologists embraced Botox, another lifestyle drug, as an avenue to increase their customer and revenue base, so too could optometrists with Nyxol.

Nyxol - Reversal of Mydriasis

There are over 80mm eye exams performed per year in the U.S. and the vast majority involve pharmaceutically induced pupil dilation (mydriasis). Mydriasis, while safe, can last anywhere from a few hours to 24-hrs (average 6-hrs), during which a patient is likely to experience the discomfort of blurred vision, sensitivity to bright light, compromising their ability to drive, read and work. Nyxol, given its proven ability to reduce pupil size, is being developed as an on-demand solution for rapid pupil diameter (PD) reduction post eye exam, allowing patients to return to normal activities, hours sooner than would naturally occur.

Nyxol's efficacy in RM was demonstrated in the small, 32-patient, Ph2 MIRA-1 study. In MIRA-1 Nyxol achieved the primary efficacy endpoint demonstrating a statistically significant improvement in the percentage of patients returning to within 0.5mm of their baseline PD at 120-minutes versus placebo. These Ph2 results are highly encouraging for Nyxol's efficacy in RM, but in the company's Ph3 planning discussions with FDA, the agency recommended a more stringent primary endpoint, PD within 0.2mm baseline vs the 0.5mm used in MIRA-1, and measuring the endpoint at 90-minutes vs 120-minutes. Ocuphire performed a post-hoc analysis of MIRA-1, using the FDA recommended PD baseline measure of 0.2mm from baseline, and found Nyxol had a statistically significant higher percentage of eyes that met the endpoint than placebo at 120-minutes. MIRA-1 did not have a pre-defined 90-minute measure of PD, so the company looked at 60-minutes, and found that Nyxol again had a higher percentage of patients within 0.2mm of baseline PD vs placebo. The 60-minute results did not reach statistical significance, though there was a healthy trend at p=0.1094.

Ocuphire plans to start the first of two Ph3 studies with Nyxol for RM before YE20, with top-line data 1Q21. The Ph3 MIRA-2 study will enroll 168 patients and will evaluate the

percentage of patients returning to within 0.2mm of their baseline PD at 90-minutes for Nyxol vs placebo as the primary endpoint, as discussed with FDA. We also note that throughout Ocuphire's SEC filings, when referring to MIRA-2, they use the language "The FDA indicated that a 90 minute primary endpoint may be acceptable, and 60 minutes should also be evaluated.", which to us implies that a 60-minute endpoint may also weigh into a future FDA approval decision for Nyxol. Given the positive trend with Nyxol vs placebo in PD at 60-minutes in MIRA-1 and the much larger sample size being used in MIRA-2 (4-5x MIRA-1), we are confident that Nyxol can show a statistical benefit vs placebo in returning to PD baseline at both 60 and 90 minutes. If successful in MIRA-2, Nyxol would then be tested in a second, similar sized, confirmatory Ph3 RM study in the 2H21.

RM a convenience market. Ocuphire is betting on patients' willingness to pay out of pocket for the convenience of having Nyxol quickly reverse their pupil dilation. According to their SEC filings, Ocuphire has estimated $5/dose pricing for Nyxol in RM. Based on this pricing they estimate the annual addressable U.S. market in RM as $400mm. We think $5/dose is very reasonable and arguably underestimates the price people may be willing to pay for the convenience of having their vision restored hours earlier by Nyxol. Although a modest market, we believe Nyxol will be adopted if priced appropriately. More importantly in the near-term for investors, we believe the Ph3 clinical hurdle in RM is highly achievable for Nyxol, giving Ocuphire a clinical win early in 2021, as it heads into other clinical readouts, for bigger indications, later in the year.

Nyxol - Night Vision Disturbances

Diminished night vision is a natural occurrence with age, but also can be exacerbated by procedures such as LASIK surgery and intraocular lens implants. Pupils open wide in dim light, which can lead to NVD, manifesting as halos, starbursts and glare, impairing vision, making driving at night particularly problematic. It is believed the effects of NVD can be minimized or eliminated by reducing pupil diameter, a known benefit of Nyxol. Ocuphire is developing Nyxol for NVD as a once-per-night drop to be taken chronically.

There have been two previous small Ph2 NVD studies performed with Nyxol. Both studies showed a consistent, and statistically significant, reduction in PD and improvement in visual acuity with Nyxol, but neither study achieved their contrast sensitivity (CS) primary endpoint. It is important to emphasize that NVD is a completely novel indication, and there is no consensus on what the proper endpoints are for its measurement in clinical studies. CS is believed to be a very good measurement for NVD, but it is qualitative, whereas visual acuity, the gold-standard eye exam, also an important measure for NVD, is quantitative. After having an end of Ph2 meeting with FDA, Ocuphire settled on visual acuity, as measured by mesopic low contrast visual acuity (LCVA), as its primary endpoint for its two Ph3 NVD studies. When looking at the earlier Ph2 NVD studies there was a measurable visual acuity benefit with Nyxol, most notably in the SNV trial where Nyxol demonstrated a statistically significant ≥ 1-line (5-letters) and ≥ 2-line (10 letters) improvement in LCVA vs placebo. Nyxol also showed a benefit for ≥ 3-lines (15-letters) of improvement (19% of patients vs 0% placebo) that trended towards significance (p=0.16). We view these visual acuity data as highly suggestive towards Nyxol's efficacy in NVD, and believe in a properly powered Ph3 study there is a good chance for clinical success.

Ocuphire is planning on initiating their first of two Ph3 NVD studies, LYNX-1, YE20, and to have top-line data in 3Q21. The study will enroll 160 patients with severe NVD and the primary endpoint will be the percentage of patients achieving ≥ 3 lines improvement in LCVA at day 8 with Nyxol vs placebo. We believe the study is well powered (~7x enrollment of the SNV study referenced above) to show a statistical benefit with Nyxol vs placebo in the primary endpoint. If LYNX-1 is successful, Ocuphire would look to initiate a second, confirmatory Ph3, by YE21.

Although NVD may be a relatively unknown disorder / indication for many, Ocuphire estimates the moderate to severe NVD population in the U.S. at 4mm. Ocuphire has indicated that $500/year is a good estimate for Nyxol in NVD, making the addressable market $2b annually. Ocuphire has market research where optometrists reported that 14% of their patients complained about night vision unprompted, and 28% when prompted. We

believe Nyxol, if approved for NVD, would be widely championed by optometrists. With an approved treatment option, NVD would provide a new revenue stream for optometrists, requiring follow-up visits and prescription refills.

Nyxol - Presbyopia

Presbyopia is an age related condition in which the eye's lens loses elasticity, affecting its ability to focus on near objects. In the U.S. there are over 100 million presbyopia patients. There are currently no approved pharmacological treatments for presbyopia, however, given the enormity of the market opportunity, there are a number of companies aggressively pushing development-stage candidates in the clinic. Currently, the available treatments for presbyopia include reading glasses, bifocals, gradients, bifocal contact lenses, and multifocal intraocular lenses.

There are two pharmacological approaches being studied for the management of presbyopia. The most popular are miotic treatments, where the goal is to reduce the pupil diameter to achieve what is known as the "pin-hole effect". Notable companies that are active here include Abbvie/Allergan, Orasis, Presbyopia Therapies and Ocuphire, among others. The other pharmacological approach is restoring lens flexibility, where ophthalmic heavy weights Novartis and Alcon traffic.

Ocuphire is trying to achieve the pin-hole effect by using a combination of Nyxol, a moderate miotic, and low-dose (0.4%) pilocarpine, a potent miotic. The combination is being developed as a kit where patients would dose themselves with Nyxol drops in the evening and pilocarpine in the morning. Pilocarpine is the miotic agent being used by the most advanced presbyopia company, Abbvie/Allergan. They recently reported positive improvement in near vision from two Ph3 presbyopia studies with their 1.25% pilocarpine formulation, and plan to submit their drug to FDA for approval in 2021. These data are validating for pilocarpine's efficacy in presbyopia, and support Ocuphire's rationale for using pilocarpine as part of their Nyxol kit. It is also worth highlighting that Ocuphire is using low-dose pilocarpine to mitigate against some of the known side effects of this potent miotic, most notably browache and headache, which were noted in >3% of the patients in the Abbvie/Allergan studies.

Ocuphire is initiating a Ph2 presbyopia study, VEGA-1, in 1Q21. This 152 patient study will evaluate the Nyxol/pilocarpine kit's benefit on near vision improvement, as measured by ≥ 3 lines improvement in distance corrected near visual acuity (DCNVA), vs placebo. In a previous study in glaucoma, ORION-1, Nyxol alone achieved a statistically significant ≥ 1 line improvement in DCNVA vs placebo, and modest benefits in ≥ 2 and ≥3 lines. The company believes that by combining a low-dose of the potent miotic pilocarpine, a drug that, at higher doses, Abbvie/Allergan already showed achieves ≥ 3 lines of improvement in DCNVA, with its moderate miotic, Nyxol, that it can achieve the desired pin-hole effect, with fewer side effects. Furthermore, pilocarpine is known to have a relatively short, 6hr, duration of action, so the addition of Nyxol, with its longer, >24hr, duration of action, could help patients maintain the desired pinhole effect throughout the day.

Arguably this is the highest risk of the three Nyxol programs, given the lack of direct proof-of-concept data for Nyxol in presbyopia. However, the demonstrated efficacy of pilocarpine combined with the suggestive DCNVA data for Nyxol from Orion-1, give this Ph2 study an above average chance at success in our opinion. Data from VEGA-1 are expected 3Q21.

Prescription eye drops for presbyopia is an arms race, and Ocuphire is behind many of the notable players in the space. However, we would highlight that just having a "horse in the race" for a market of this size is valuable. Being 4th or 5th to a >$10b prescription eye-drop market, can still yield meaningful sales, especially with a product with some differentiation, which we believe Ocuphire's could have with its Nyxol / pilocarpine kit.

Nyxol - Path to FDA Approval

Ocuphire estimates that it can submit a 505(b)2 for Nyxol in RM and NVD to FDA in 2023. This timing is based on the successful completion of two Ph3 studies for both indications,

and a 500-patient healthy volunteer study, to confirm safety of chronic Nyxol use up to 12-months. A presbyopia 505(b)2 submission would follow, likely in 2024. Ocuphire has method of use and formulation patents issued in the U.S. for Nyxol through to 2034.

APX3330

Unlike Nyxol, which we view as being relatively derisked, APX3330 carries a more traditional biotech high risk / high reward profile for an asset entering a Ph2 proof-of-concept study. Ocuphire licensed the ophthalmic and diabetes rights for APX3330 (and related next gen compounds) from Apexian Pharmaceuticals in January 2020. APX3330 has been in 11 human studies and dosed in over 300 patients. APX3330, an oral ref-1 antagonist, was originally tested in several hepatitis and oncology studies, but Ocuphire feels its MOA is better suited for ophthalmology. Ref-1 inhibition appears to have benefit upstream of blockbuster anti-VEGF injectable drugs, Lucentis and Eylea, in the hypoxia (angiogenesis) pathway, as well as being upstream of steroids in the inflammatory pathway. Ocuphire believes this unique dual path MOA makes APX3330 ideally suited for back of the eye indications. Ocuphire initially plans to focus its development of APX3330 on diabetic macular edema (DME) and diabetic retinopathy (DR), but will also look at wet age-related macular degeneration (wAMD) as another future indication.

Ocuphire will be starting the Ph2, ZETA-1, study in 1Q21, enrolling 100 patients with DR or DME. Patients will be randomized 1:1 to receive either APX3330 300mg BID or placebo, with the primary endpoint being the percent of patients with a ≥2 step improvement on the Diabetic Retinopathy Screening Score (DRSS) at week 24. Top-line data are expected YE21.

A positive outcome from ZETA-1 would be huge for Ocuphire. An oral therapy for DR / DME would be highly differentiated relative to the highly effective, but also inconvenient, anti-VEGF injectables. Success in DR / DME, will also beget Ocuphire pursuing wAMD with APX3330. The total addressable market for APX3330 in DR / DME / wAMD is enormous, as demonstrated by the >$10b annual sales done by the anti-VEGF class.

Ocuphire Team

Ocuphire's CEO Mina Sooch has assembled an impressive management team, board and scientific advisory committee. We would highlight board chair Cam Gallagher, who also sits on the board of VelosBio, which is in the process of being acquired by Merck for $2.8b, and prior was a director and officer at Retrosense Therapeutics, an ophthalmology company which sold to Allergan in 2016 for $555mm. Also on the board are Sean Ainsworth who founded and was the CEO of Retrosense when acquired by Allergan, and James Manusco, who was CEO of Astex Pharma when it sold to Otsuka for $886mm.

Financial Summary

On November 5th, Occuphire completed an RTO with Rexahn Pharmaceuticals (formerly Nasdaq: REXN) and a concurrent $21.15mm private placement (1,249,996 shares at an implied value of $16.92). Insiders, including management and board of directors, invested $1.15mm in the private placement, and the balance (~$20mm) were outside investors. The lead investor was Altium Capital, a life-science focused hedge fund, who purchased roughly $10mm of the financing. This was a complicated, structured financing, with a number of price protection and reset provisions. Investors in the financing receive price-protection through the first 10-days of trading, whereby they can receive additional shares based on a calculation using the five lowest volume-weighted averaged trading prices (VWAP) during this period. These additional shares will be issued at a 15% discount to the VWAP price (the reset price) calculated based on the formula above. The finance investors will also receive full warrant coverage at a 20% premium to the reset price. For the purposes of illustration, if we assume a calculated VWAP price of $6.14, after the 15% discount, the finance investors would receive ~2.80mm additional shares. Based on this assumption, the shares outstanding would be 9.89mm (current 7.09mm O/S + 2.80mm) and a market cap of ~$60mm for Ocuphire. There would also be 4.05mm cashless warrants with an exercise price of $6.26. There are additional price protection provisions for the financing investors that cover deals done at a discount to the reset price over the next two years. We aren't going to get into the details of these provisions, other than to say, they could be onerous on the company if it were forced to finance substantially below the reset price. We recommend

investors reference Ocuphire's S-4 filing with SEC for further details on the pre-merger financing.

As we stated, this is a complicated deal, but investors should have good clarity on the cap structure, at least for the near-term, once this initial 10-day period has expired. In our example above, we think Ocuphire at a market cap of ~$60mm (EV <$40mm), is an attractive investment, especially given the cadence of clinical news expected throughout 2021. Assuming clinical success, especially with the early Nyxol readouts, Ocuphire should be in a position to finance from a position of strength, negating the onerous nature of the price protection provisions. However, it is important to highlight that in a situation where Ocuphire experiences meaningful clinical sebacks with Nyxol in 2021, they could find themselves in a very difficult position, given the price protection provisions afforded to the financing investors.

Notable Risks

We have already outlined the clinical risk associated with Ocuphire's two assets, and the finance risk associated with the structure of their financing. An addition to clinical and financial risk, we would highlight the potential for COVID-19 related delays to all of the Ocuphire clinical programs. Material delays to these studies would put financial pressure on the company and precipitate the need for additional capital earlier in 2021 than the company has budgeted. Regulatory risks always exist for development stage companies, but we don't foresee any notable regulatory risks for Ocuphire in the near term, at least until the company draws closer to NDA filings with Nyxol.

Executive Summary

Ocuphire Pharma is a clinical-stage ophthalmic biopharmaceutical company focused on developing and commercializing therapies for the treatment of eye disorders. Their pipeline includes two small-molecule candidates, Nyxol® eye drops and APX3330 oral tablets.

Nyxol Eye Drops

Nyxol is a once-daily preservative-free eye drop formulation of phentolamine mesylate, a non-selective alpha-1 and alpha-2 adrenergic antagonist, designed to reduce pupil size and improve visual acuity.
Ocuphire is developing Nyxol for the following indications:

1. Dim light or night vision disturbances
2. Pharmacologically induced mydriasis
3. Presbyopia

To date Nyxol has been tested in three Phase 1 and four Phase 2 clinical trials. A summary of these trials has been provided in the table below.

Summary of Completed Nyxol Clinical Trials

Name	Population	Phase	Description
OP-NYX-001	Healthy Volunteers	Phase 1	A double-masked, randomized, single dose, 3-arm controlled, parallel trial to determine the efficacy and safety of phentolamine mesylate.
OP-NYX-002	Healthy Volunteers	Phase 1	A double-masked, randomized, placebo-controlled, single-dose, incomplete block, 3-period crossover, dose escalation trial evaluating the tolerability and efficacy of phentolamine mesylate.
OP-NYX-004	Night Vision Disturbances Patients	Phase 1/2	A double-masked, randomized, placebo-controlled, single-dose, incomplete block 3-period crossover, dose escalation trial to determine the efficacy and safety of phentolamine mesylate.
OP-NYX-SNV NCT04004507	Severe Night Vision Disturbances Patients	Phase 2	A double-masked, randomized, placebo-controlled, single-dose trial to assess the efficacy and safety of phentolamine mesylate ophthalmic solution.
OP-NYX-01a2 NCT01703559	Severe Night Vision Disturbances Patients	Phase 2	A double-masked, randomized, placebo-controlled, single-dose, 3-arm trial to assess the efficacy and safety of Nyxol.
OPI-NYXG-201 NCT03960866 ORION-1	Glaucoma and Ocular Hypertension, Elderly Patients	Phase 2b	A double-masked, randomized, placebo-controlled, multiple-dose, multi-center trial to assess the efficacy and safety of Nyxol.
OPI- NYXRM-201 NCT04024891 MIRA-1	Healthy Patients/ Reversal of Mydriasis	Phase 2b	A double-masked, randomized, placebo-controlled, crossover, single-dose, multi-center trial to assess the efficacy and safety of Nyxol in reducing pharmacologically induced mydriasis.

The results of these trials support the following key points:

- Nyxol reduces pupil diameter with durable effects. In multiple Phase 2 trials, Nyxol reduced pupil diameter by approximately 20% (~1 – 1.5 mm) in both dim and bright conditions, and the reductions were sustained over 24 hours.
- Nyxol improves low contrast visual acuity. When studied in patients with night vision disturbances 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.
- Nyxol has a promising safety profile. To date, Nyxol has been observed to be well tolerated, with unchanged or decreased intraocular pressure, in the seven completed Phase 1 and Phase 2 clinical trials conducted. Nyxol produces a transient, mild hyperemia (eye redness) effect that disappears within four to eight 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.
- Nyxol is designed for convenient, once-daily administration. Nyxol is being evaluated for chronic use with once-daily administration before bedtime. Nyxol has shown in multiple Phase 2 trials to have an over 24-hour durable effect, which could allow for better patient compliance.
- Nyxol is a stable, cost-effective ophthalmic formulation. Nyxol is a single-use, preservative-free, proprietary eye drop formulation with good stability for eventual commercialization. Its active pharmaceutical ingredient, phentolamine mesylate USP grade, is a small molecule with advantages of standardized, scalable, lower-cost manufacturing processes.

Ocuphire plans to initiate three Nyxol clinical trials in 2020-2021. A summary of these trials has been provided in the table below.

Summary of Planned Nyxol Clinical Trials

Name	Population	Phase	Description
LYNX-1	Severe Night Vision	Phase 3	A double-masked, randomized, placebo-controlled, multi-center, multi-dose trial in patients with severe NVD in the fourth quarter of 2020 in the U.S. The LYNX-1 trial will enroll approximately 175-225 patients for the treatment of NVD. The trial is expected to include severe self-reported NVD and among other criteria include patients showing improvement potential in mesopic LCVA during illumination of the contralateral eye with a flashlight. Eligible participants are expected to be administered a single drop of 1% Nyxol or Placebo in each eye daily before bedtime for 14 days.
MIRA-2	Healthy Patients/ Reversal of Mydriasis	Phase 3	A double-masked, randomized, placebo-controlled, multi-center trial in normal healthy patients in the fourth quarter of 2020 in the U.S. The MIRA-2 trial is expected to evaluate the effect of 1% Nyxol to reverse pharmacologically induced mydriasis. The trial is expected to enroll approximately 125-175 healthy patients. Eligible patients are expected to be administered a mydriatic (either phenylephrine and tropicamide) and be given one or two drops of 1% Nyxol approximately one hour later after max pupil diameter, and then measured at multiple time points from 30 minutes to 6 hours and 24 hours.
VEGA-1	Presbyopia Patients	Phase 2	A proof of concept, double-masked, randomized, placebo-controlled, multi-center trial in patients with presbyopia in the first quarter of 2021. The VEGA-1 trial is expected to be designed to evaluate the effect of a kit combination with Nyxol and low dose pilocarpine for temporary treatment of presbyopia. The trial is expected to enroll approximately 75-125 patients with a clinical diagnosis of presbyopia (20/50 or worse near vision).

Assuming successful and timely completion of the Phase 3 trials, Ocuphire anticipates submitting a new drug application for Nyxol to the U.S. Food and Drug Administration in 2023 using the 505(b)(2) pathway.

APX33330 Oral Tablets

APX3330 is a twice-a-day oral tablet, designed to inhibit angiogenesis and inflammation pathways relevant to retinal and choroidal vascular diseases.

APX3330 is currently being developed for the following indications:
1. Diabetic retinopathy
2. Diabetic macular edema

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.
To date APX3330 has been tested in six Phase 1 and five Phase 2 trials in healthy subjects, patients with chronic hepatitis B and C, advanced liver cirrhosis patients and advanced solid tumor patients. A summary of these completed trials has been provided in the table below.

Summary of Completed APX3330 Clinical Trials

Name	Population	Phase	Description
APX_ CLN_0001	Healthy Volunteers	Phase 1	A randomized, single-dose, placebo-controlled trial of APX3330 to investigate the safety and pharmacokinetics during oral dosing of APX3330 to healthy adult males. A total of 18 patients were treated with single oral doses of APX3330 (10 mg, 30 mg, 60 mg, 120 mg, 180 mg or 240 mg) or the placebo in a blind manner.
APX_ CLN_0002	Healthy Volunteers	Phase 1	An 8-day, randomized, repeat-dose, placebo-controlled trial to investigate the safety and pharmacokinetics of orally dosed APX3330 in healthy adult male patients. A total of 18 patients were treated with oral dosing of APX3330 (120 mg or 240 mg) or the placebo in a blind manner once or twice a day for 8 successive days.
APX_ CLN_0003	Healthy Volunteers	Phase 1	A 7-day repeat-dose trial (120 mg) in 6 healthy patients to determine the effects of food on orally administered APX3330.
APX_ CLN_0004	Healthy Volunteers	Phase 1	A single-dose trial (120 mg) in 6 healthy patients to determine the effect of meals on the pharmacokinetics of APX3330.
APX_ CLN_0005	Chronic Hepatitis B Patients	Phase 2	A 12-week dose-escalation trial (20 mg, 60 mg, 120 mg, 240 mg) in 40 chronic hepatitis B patients. Patients received oral administration of one tablet per dose (2 tablets in the case of the administration of 240 mg) twice a day, after breakfast and after dinner.
APX_ CLN_0006	Chronic Hepatitis C Patients	Phase 2	A 12-week dose-escalation trial (20 mg, 60 mg, 120 mg, 240 mg) in 51 chronic hepatitis C patients. The objective of the trial was to investigate the safety, efficacy and utility of APX3330 in treating patients with chronic hepatitis C.
APX_ CLN_0007	Chronic Hepatitis C Patients	Phase 2	A 12-week double-masked, randomized placebo-controlled trial (0 mg, 120 mg, 240 mg) in chronic hepatitis C patients that had failed previous interferon treatment. Safety was evaluated in 196 completed patients. The mean treatment period in each group was 82 days in the placebo group, 79 days in the 120 mg group and 78 days in the 240 mg group. The primary endpoints of this trial were measurement of the rate of change in the glutamic pyruvate transaminase level, degree of improvement in liver function and assessment of general performance status.
APX_ CLN_0008	Healthy Volunteers	Phase 1	A 3-step, single-dose, single-blind trial (300 mg, 420 mg, 600 mg) in 27 healthy patients to investigate the safety and PK of higher doses.
APX_ CLN_0009	Advanced Liver Cirrhosis Patients	Phase 2	A 2-week repeated-dose trial (120 mg) in 30 patients with acute severe hepatitis, including patients with advanced liver cirrhosis. Efficacy endpoints included objective measures of liver function and subjective improvement of patient functional status. Safety measures included the assessment of the general tolerability of the drug (i.e., changes in vital signs) and changes in clinical laboratory values.
APX_ CLN_0010	Advanced Liver Cirrhosis Patients	Phase 2	A 4-week repeated-dose trial (120 mg) in 30 patients with alcoholic hepatitis, including patients with liver cirrhosis. Efficacy endpoints included objective measures of liver function and subjective improvement of patient functional status. Safety measures included the assessment of the general tolerability of the product candidate (i.e., changes in vital signs) and changes in clinical laboratory values.
APX_ CLN_0011	Advanced Solid Tumor Patients	Phase 1	A multi-center, open-label, dose-escalation 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.

The results of these preclinical and clinical studies support the following key points:

- APX3330 has the potential to be an oral therapy. Compared to intravitreal anti-VEGF injections, associated with systemic adverse events and ocular complications, twice-a-day oral administration of APX3330 could be a convenient alternative treatment for retinal disease.
- APX3330's upstream target is 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 by working upstream of the current anti-VEGF therapies, thus Ocuphire believes it could complement anti-VEGF therapies and potentially reduce the frequency of doctor visits.
- APX3330 has a promising safety profile. In eleven completed Phase 1 and Phase 2 clinical trials, APX3330 was well tolerated with no significant acute neurologic, cardiovascular, liver, or pulmonary events.
- APX3330 is a stable, cost-effective oral tablet. APX3330 is formulated as an oral tablet with stability suitable for eventual commercialization. Its active pharmaceutical ingredient is a small molecule with the advantages of standardized, scalable lower-cost manufacturing processes.

Ocuphire plans to initiate a Phase 2 clinical trial involving APX3330 in early 2021. A summary of this trial has been provided in the Table below.

Summary of Planned APX3330 Clinical Trial

Name	Population	Phase	Description
ZETA-1	Moderately Severe Nonproliferative Diabetic Retinopathy to Mild Proliferative Diabetic Retinopathy	Phase 2	A double-masked, randomized, placebo-controlled, multi-center trial in patients with diabetic retinopathy and diabetic macular edema. The ZETA-1 trial is expected to enroll 60-100 patients to evaluate the effect of 600 mg of APX3330 (300 mg twice a day) in treating patients with moderately severe nonproliferative diabetic retinopathy to mild proliferative diabetic retinopathy, as well as patients with diabetic macular edema without loss of central vision.

Based on the Phase 2 safety, tolerability and efficacy results of APX3330 in patients with diabetic retinopathy/ diabetic macular edema, Ocuphire expects to request an end of phase 2 meeting with the U.S. Food and Drug Administration. The meeting will be to finalize the design of the Phase 3 registration trials as well as defining a chronic safety exposure trial and any further animal toxicology studies necessary for the New Drug Application submission.

In conclusion, Ocuphire is developing two ophthalmic drugs, Nyxol and APX3330, for multiple eye related indications. The two programs have promising clinical data, convenient dosing routes and schedules, and significant commercial potential. Ocuphire have developed a comprehensive clinical development plan which if successful should move these potential products to the market in the coming years.

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1 Introduction

1.1 Ocuphire Pharma

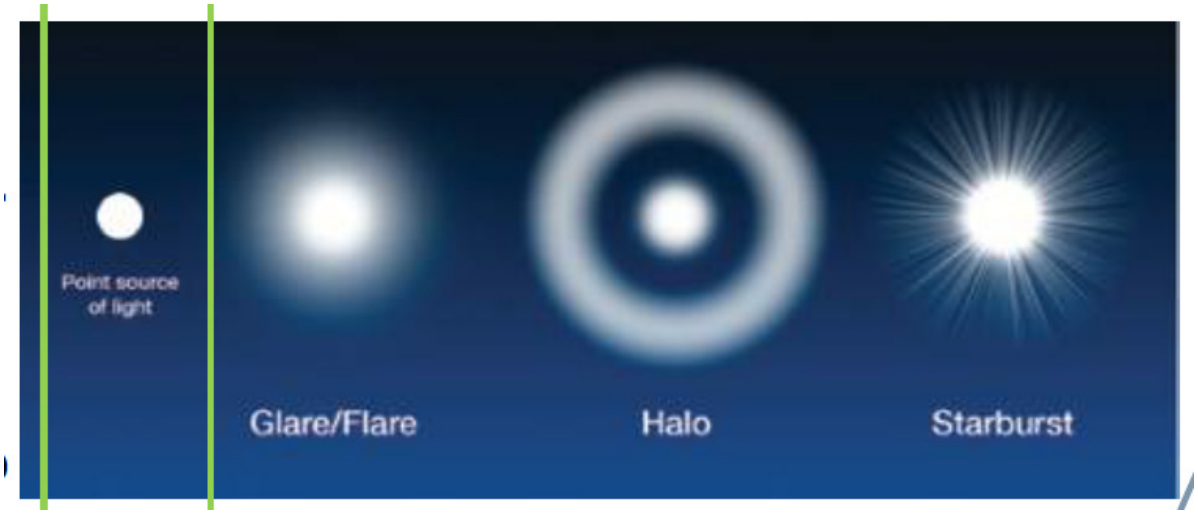
Ocuphire Pharma (Ocuphire) is a clinical-stage ophthalmic biopharmaceutical company focused on developing and commercializing therapies for the treatment of several eye disorders. Their pipeline currently includes two small-molecule candidates, Nyxol® eye drops and APX3330 oral tablets.

1.1.1 Nyxol

Ocuphire's lead candidate, Nyxol, is a once-daily preservative-free eye drop formulation of phentolamine mesylate (PM), a non-selective alpha-1 and alpha-2 adrenergic antagonist designed to reduce pupil size and improve visual acuity. It is currently being developed for the following indications:

1. Dim light or night vision disturbances (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 (Figure 1), and decreased contrast sensitivity (CS). Night vision disturbances is a new indication with no United States (U.S.) Food and Drug Administration (FDA) approved therapies. In the U.S., there are approximately 15-20 million moderate-to-severe NVD patients.
2. Pharmacologically-induced mydriasis (RM) – a pharmacologically induced dilation of the pupils, leading to an increased sensitivity to light and an inability to focus, making it difficult to read, work, and drive that can last from 6 to 24 hours. Reversal of mydriasis is a single-use indication with no commercially available therapies. In the U.S. more than 80 million eye exams are conducted each year, involving pharmacologically induced mydriasis.
3. 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 glasses to read or see objects close to them. There are currently no approved pharmacological treatments for presbyopia. The available treatments include reading glasses, bifocals, gradients, bifocal contact lenses, and multifocal intraocular lenses. In the U.S. there are over 100 million presbyopia patients.

Figure 1 Light Scattering Patterns



(Ocuphire Corporate Business Presentation)

1.1.2 APX3330

Ocuphire's second candidate, APX3330, is a twice-a-day oral tablet, designed to inhibit angiogenesis and inflammation pathways relevant to retinal and choroidal vascular diseases. It is currently being developed for the following indications:

1. Diabetic retinopathy (DR) – a leading cause of vision loss in adults aged 20–74 years and is the result of chronic elevations of glucose in the blood that lead to cell damage in the retina.
2. Diabetic macular edema (DME) – one of the most common complications of DR where there is vascular leakage in the macula, the part of the eye that is necessary for central and color vision.

For DR and DME, intraocular injections targeting vascular endothelial growth factor (VEGF) are approved globally, but these chronic therapies require frequent biweekly or monthly office visits and are prone to side effects such as hemorrhage, intraocular infection, and increased risk of blood clots.

According to the National Eye Institute, there are over 7 million patients with DR and 750,000 patients with DME in the U.S. These retinal and choroidal vascular diseases are leading causes of severe, permanent vision loss.

1.1.3 Clinical Development Plan

Ocuphire's goal is to build a leading ophthalmic biopharmaceutical company that discovers, develops, and commercializes best-in-class therapies for patients. The Company's clinical development plans for Nyxol and APX3330 have been summarized in Figure 2 below.

Figure 2 Ocuphire Pharma's Clinical Development Plan

	Product Candidate	Indication	Development Stage				Anticipated Milestones
			Pre-clinical	Phase 1	Phase 2	Phase 3	
Ocuphire-Focused Development	0.75% Nyxol® Eye Drop	Dim Light or Night Vision Disturbances (NVD)					Initiate Phase 3 LYNX-1 trial 4Q2020; Data expected in 3Q21 (n=160)
	0.75% Nyxol® Eye Drop	Reversal of Mydriasis (RM)					Initiate Phase 3 MIRA-2 trial 4Q2020; Data expected in 1Q21 (n=168)
	0.75% Nyxol® + Low-Dose Pilocarpine Eye Drops	Presbyopia (P)					Initiate Phase 2 VEGA-1 trial 1Q2021; Data expected in 2Q21 (n=152)
	APX3330 Oral Pill	Diabetic Retinopathy (DR)/ Macular Edema (DME)					Initiate Phase 2 ZETA-1 trial 1Q2021; Data expected in 4Q21 (n=100)
Partnering-Focused Development	APX2009 Intravitreal	DME, Wet Age-Related Macular Degeneration (wAMD)					Next steps: IND enabling studies (with partner funding)
	Combo (0.75% Nyxol® + Latanoprost) Eye Drops	Glaucoma (16 to 24 mmHg)					Next steps: 2nd line add-on Phase 2 trial (with partner funding)

Note: 0.75% Nyxol (Phentalomine Ophthalmic Solution) is the same as 1% Nyxol (Phentalomine Mesylate Ophthalmic Solution)

(Ocuphire Corporate Business Presentation)

Ocuphire plans to initiate two Phase 3 studies of Nyxol (LYNX-1 in NVD and MIRA-2 in RM) in Q4 of 2020. Top-line results are expected starting in Q1 of 2021 and continuing throughout the remainder of the year. In addition to the Phase 3 trials outlined above, Ocuphire also intends to initiate one Phase 2 study of Nyxol (VEGA-1 in presbyopia) and one Phase 2 study of APX3330 (ZETA-1 in DR and DME) in Q1 of 2021.

Assuming successful and timely completion of these trials, Ocuphire anticipates submitting a New Drug Application (NDA) for Nyxol to the FDA in 2023 using the 505(b)(2) pathway. Ocuphire further anticipates that in the long term, it will also submit marketing applications with regulators in other global markets including the European Medicines Agency (EMA) and Japan's Pharmaceuticals and Medical Devices Agency (PDMA), and potentially other markets such as China.

As part of Ocuphire's growth strategy, they also plan to continue exploring opportunities to acquire additional ophthalmic assets and to seek strategic partners for late stage development, regulatory preparation, and commercialization of drugs in key global markets.

1.2 Report Objective

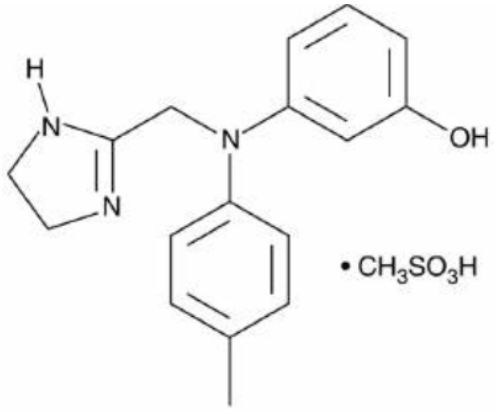
The objective of this report is to summarize the information available on Ocuphire's portfolio of eye products. This information will then be used to assess the scientific merit of Ocuphire's current assets and determine their potential future commercial prospects.

2 Nyxol

Phentolamine mesylate ([(2E)-2-[(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4-cyclohexadien-1-yl)methylene]-undecanoic Acid), the active ingredient in Nyxol (Figure 3), is an adrenergic receptor antagonist. Alpha-adrenergic receptor antagonists prevent the stimulation of alpha-adrenergic receptors at the nerve endings of the sympathetic nervous system and are classified either as:

- non-selective alpha adrenoreceptor antagonists,
- alpha-1 selective antagonists,
- alpha-2 selective antagonists and
- ergot derivatives.

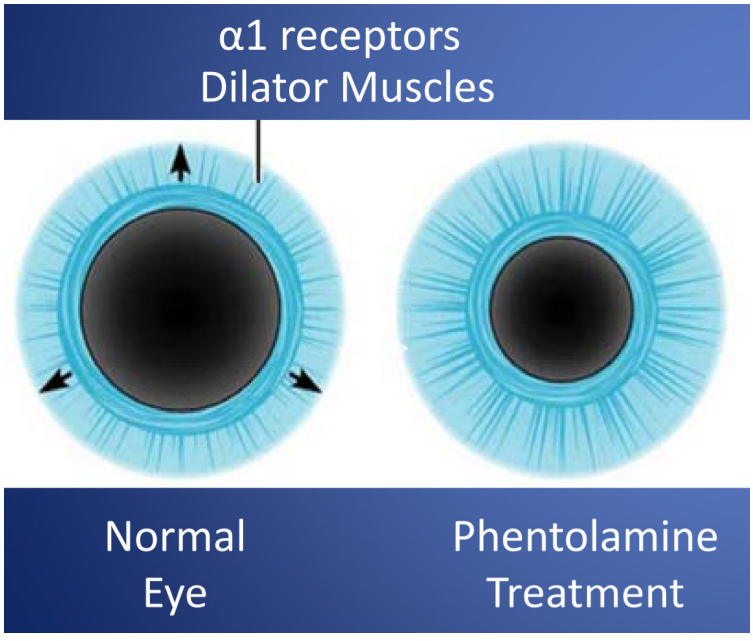
Phentolamine mesylate is a competitive non-selective antagonist of alpha-adrenergic receptors since it binds both alpha-1 and alpha-2 receptors with similar affinities.
Figure 3 Phentolamine Mesylate Molecular Structure



(Ocuphire Corporate Business Presentation)

Alpha-1 and alpha-2 adrenergic receptors are G-protein coupled receptors (GPCR); however, the downstream effects of the two are different. The alpha-1 receptor is a Gq type, resulting in activation of phospholipase C, increasing inositol trisphosphate (IP3) and diacylglycerol (DAG), and ultimately increasing the intracellular calcium concentrations leading to smooth muscle contraction and glycogenolysis (Biazi et al., 2018). The alpha-2 receptor acts as an allosteric inhibitor through Gi function, leading to an inhibition of adenylyl cyclase, decreasing the formation of cyclic adenosine monophosphate (cAMP). It also leads to a reduced amount of cytoplasmic calcium, which decreases neurotransmitter release and central vasodilation (Durkee et al., 2019). Alpha-adrenergic receptors are widely distributed in the eye (Potter, 1981), especially in the smooth muscle cells of the iris, the blood vessels of the conjunctiva as well as those of the ciliary processes and the aqueous outflow tract. Studies of alpha-adrenergic receptor inhibition in the eye suggest that the alpha-2-adrenergic receptor regulates intraocular pressure (IOP) (Mittag et al., 1985). Nyxol itself, is a preservative-free ophthalmic solution containing 1% phentolamine mesylate, which inhibits the iris dilator muscles, effectively decreasing the size of the pupil opening (Figure 4). A smaller pupil diameter (PD), results in less light scattered on the retina by imperfections in the periphery of the cornea and lens, resulting in better low contrast visual acuity (LCVA) as well as distance and near high contrast visual acuity (HCVA).

Figure 4 Proposed Mechanism of Action for Nyxol



(Ocuphire Corporate Business Presentation)

To date Nyxol has been dosed in over 150 patients across three Phase 1 and four Phase 2 clinical trials. A brief summary of these completed trials has been provided in Table 1. A more detailed description of the Phase 2 studies can be found in the sections below.

Table 1 Summary of Completed Nyxol Clinical Trials

Trial Name	Patient Population	Trial Phase	Trial Description
OP-NYX-001	Healthy Volunteers	Phase 1	A double-masked, randomized, single dose, 3-arm controlled, parallel trial to determine the efficacy and safety of phentolamine mesylate.
OP-NYX-002	Healthy Volunteers	Phase 1	A double-masked, randomized, placebo-controlled, single-dose, incomplete block, 3-period crossover, dose escalation trial evaluating the tolerability and efficacy of phentolamine mesylate.
OP-NYX-004	Night Vision Disturbances Patients	Phase 1/2	A double-masked, randomized, placebo-controlled, single-dose, incomplete block 3-period crossover, dose escalation trial to determine the efficacy and safety of phentolamine mesylate.
OP-NYX-SNV NCT04004507	Severe Night Vision Disturbances Patients	Phase 2	A double-masked, randomized, placebo-controlled, single-dose trial to assess the efficacy and safety of phentolamine mesylate ophthalmic solution. A more detail description of this trial can be found in Section 2.1.1
OP-NYX-01a2 NCT01703559	Severe Night Vision Disturbances PatientS	Phase 2	A double-masked, randomized, placebo-controlled, single-dose, 3-arm trial to assess the efficacy and safety of Nyxol. A more detail description of this trial can be found in Section 2.1.2
OPI-NYXG-201 NCT03960866 ORION-1	Glaucoma and Ocular Hypertension, Elderly Patients	Phase 2b	A double-masked, randomized, placebo-controlled, multiple-dose, multi-center trial to assess the efficacy and safety of Nyxol. A more detail description of this trial can be found in Section 2.4.1
OPI- NYXRM-201 NCT04024891 MIRA-1	Healthy Patients/ Reversal of Mydriasis	Phase 2b	A double-masked, randomized, placebo-controlled, crossover, single-dose, multi-center trial to assess the efficacy and safety of Nyxol in reducing pharmacologically induced mydriasis. A more detail description of this trial can be found in Section 2.2.1

The active pharmaceutical ingredient in Nyxol (phentolamine mesylate) has previously been approved by the FDA for two other drugs:

- REGITINE®
  - Prevention or control of hypertensive episodes that may occur in a patient with pheochromocytoma as a result of stress or manipulation during preoperative preparation and surgical excision.
  - Prevention or treatment of dermal necrosis and sloughing following intravenous administration or extravasation of norepinephrine.
  - Diagnosis of pheochromocytoma by the phentolamine mesylate for Injection, United Stated Pharmacopeia (USP) blocking test.
- OraVerse®
  - Reversal of the soft-tissue anesthesia, i.e., anesthesia of the lip and tongue, and the associated functional deficits resulting from an intraoral submucosal injection of a local anesthetic containing a vasoconstrictor.

2.1 Night Vision Disturbances

Night vision is the ability to see in low light conditions. There are a few main differences between daytime vision and night vision:

- The pupils become larger and the eyes let in more light when it is dark outside.
- A different, more sensitive kind of cell in the eye (rod cells) collects the light for night vision.
- Night vision is mostly or completely in black and white. Color vision is poor in very low light conditions.

(Goel, 2018)

Night vision disturbances is a collective term for eye-related disorders, such as glared disability, contrast sensitivity, and image degradation. NVD is a natural part of aging as well as a common side effect of several conditions and procedures. NVD are induced by a variety of factors, including night myopia (44%), cortical cataracts (30%), post-intraocular lens implants (15%), laser-assisted in situ keratomileusis (LASIK) (10%), and keratoconus. 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.

Ocuphire has studied the effects of Nyxol on NVD in two Phase 2 clinical trials:

1. NCT04004507 - Single Dose Study of Phentolamine Mesylate Eye Drops in Patients with Severe Night Vision Disturbances (SNV)
2. NCT01703559 - The Safety and Efficacy of Phentolamine Mesylate Ophthalmic Solution in Subjects with Severe Night Vision Disturbances

Supportive data has also been generated from two additional Phase 2 clinical trials:

- NCT03960866 - Safety and Efficacy of Ophthalmic Phentolamine Mesylate in Glaucoma
- NCT04024891 - Safety and Efficacy of Ophthalmic Phentolamine Mesylate to Reverse Pharmacologically Induced Mydriasis

Ocuphire expects to initiate a Phase 3 clinical trial for Nyxol in NVD in the second half of 2020. For NVD, the approvable FDA primary endpoint is percent of subjects with three lines of improvement in mesopic low contrast best-corrected distance visual acuity at a single timepoint.

2.1.1 Completed NVD Clinical Trial NCT04004507

2.1.1.1 NCT04004507 Design

Clinical trial NCT04004507 (NYX-SNV) was a double-masked, placebo-controlled, single-dose Phase 2 study in 24 patients experiencing severe night vision difficulties to evaluate ocular and systemic safety and efficacy following administration of one drop of phentolamine mesylate 1.0% in each eye for one day.

The objectives of this study were to:

- Assess the effect of ophthalmic phentolamine mesylate in mesopic conditions:
  - Contrast sensitivity
  - Low contrast visual acuity
  - Wavefront aberrometry
  - Subjective questionnaire
- Assess the safety of ophthalmic phentolamine mesylate

A brief overview of clinical trial NCT04004507 can be found in Table 2.

Table 2 Overview of Clinical Trial NCT04004507

Overview of Clinical Trial NCT04004507 (ClinicalTrials.gov)	
Title	Single Dose Study of Phentolamine Mesylate Eye Drops in Patients with Severe Night Vision Disturbances (SNV)
Condition	Decrease in Night Vision Disturbance; Vision, Loss
Type	Interventional
Phase	Phase 2

Design	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Investigator, Outcomes Assessor) Primary Purpose: Treatment
Intervention	Drug: Phentolamine Mesylate Ophthalmic Solution 1% Topical Sterile Ophthalmic Solution Other: Phentolamine Mesylate Ophthalmic Solution Vehicle (Placebo) Topical Sterile Ophthalmic Solution
Arms	Experimental: Phentolamine Mesylate Ophthalmic Solution 1% 1 drop in each eye (QD) for one day. Intervention: Drug: Phentolamine Mesylate Ophthalmic Solution 1% Placebo Comparator: Phentolamine Mesylate Ophthalmic Solution Vehicle 1 drop in each eye (QD) for one day. Intervention: Other: Phentolamine Mesylate Ophthalmic Solution Vehicle (Placebo)
Primary Outcome	Contrast Sensitivity [Time Frame: 1 day] Average change in monocular contrast sensitivity scores under mesopic conditions at each of five spatial frequencies with and without glare
Secondary Outcomes	Visual Acuity [Time Frame: 1 day] Average number of letters of improvement in the following parameters: Distance high-contrast visual acuity under mesopic conditions (monocular, measured at 4 meters) Distance high-contrast visual acuity under photopic conditions (monocular, measured at 4 meters) Distance low-contrast visual acuity under mesopic conditions (monocular, measured at 4 meters) Distance low-contrast visual acuity under photopic conditions (monocular, measured at 4 meters) Wavefront Aberrometry [Time Frame: 1 day] Wavefront aberrometry under mesopic conditions Self-Reported Vision Quality [Time Frame: 1 day] Subjective patient evaluations of vision quality Pupil Diameter [Time Frame: 1 day] Average change in pupil diameter
Enrollment	24

Eligibility Criteria	Inclusion Criteria: - Male or female patients ≥ 18 years of age - Currently experiencing severe night vision difficulty as reported subjectively - At least two patches below the normal range at any two frequencies in Contrast Sensitivity done under mesopic conditions with glare - Improvement in low contrast visual acuity (LCVA) in dim light during illumination of contralateral eye - Good general health - Written informed consent to participate in this trial - Ability to comply with all protocol mandated procedures and to attend all scheduled office visits Exclusion Criteria: - Patients with untreated cataracts grades 1-4 - Patients who wear contact lenses - Less than 5 weeks post-refractive surgery (LASIK or PRK) - Less than 5 weeks post intraocular lens insertion - Low blood pressure (systolic <120 mmHg or diastolic <80 mmHg)
Investigators	Principal Investigator: Marguerite McDonald, MD, FACS Ophthalmic Consultants of Long Island, New York (NY)
Location	United States
Sponsor	Ocuphire Pharma, Inc.
Status	Completed
LASIK = Laser-assisted In Situ Keratomileusis; LCVA = Low Contrast Visual Acuity; mmHg = Millimeters of Mercury; NY = New York; PRK = Photorefractive Keratectomy; QD = Daily; SNV = Severe Night Vision Disturbances	

2.1.1.2 NCT04004507 Demographics

The demographic information for patients in clinical trial NCT04004507 can be found in Table 3. The majority of patients in both groups were female with a median age of 39 years. All patients suffered from severe night vision complaints.

Table 3 Demographic Information from Clinical Trial NCT04004507

Parameter	Treatment Group	
	Placebo	PM
Subjects, n	8	16
Males, n (%)	3 (37.5%)	4 (25%)
Mean Age, yrs, (SD)	47.4 (13.5)	42.1 (14.6)
Night Vision Complaints Halos Glare Sensitivity Starbursts Depth Perception	 87.5% 87.5% 62.5% 62.5%	 56.3% 93.8% 68.8% 68.8%
n = Number; PM = Phentolamine Mesylate; SD = Standard Deviation		

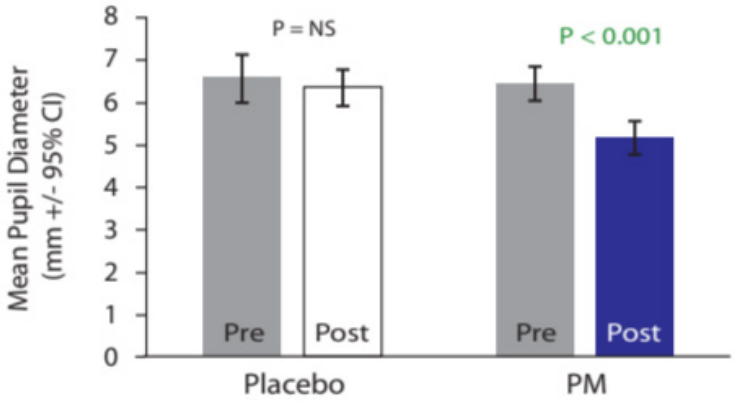
(McDonald et al., 2010)

2.1.1.3 NCT04004507 Efficacy

Pupil Diameter

Mean pupil diameter decreased an average of 1.3 mm ($p < 0.0001$), or ~20%, for phentolamine mesylate treated patients, whereas mean pupil diameter of placebo patients did not significantly change between pre- and post-treatment (Figure 5).

Figure 5 Mean Pupil Diameter After Treatment with Placebo or Phentolamine Mesylate



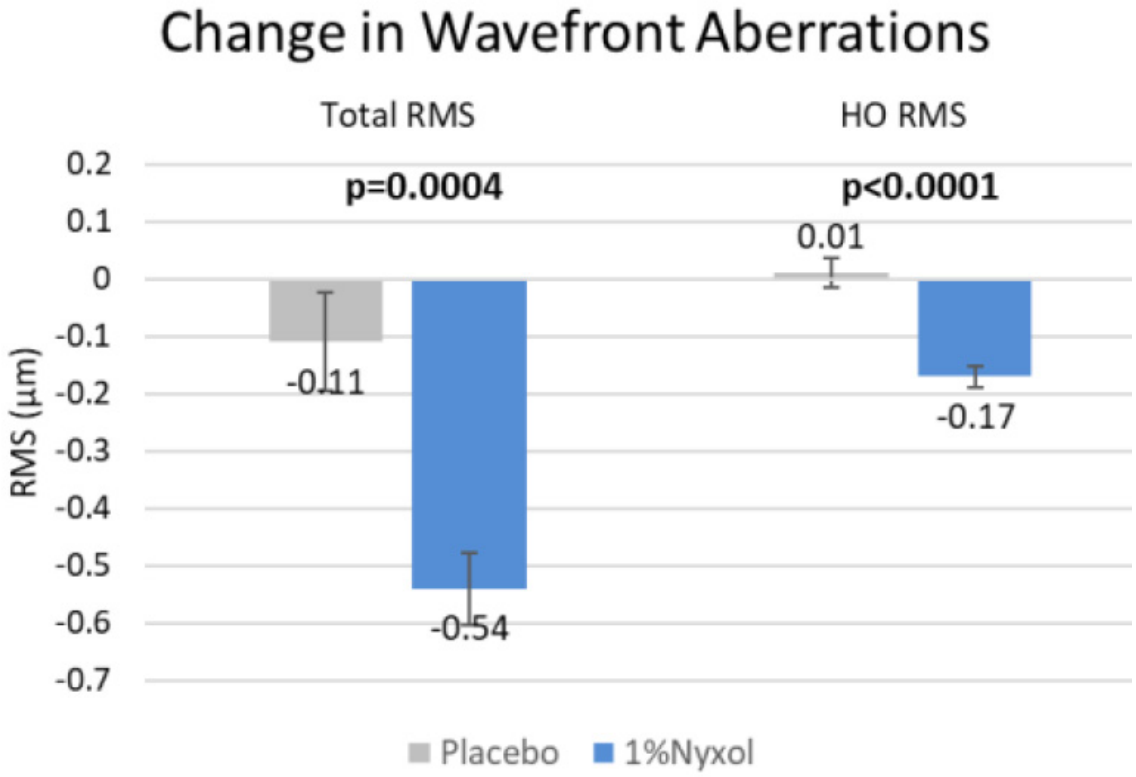
(McDonald et al., 2010)

Root-mean Square Error

Total wavefront RMS (root-mean square) error is the summation of all aberrations measured with a wavefront device (VISX-CustomVue Aberrometer), delineated in microns (μm). Higher order RMS error is the summation of higher order aberrations including trefoil, coma, and spherical aberrations that because of their complex nature cannot be corrected with regular corrective lenses. Reduction in higher "errors" is consistent with improvements in NVD vision.

In a post-hoc analysis, the difference between the phentolamine mesylate and placebo treatment arms for both total RMS (0.42 μm, p=0.0004) and higher order RMS (0.17 μm, p<0.0001) were significantly different, with phentolamine mesylate treated eyes showing improvement with a larger reduction in error (Figure 6).

Figure 6 Change in Total and Higher Order Wavefront Aberrations



(Ocuphire Corporate Business Document)

Mesopic and Photopic Low Contrast Distance Visual Acuity

In this small trial, there was a positive trend of 3-lines (15-letter or greater) of improvement in mesopic low contrast distance visual acuity (MLCVA) (19% phentolamine mesylate versus 0% for Placebo, p = 0.16) and photopic low contrast distance visual acuity (PLCVA) (19% phentolamine mesylate versus 0% for Placebo, p = 0.16). However, the trial was under powered to show a statistical difference.

Additionally, greater fractions of phentolamine mesylate treated eyes registered a 1-line (5-letter or greater) improvement in MLCVA (69% phentolamine mesylate versus 31% for Placebo, p = 0.029) and PLCVA (63% phentolamine mesylate versus 13% for Placebo, p = 0.017), as well as a 2-line (10-letter or greater) improvement in MLCVA (34% phentolamine mesylate versus 6% for Placebo, p < 0.03) and PLCVA (28% phentolamine mesylate versus 0% for Placebo, p < 0.02) (Table 4).

Table 4 Improvement in MLCVA and PLCVA Following Treatment with Phentolamine Mesylate or Placebo

Improvement	MLCVA			PLCVA		
	PM	Placebo	P Value	PM	Placebo	P Value
1-line	69%	31%	p=0.029	63%	13%	p=0.017
2-line	34%	6%	p<0.03	28%	0%	P<0.02
3-line	19%	0%	p=0.16	19%	0%	p=0.16
MLCVA = Mesopic Low Contrast Distance Visual Acuity; PLCVA = Photopic Low Contrast Distance Visual Acuity; PM = Phentolamine Mesylate						

(Ocuphire Corporate Business Document)

Contrast Sensitivity

Contrast sensitivity refers to a measure of how much contrast (shade of gray over white background) a person requires to see a target. The number of light-dark cycles of the grating that subtend 1 deg visual angle is a measure of the spatial frequency of the grating, expressed in cycles per degree (cpd).

On a prespecified endpoint of CS improvement, the incidence of eyes experiencing a two-patch (equivalent to 50% or .3 log improvement) or greater improvement in CS with glare was greater in the phentolamine mesylate treatment group versus placebo at 3 cpd (34.4% versus 25.0%, p = NS), 6 cpd (34.4% versus 12.5%, p = NS), 12 cpd (50.0% versus 12.5%, p < 0.010), and 18 cpd (31.3% versus 6.3%, p < 0.046) (Table 5).

Table 5 Improvement in Contrast Sensitivity Following Treatment with Phentolamine Mesylate or Placebo

cpd	Improvement in Contrast Sensitivity		
	PM	Placebo	P Value
3	34.4%	25.0%	p=NS
6	34.4%	12.5%	p=NS
12	50.0%	12.5%	p<0.010
18	31.3%	6.3%	p<0.046
cpd = Cycles per Degree; NS = Not Significant; PM = Phentolamine Mesylate			

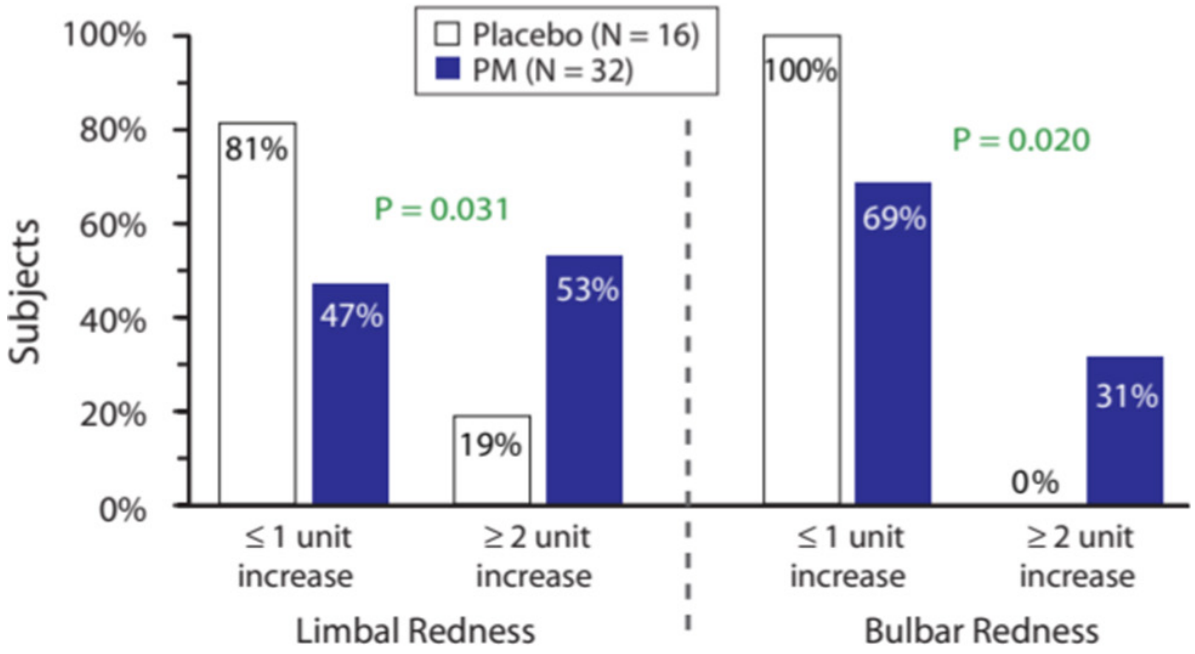
(Ocuphire Corporate Business Document)

2.1.1.4 NCT04004507 Safety

No serious adverse events (SAEs) or other adverse events (AEs) were reported during this trial. Overall, study treatment appeared to be well-tolerated. No meaningful differences in mean heart rate (HR) or mean systolic and diastolic blood pressure (BP) between treatment groups were observed. Treatment with phentolamine mesylate caused a statistically significant elevation in mean change from baseline in eye redness (Figure 7) between the two treatment groups (+38.6 mm phentolamine mesylate versus +12.1 mm for Placebo; p < 0.0004; where 0 mm equals no redness and 100 mm equals maximal redness).

The mean change in IOP of phentolamine mesylate treated eyes from screening to 2–3 hours post-treatment (-1.8 mmHg) was significant ($p < 0.0004$).

Figure 7 Eye Redness: Changes in Slit Lamp Findings after Treatment



(McDonald et al., 2010)

2.1.2 Completed NVD Clinical Trial NCT01703559

2.1.2.1 NCT01703559 Design

Clinical trial NCT01703559 was a randomized, double-masked, multiple dose Phase 2 parallel evaluation of the safety and efficacy of phentolamine mesylate ophthalmic solution in 60 subjects with severe night vision complaints, evaluating ocular and systemic safety and efficacy following administration of phentolamine mesylate (0.05% or 1%) in both eyes for 15 days.

Subjects were randomized into three groups with a 1:1:1 randomization. The groups received one of the following treatments once daily for 15 days:

- Phentolamine mesylate ophthalmic solution 0.5%
- Phentolamine mesylate ophthalmic solution 1.0%
- Placebo

After 15 days, all subjects were given the opportunity to receive an additional six doses of 1.0% phentolamine mesylate to be taken once daily as needed over the next two weeks. There was a post-dosing follow-up evaluation seven days after the last dose. Study participants completed a night vision questionnaire at pre-treatment and after 15 and 29 days.

Efficacy evaluations included:

- Contrast sensitivity (mesopic, with and without glare),
- Mesopic distance high contrast visual acuity (HCVA) and
- Mesopic distance low contrast visual acuity (LCVA).

Safety evaluations included photopic distance HCVA, a complete ophthalmic examination and measurement of heart rate and blood pressure.

A brief overview of study NCT01703559 can be found in Table 6.

Table 6 Overview of Clinical Trial NCT01703559

Overview of Clinical Trial NCT01703559 (ClinicalTrials.gov)	
Title	The Safety and Efficacy of Phentolamine Mesylate Ophthalmic Solution in Subjects With Severe Night Vision Disturbances
Condition	Night Vision Complaints Decrease in Night Vision Disturbance; Vision, Loss
Type	Interventional
Phase	Phase 2
Design	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) Primary Purpose: Treatment
Intervention	Drug: Phentolamine Mesylate Ophthalmic Solution 1.0% Phentolamine mesylate (Nyxol) ophthalmic solution 1.0% is a non-selective alpha-1 and alpha-2 adrenergic antagonist Other Names: Nyxol® Nyxol Drug: Phentolamine Mesylate Ophthalmic Solution 0.5% Phentolamine mesylate (Nyxol) ophthalmic solution 0.5% is a non-selective alpha-1 and alpha-2 adrenergic antagonist Other Names: Nyxol® Nyxol Other: Phentolamine Mesylate Ophthalmic Solution Vehicle (Placebo) Placebo (vehicle) is a sterile, isotonic, buffered aqueous solution containing mannitol and sodium acetate
Arms	Placebo Comparator: Placebo Administered once daily in both eyes for 15 days Intervention: Other: Phentolamine Mesylate Ophthalmic Solution Vehicle (Placebo) Experimental: Phentolamine Mesylate Ophthalmic Solution 0.5% Administered once daily in both eyes for 15 days Intervention: Drug: Phentolamine Mesylate Ophthalmic Solution 0.5% Experimental: Phentolamine Mesylate Ophthalmic Solution 1.0% Administered once daily in both eyes for 15 days Intervention: Drug: Phentolamine Mesylate Ophthalmic Solution 1.0%
Primary Outcome	Proportion of Eyes With ≥ 0.3 Log Increase in Mesopic Contrast Sensitivities for at Least two Holladay Automated Contrast Sensitivity System (HACSS) Frequencies [Time Frame: Days 1, 4, 8, 15, and 32] Proportion of eyes with an increase ≥ 0.3 log (2 or more patches) in mesopic contrast sensitivity with glare at one or more frequencies at 1.5, 3, 6, 12, and 18 cycles per degree, measured with the HACSS methodology (categorical analysis)

Secondary Outcomes	Pupil Diameter - Change from Day 1 Pre-Dose Baseline [Time Frame: Day 1 post-dose and Days 4, 8, and 15] Mesopic Contrast Sensitivity with Glare at 1 or More Frequencies at 1.5, 3, 6, 12, and 18 Cycles Per Degree, Measured with the HACSS Methodology - Change from Day 1 Pre-Dose Baseline [Time Frame: Day 1 post-dose and Days 4, 8, and 15] Mesopic Contrast Sensitivity without Glare at 1 or More Frequencies at 1.5, 3, 6, 12, and 18 Cycles Per Degree, Measured with the HACSS Methodology - Change from Day 1 Pre-Dose Baseline [Time Frame: Day 1 post-dose and Days 4, 8, and 15] Mesopic Distance High Contrast Visual Acuity (HCVA), Measured with Electronic Early Treatment Diabetic Retinopathy Study (eETDRS) Charts - Change from Day 1 Pre-Dose Baseline [Time Frame: Day 1 post-dose and Days 4, 8, and 15] Mesopic Distance Low Contrast Visual Acuity (LCVA), Measured with eETDRS Charts - Change from Day 1 Pre-Dose Baseline [Time Frame: Day 1 post-dose and Days 4, 8, and 15]
Enrollment	60

Eligibility Criteria	Inclusion Criteria: - 18 to 45 years of age experiencing severe night vision difficulty (as reported subjectively) - 0.3 log improvement at least one eye using the HACSS test at two of four spatial frequencies (3, 6, 12, and 18 cycles per degree) under low and high mesopic room illumination with glare - Photopic visual acuity (corrected or uncorrected) of 20/25 or better - Able and willing to give informed consent and comply with all protocol-mandated procedures Exclusion Criteria: - Cataracts (nuclear sclerosis or anterior subcapsular) of 1+ or greater - Contact lens wear within four weeks of enrollment - Ocular trauma within the past six months, or ocular surgery or laser treatment within the past three months - Refractive surgery or cataract surgery in either eye - Use of ocular medication within four weeks of Visit 1 - Clinically significant ocular disease (e.g., corneal edema, uveitis, severe keratoconjunctivitis sicca, glaucoma, retinal degenerative disease) which might interfere with the study - Any abnormality preventing reliable applanation tonometry of either eye - Central corneal thickness greater than 600 µ - Known hypersensitivity or contraindication to PM, or any component of the formulation, or to topical anesthetics. - Contraindications to phentolamine (including history of myocardial infarction, cerebrovascular spasm, cerebrovascular occlusion, coronary insufficiency, angina, or other evidence suggestive of coronary artery disease) - Low blood pressure: systolic < 100 mmHg or diastolic < 60 mmHg - A history of heart rate abnormalities, such as tachycardia or arrhythmias. - Clinically significant systemic disease (e.g., uncontrolled diabetes, myasthenia gravis, hepatic, renal, cardiovascular, or endocrine disorders) which might interfere with the study - Use of any systemic alpha-adrenergic antagonists up to four weeks prior to screening or during the study - Changes of systemic medication that could have a substantial effect on ocular autonomic pupil tone four weeks prior to screening, or anticipated during the study - Participation in any investigational study within the past 30 days - Women of childbearing potential who are pregnant, nursing, planning a pregnancy, or not using a medically acceptable form of birth control. An adult woman is considered to be of childbearing potential unless she is one year post-menopausal or three months post-surgical sterilization. All females of childbearing potential must have a negative serum pregnancy test result at the screening examination and must not intend to become pregnant during the study
Investigators	Principal Investigator: Dennis Swearingen, MD Celerion
Location	United States
Sponsor	Ocuphire Pharma, Inc.
Status	Completed
eETDRS = Electronic Early Treatment Diabetic Retinopathy Study; HACSS = Holladay Automated Contrast Sensitivity System; HCVA = High Contrast Visual Acuity; LCVA = Low Contrast Visual Acuity; mmHg = Millimeters of Mercury	

2.1.2.2 NCT01703559 Demographics

The demographic information for patients in clinical trial NCT01703559 can be found in Table 7. There were slightly more women then men participants. Most patients were white, in their mid 30's with brown eyes.

Table 7 Demographic Information from Clinical Trial NCT01703559

Parameter		Treatment Group			
		1% PM	.5% PM	Placebo	Overall
Gender	Female	13	10	12	35
	Male	7	10	8	25
Race	Black	3	3	3	9
	Native Americans	0	1	0	1
	Other	0	0	2	2
	White	17	16	15	48
Ethnicity	Hispanic	11	12	11	34
	Not Hispanic	9	8	9	26
Iris Color	Blue	1	1	3	5
	Brown	15	15	14	44
	Green	1	2	0	3
	Hazel	3	1	3	7
	Other	0	1	0	1
Age (year)	n	20	20	20	60
	Mean	35.1	32.3	34.5	34
Central Corneal Thickness Right Eye (micron)		550.4	556	550.5	552.3
n = Number; PM = Phentolamine Mesylate					

(Holladay et al., 2018)

2.1.2.3 NCT01703559 Efficacy

Pupil Diameter

Treatment with either 0.5% or 1.0% phentolamine mesylate resulted in a consistent and significant reduction of pupil diameter from Day 1 pre-dose at both Day 8 and Day 15 pre- and post-dose compared to placebo ($p \leq 0.0008$). There was evidence of dose proportionality with eyes receiving 1.0% phentolamine mesylate having a lower pupil diameter compared to placebo up to Day 15 ($p < 0.001$). Phentolamine mesylate demonstrated 24-hour effects which suggested the potential to be a chronic use product.

Low Contrast Visual Acuity

In a post-hoc analysis, a gradual improvement was seen in mesopic LCVA in all treated eyes with 65% of eyes receiving 1.0% phentolamine mesylate showing at least 1-line of improvement compared to 35% of eyes receiving placebo on Day 15 ($p = 0.02$). These results are supportive of the pre-specified LCVA results from SNV.

Contrast Sensitivity

Contrast sensitivity measurements were taken before dosing on Days 1, 4, 8, and 15. By Day 8, the percent of eyes with a 50% CS improvement pre-dose in the 1.0% treatment arm was significantly higher than both pre-dose on Day 1 ($p = .0103$ by two-tailed Fisher's exact test of proportions) as well as placebo on Day 8 ($p = .0269$). There was numerical evidence of dose proportionality, with more eyes receiving 1.0% phentolamine mesylate having a higher mean CS than those receiving 0.5% phentolamine mesylate.

2.1.2.4 NCT01703559 Safety

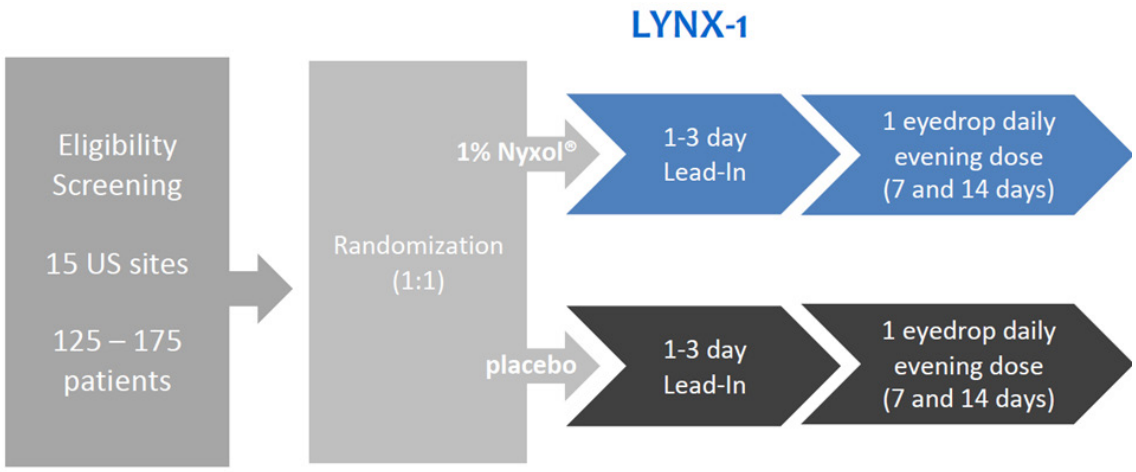
Overall, multiple doses of up to 1% phentolamine mesylate appeared well tolerated in patients with severe night vision complaints, with no clinically meaningful changes in vital signs. There were no deaths or SAEs in this trial and no patients were discontinued due to AEs. Overall, 50 (83%) patients experienced a total of 179 treatment emergent adverse events (TEAEs) during the trial, of which 173 were mild in severity and six were moderate (including headaches, blurred vision, event of postural dizziness, eye irritation).

Following active treatments, the majority of post-dose (2 to 3 hours after dose) eye redness through Day 15 was moderate, with a higher percentage following administration of 1.0% compared to 0.5% phentolamine mesylate. Eye redness returned to pre-dose baseline by the next study visit, suggesting that once daily dosing prior to bedtime may result in pupil effects with little or no redness during the waking hours of the day.

Changes in lens opacity, cornea staining erosion, and palpebral edema were minimal following all treatments. There were no abnormal findings in bulbar edema, cornea edema erosion, anterior chamber cells, and anterior chamber flare. There was a trend towards a greater mean improvement in high contrast distance visual acuity in eyes treated with phentolamine mesylate than in those treated with Placebo.
Eye redness was experienced by all subjects, including placebo subjects. Post-dose, the majority of active treatment patients exhibited an increase in eye redness. For example, on Day 15 the 1% phentolamine mesylate mean eye redness was statistically different from placebo (1.98 (mild-moderate) versus 0.71 (none-mild); $p<0.0001$). Pre-dose eye redness on Days 4, 8, and 15, returned to Day 1 pre-dose baseline, less than 20 hours post-dose from the previous day.

2.1.3 Planned NVD Clinical Trial – LYNX-1

Ocuphire expects to initiate LYNX-1, a Phase 3 double-masked, randomized, placebo-controlled, multi-center, multi-dose trial in patients with severe NVD in the second half of 2020 in the U.S. (Figure 8). The LYNX-1 trial will enroll approximately 125-175 patients for the treatment of NVD. The trial is expected to include severe self-reported NVD and among other criteria include patients showing improvement potential in mesopic LCVA during illumination of the contralateral eye with a flashlight. Eligible participants are expected to be administered a single drop of 1% Nyxol or placebo in each eye daily before bedtime for 14 days.
Figure 8 Phase 3 Night Vision Disturbance Clinical Trial Design (LYNX-1)



(Ocuphire Corporate Business Presentation)

A brief overview of the LYNX-1 study can be found in Table 8.

Table 8 Overview of Clinical Trial LYNX-1

Overview of LYNX-1 Clinical Trial	
Title	LYNX-1
Condition	Severe Night Vision Disturbance
Type	Interventional
Phase	Phase 3

Design	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) Primary Purpose: Treatment
Intervention	Drug: Phentolamine Mesylate Ophthalmic Solution 1.0% Phentolamine mesylate (Nyxol) ophthalmic solution 1.0% is a non-selective alpha-1 and alpha-2 adrenergic antagonist Other Names: Nyxol® Nyxol Other: Phentolamine Mesylate Ophthalmic Solution Vehicle (Placebo) Placebo (vehicle) is a sterile, isotonic, buffered aqueous solution containing mannitol and sodium acetate
Arms	Placebo Comparator: Placebo Administered once daily Intervention: Other: Phentolamine Mesylate Ophthalmic Solution Vehicle Experimental: Phentolamine Mesylate Ophthalmic Solution 1.0% Administered once daily Intervention: Drug: Phentolamine Mesylate Ophthalmic Solution 1.0%
Primary Outcome	Improvement of three lines or greater in mesopic low contrast best-corrected distance visual acuity
Secondary Outcomes	Pupil diameter Wavefront aberrometry (measured on OPD-Scan III analyzer) Near visual acuity Psychometric questionnaires
Enrollment	125-175
Eligibility Criteria	18 years and older Subjects currently experiencing self-reported NVDs Minimum pupil diameter of 6 mm in mesopic conditions Fidelity screen (pupil response to light) Minimum value and improvement potential in mesopic low contrast distance visual acuity during illumination of contralateral eye Otherwise healthy subjects with no pre-existing ocular conditions Several days lead-in with placebo drop
Location	United States
Sponsor	Ocuphire Pharma Inc.
Status	Not yet started
NVD = Night Vision Disturbance	

Patient safety is expected to be assessed through AE monitoring, conjunctival redness monitoring, IOP monitoring and assessments of heart rate and blood pressure.

The status of the LYNX-1 trial is that Ocuphire is finalizing the protocol and budget and are in the process of selecting their Contract Research Organization (CRO) and trial sites. Ocuphire expects to report top-line data for this Phase 3 registration trial in the third quarter of 2021.

2.2 Reversal of Mydriasis

Pupillary dilatation (mydriasis) is routinely carried out as part of ophthalmological examinations to aid diagnosis (diagnostic mydriasis), treatment and follow up of a wide range of ocular disorders. It facilitates the examination of the peripheral lens, ciliary body, and retina producing better diagnostic and therapeutic outcomes compared to the natural undilated pupil (Siegel et al., 1990; Parisi et al., 1996; Klein et al., 1985). It is also used in the treatment of iritis by preventing the formation of posterior synechia and relieving pain caused by ciliary spasm (American Academy of Ophthalmology, 2007-2008).

Diagnostic mydriasis is usually achieved using mydriatics which are either parasympatholytics or sympathomimetic agents. The parasympatholytics cause pupillary dilatation and accommodation paralysis. The sympathomimetics potentiate or mimic the action of adrenaline by stimulating the dilator pupillae muscle.

Examples of parasympatholytics include:
- Atropine
- Homatropine
- Cyclopentolate and
- Tropicamide

Examples of sympathomimetics include:
- Phenylephrine
- Ephedrine and
- Hydroxyamphetamine

(Kanski, 1969).

An estimated 200 million comprehensive eye exams take place globally each year, including 80 million in the U.S. In addition, 4 million eyes are dilated for surgical procedures. Pharmacologically induced mydriasis leads to an increased sensitivity to light and an inability to focus, making it difficult to read, work, and drive that can last from 6 to 24 hours. Nyxol may potentially expedite the reversal of mydriasis prior to natural reversal. There are currently no approved products on the market for reversal of mydriasis.

The approvable FDA primary endpoint, for reversal of mydriasis, is percent of subjects returning to baseline (within ≤ 0.2 mm) pupil diameter at 90 minutes or less.

2.2.1 Completed Mydriasis Reversal Clinical Trial NCT04024891

2.2.1.1 NCT04024891 Design

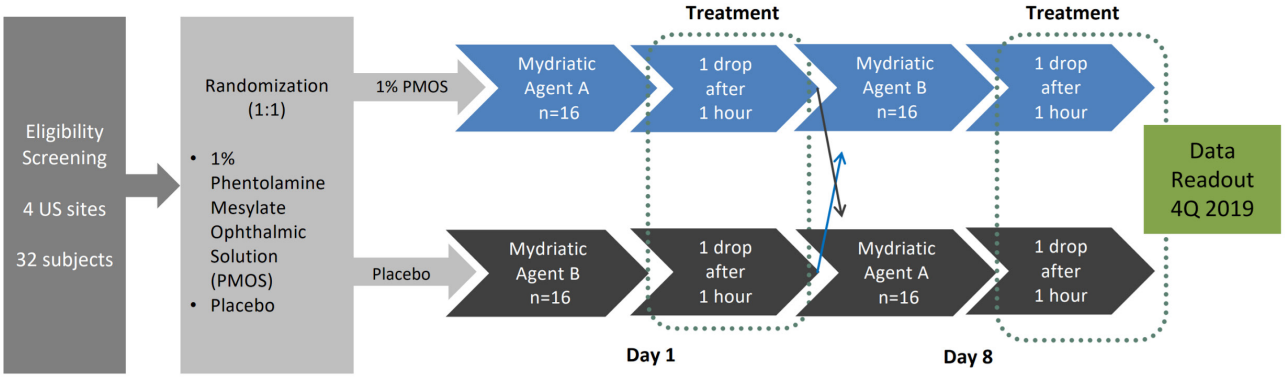
Clinical trial NCT04024891 (MIRA-1) was a randomized, 2-arm cross-over, double-masked Phase 2b study in approximately 32 healthy subjects, evaluating safety and efficacy of Nyxol in subjects with pharmacologically induced mydriasis (Figure 9).

At the first visit subjects were screened for study eligibility. After screening, eligible subjects were randomized 1:1 to one of the two treatment sequences:
- Treatment sequence 1: Placebo (Visit 1), Nyxol (Visit 2).
- Treatment sequence 2: Nyxol (Visit 1), Placebo (Visit 2).

Randomization was stratified by mydriatic agent (2.5% phenylephrine or 1% tropicamide). Approximately one half of the randomized subjects received 2.5% phenylephrine and one half received 1% tropicamide. Subjects received their mydriatic agent one hour before treatment. Each subject received the same mydriatic agent throughout the study.

At each visit, pupil diameter (PD), accommodation, near and distance visual acuity (VA) and redness in each eye were measured before (-1 hour/baseline) and one hour after (maximum/0 minutes) the mydriatic agent instillation in each eye (i.e., right before the study treatment was administered), and at 30 minutes, 1 hour, 2 hours, 4 hours and 6 hours after treatment dosing.

Figure 9 Design of Clinical Trial NCT04024891



(Karpecki et al., 2020)

A brief overview of study NCT04024891 can be found in Table 9.

Table 9 Overview of Clinical Trial NCT04024891

Overview of Clinical Trial NCT04024891 (ClinicalTrials.gov)	
Title	Safety and Efficacy of Ophthalmic Phentolamine Mesylate to Reverse Pharmacologically Induced Mydriasis
Condition	Mydriasis Dilation
Type	Interventional
Phase	Phase 2
Design	Allocation: Randomized Intervention Model: Crossover Assignment Intervention Model Description: Parallel Assignment Masking: Triple (Participant, Investigator, Outcomes Assessor) Primary Purpose: Treatment
Intervention	Drug: Phentolamine Mesylate Ophthalmic Solution 1% 1% phentolamine mesylate ophthalmic solution (Nyxol), a non-selective alpha-1 and alpha-2 adrenergic antagonist Other Names: Nyxol® Nyxol Other: Phentolamine Mesylate Ophthalmic Solution Vehicle (Placebo) Topical Sterile Ophthalmic Solution
Arms	Experimental: Phentolamine Mesylate Ophthalmic Solution 1% 1 drop in each eye, 1 hour post medically-induced mydriasis Intervention: Drug: Phentolamine Mesylate Ophthalmic Solution 1% Placebo Comparator: Phentolamine Mesylate Ophthalmic Solution Vehicle 1 drop in each eye, 1 hour post medically-induced mydriasis Intervention: Other: Phentolamine Mesylate Ophthalmic Solution Vehicle (Placebo)
Primary Outcome	Pupil Diameter (Change from Max) [Time Frame: 2 hours] Change in pharmacologically induced mydriatic (maximum) pupil diameter at 2 hours post-treatment in the study eye.

Secondary Outcomes	Pupil Diameter (Change from Max) [Time Frame: 30 min, 1 hours, 4 hours, 6 hours] Change in pharmacologically induced mydriatic (maximum) pupil diameter at remaining timepoints (30 min, 1 hours, 4 hours, 6 hours) Accommodation Measured by the Near Point Rule (Diopters) (Change from Baseline) [Time Frame: 0 min, 30 min, 1 hour, 2 hours, 4 hours, 6 hours] Change from baseline (-1 hour) in accommodation at each timepoint (0 min, 30 min, 1 hour, 2 hours, 4 hours, 6 hours) Worsening of accommodation is defined as an amplitude decrease of greater than 1 diopter compared to baseline Best Corrected Distance Visual Acuity (BCDVA) Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Light Box Chart (Letters) at 4 Meters (Change from Baseline) [Time Frame: 0 min, 30 min, 1 hour, 2 hours, 4 hours, 6 hours] Change from baseline (-1 hour) in BCDVA at each timepoint (0 min, 30 min, 1 hour, 2 hours, 4 hours, 6 hours) Distance-Corrected Near Visual Acuity (DCNVA) Measured by Standard Reading Card (Original Series Sloan Letter ETDRS Card at 16 Inches, LogMAR Units) (Change from Baseline) [Time Frame: 0 min, 30 min, 1 hour, 2 hours, 4 hours, 6 hours] Change from baseline (-1 hour) in DCNVA at each timepoint (0 min, 30 min, 1 hour, 2 hours, 4 hours, 6 hours) Conjunctival Hyperemia (Eye Redness) Assessed Visually with the Brien Holden Vision Institute (formerly Corneal and Contact Lens Research Unit, or CCLRU) Bulbar Redness Scale (0-3) (Change from Baseline) [Time Frame: 0 min, 30 min, 1 hour, 2 hours, 4 hours, 6 hours] Change from baseline (-1 hour) in conjunctival hyperemia at each timepoint (0 min, 30 min, 1 hour, 2 hours, 4 hours, 6 hours), for study eye and non-study eye; in all subjects, in subjects taking Lumify®, and in subjects not taking Lumify®
Enrollment	32

Eligibility Criteria	Inclusion Criteria: - Males or females ≥ 18 and ≤ 45 years of age with brown irides (irises) only - Otherwise healthy and well controlled subjects - Able to comply with all protocol mandated procedures and to attend all scheduled office visits - Willing to give written informed consent to participate in this study Exclusion Criteria - Clinically significant ocular disease as deemed by the Investigator (e.g., cataract, glaucoma, corneal edema, uveitis, severe keratoconjunctivitis sicca) that might interfere with the study - Unwilling or unable to discontinue use of contact lenses during treatment visits - Ocular trauma, ocular surgery or non-refractive laser treatment within the 6 months prior to screening - Ocular medication of any kind within 30 days of screening, with the exception of a) lid scrubs (which may have been used prior to, but not after screening) or b) lubricating drops for dry eye (preservative-free artificial tears), which may be used in between the study treatment days - Recent or current evidence of ocular infection or inflammation. Current evidence of clinically significant blepharitis, conjunctivitis, or a history of herpes simplex or herpes zoster keratitis at screening - History of diabetic retinopathy - Closed or very narrow angles that in the Investigator's opinion are potentially occludable if the subject's pupil is dilated - History of any traumatic (surgical or nonsurgical) or non-traumatic condition affecting the pupil or iris (e.g., irregularly shaped pupil, neurogenic pupil disorder, iris atrophy, iridotomy) - Known allergy or contraindication to any component of the mydriatic agents or the vehicle formulation - Known hypersensitivity or contraindication to α- and/or β-adrenoceptor antagonists (e.g., chronic obstructive pulmonary disease or bronchial asthma; abnormally low blood pressure (BP) or heart rate (HR); second- or third-degree heart blockage or Congestive Heart Failure (CHF); severe diabetes) - Clinically significant systemic disease (e.g., uncontrolled diabetes, myasthenia gravis, cancer, hepatic, renal, endocrine or cardiovascular disorders) that might interfere with the study - Initiation of treatment with or any changes to the current dosage, drug or regimen of any topical or systemic adrenergic or cholinergic drugs up to 7 days prior to screening, or during the study - Participation in any investigational study within 30 days prior to screening - Women of childbearing potential who are pregnant, nursing, planning a pregnancy, or not using a medically acceptable form of birth control. Acceptable methods include the use of at least one of the following: intrauterine device (IUD), hormonal (oral, injection, patch, implant, ring), barrier with spermicide (condom, diaphragm), or abstinence. An adult woman is considered to be of childbearing potential unless she is 1 year postmenopausal or 3 months post-surgical sterilization. All females of childbearing potential must have a negative urine pregnancy test result at Visit 1/ Screening and Visit 2 examinations and must intend to not become pregnant during the study
Investigators	Not provided
Location	United States
Sponsor	Ocuphire Pharma, Inc.
Status	Completed
BCDVA = Best Corrected Distance Visual Acuity; BP = Blood Pressure; CCLRU = Corneal and Contact Lens Research Unit; DCNVA = Distance-Corrected Near Visual Acuity; ETDRS = Early Treatment Diabetic Retinopathy Study; HR = Heart Rate; IUD = Intrauterine Device.	

2.2.1.2 NCT04024891 Demographics

The demographic information for patients in clinical trial NCT04024891 can be found in Table 10. Thirty-two patients (median age of 27) were randomized in a 1:1 ratio to one of two treatment sequences (placebo at visit 1 followed by 1% phentolamine mesylate at visit 2 or 1% phentolamine mesylate at visit 1 followed by placebo at visit 2).

Table 10 Demographic Information from Clinical Trial NCT04024891

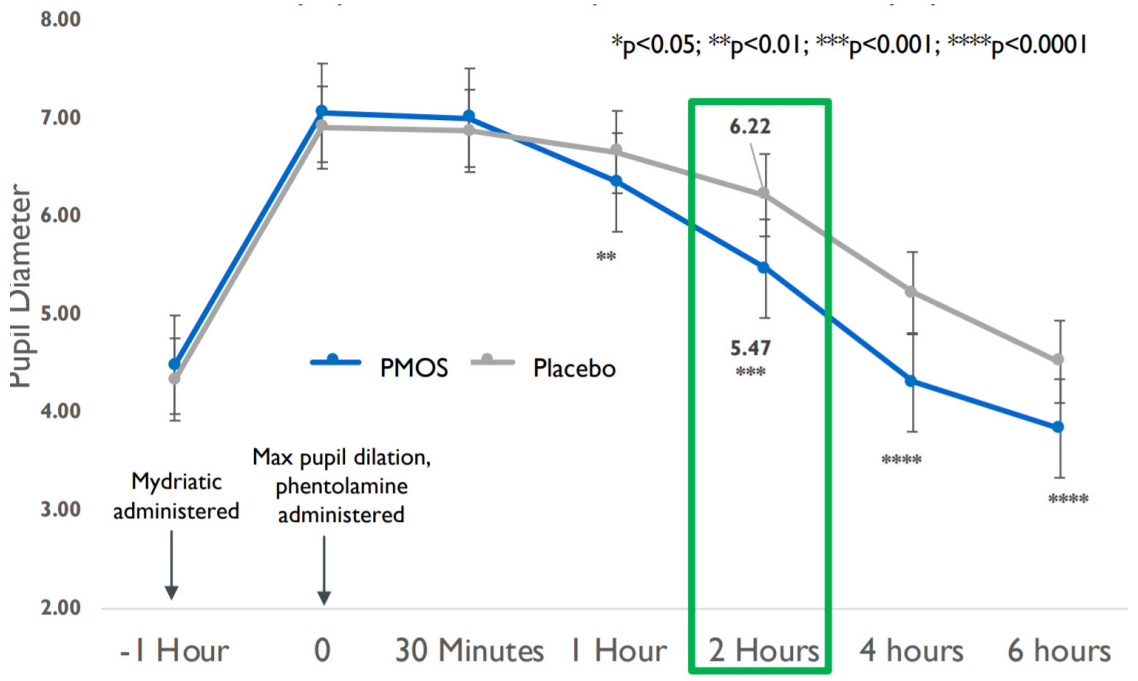
Parameters	Treatment Group		
	Placebo to PM	PM to Placebo	Total
n (full analysis set)	15	16	31
Age (years) median	30.0	26.0	27.0
Gender (female) n (%)	10 (67%)	9 (44%)	19 (61%)
Race (white) n (%)	14 (93%)	15 (94%)	29 (94%)
Iris Color (brown) n (%)	15 (100%)	16 (100%)	31 (100%)
PM = Phentolamine Mesylate			

(Karpecki, 2020)

2.2.1.3 NCT04024891 Efficacy

Phentolamine mesylate treatment demonstrated a statistically significantly ability to expedite reversal of mydriasis in the study eye as measured by mean change in pupil diameter from baseline at two hours, compared with placebo treatment (-1.69 mm vs -0.69 mm , p<0.0001) (Figure 10).

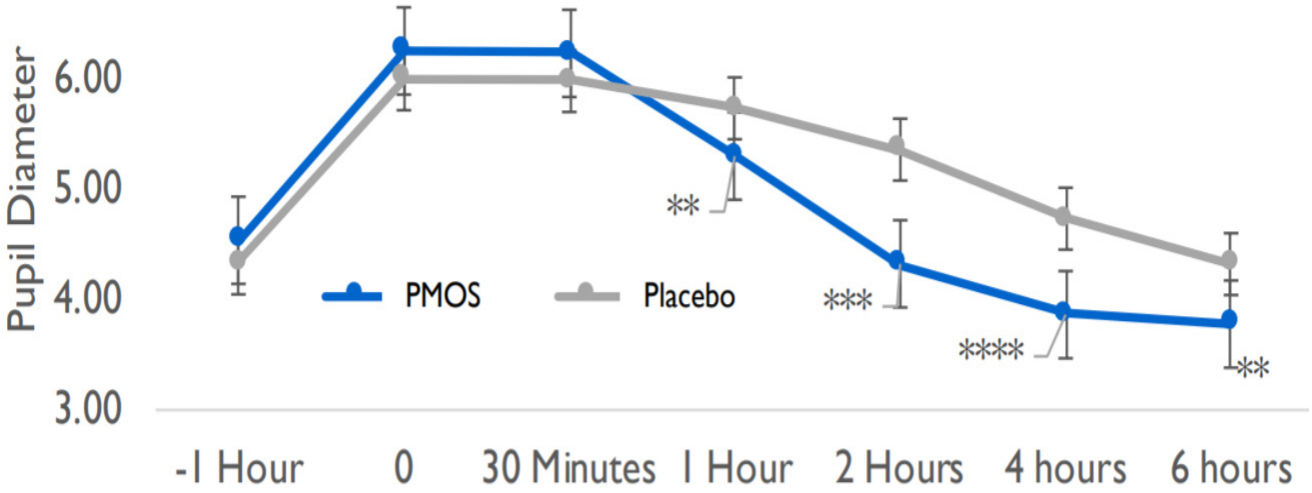
Figure 10 Pupil Diameter after Administration of Phenylephrine 2.5% or Tropicamide 1.0%



(Karpecki, 2020)

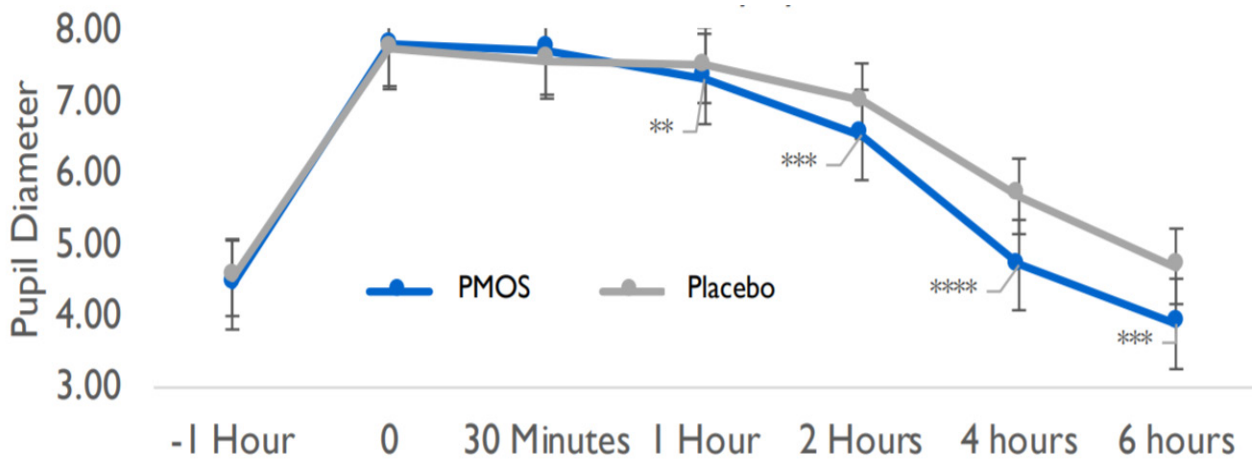
A statistically significant difference favoring phentolamine mesylate treatment was also observed at all time points tested from one hour through six hours in the study eye and non-study eye. These statistically significant differences were maintained when analyzed separately by the mydriatic agents, 2.5% phenylephrine (Figure 11) and 1% tropicamide (Figure 12).

Figure 11 Reduction in Pupil Diameter after Patients Received Phenylephrine 2.5% in Study Eye



(Karpecki, 2020)

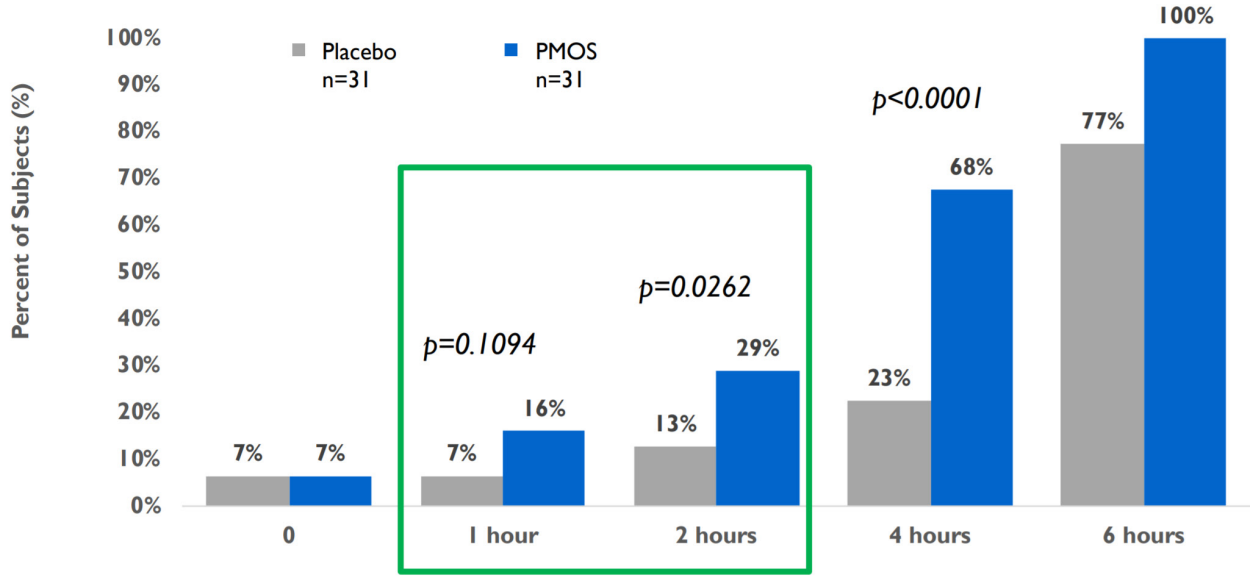
Figure 12 Reduction in Pupil Diameter after Patients Received Tropicamide 1.0% in Study Eye



(Karpecki, 2020)

A statistically significant time savings of two hours was observed for patients to achieve reversal of mydriasis with phentolamine mesylate treatment versus placebo treatment using a pupil diameter threshold of ≤ 0 mm above baseline ($p < 0.001$). The placebo outcomes demonstrate that natural reversal of mydriasis takes longer with tropicamide than with phenylephrine. Phentolamine mesylate was effective at inducing reversal of mydriasis with both mydriatic agents (Figure 13).

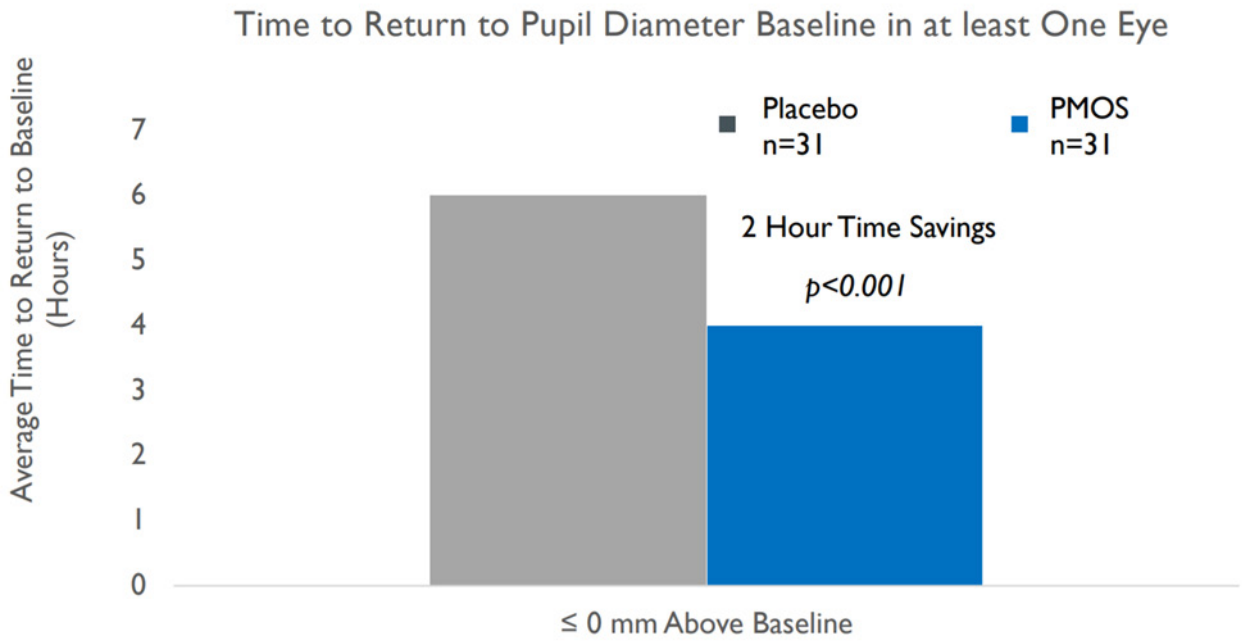
Figure 13 Percent of Subjects Returning to ≤ 0.2 mm within Baseline after Treatment with either Phenylephrine or Tropicamide



(Karpecki, 2020)

Phentolamine mesylate had an average time savings of two hours to return pupil diameter at or below baseline (Figure 14).

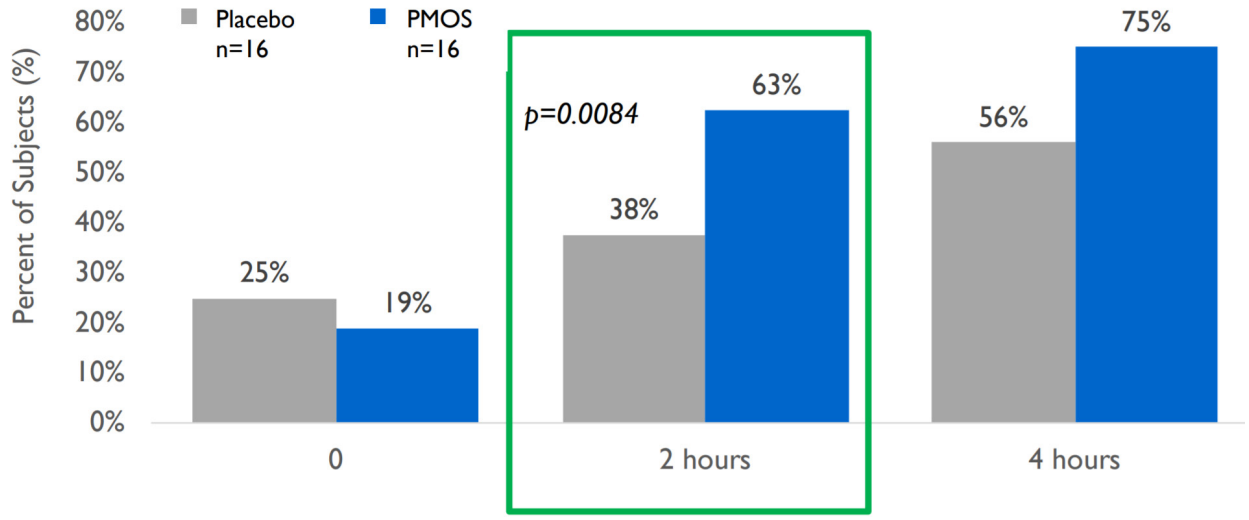
Figure 14 Time to Return to Pupil Diameter Baseline in at least One Eye



(Karpecki, 2020)

Phentolamine mesylate demonstrated a faster return of accommodative power compared to placebo in subjects treated with tropicamide mydriatic agent (Figure 15).

Figure 15 Percent of Subjects Returning to Accommodation within ≤ 1 D of Baseline in at Least One Eye after Treatment with Tropicamide



(Karpecki, 2020)

2.2.1.4 NCT04024891 Safety

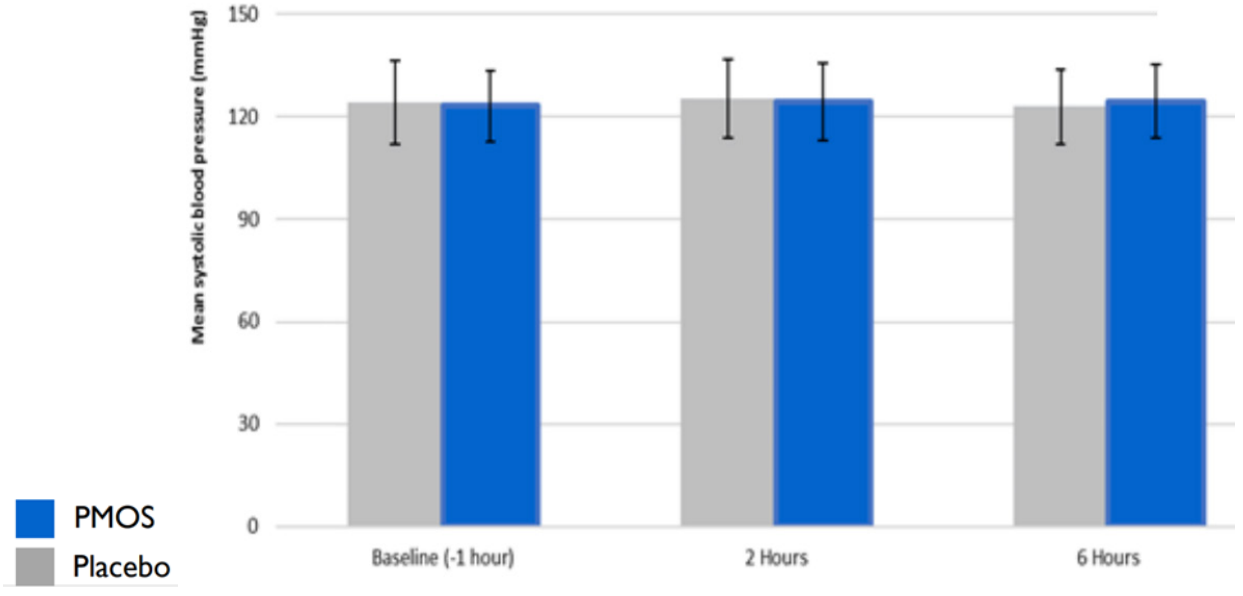
When treated with phentolamine mesylate, 35.5% of patients experienced a TEAE. All of the TEAEs were mild cases of conjunctival hyperemia. There were no serious TEAEs or TEAEs leading to withdrawal or study medication discontinuation. No other TEAEs were observed with phentolamine mesylate treatment.

Phentolamine mesylate was associated with mild-to-moderate conjunctival hyperemia in the majority of eyes. This hyperemia peaked at 30 minutes and declined steadily thereafter from four to six hours. It should be noted that no patients requested to use LUMIFY (brimonidine) at two hours to reduce any signs or symptoms of redness. The majority of patients did not report ocular discomfort at the time of instillation of either phentolamine mesylate or placebo. Any discomfort that occurred was mild in intensity.

There was no clinically meaningful change in IOP from baseline between eyes treated with phentolamine mesylate and eyes treated with placebo. No patients with either phentolamine mesylate treatment or placebo treatment had a ≥ 3-line worsening in BCDVA or DCNVA at any time point in either eye.

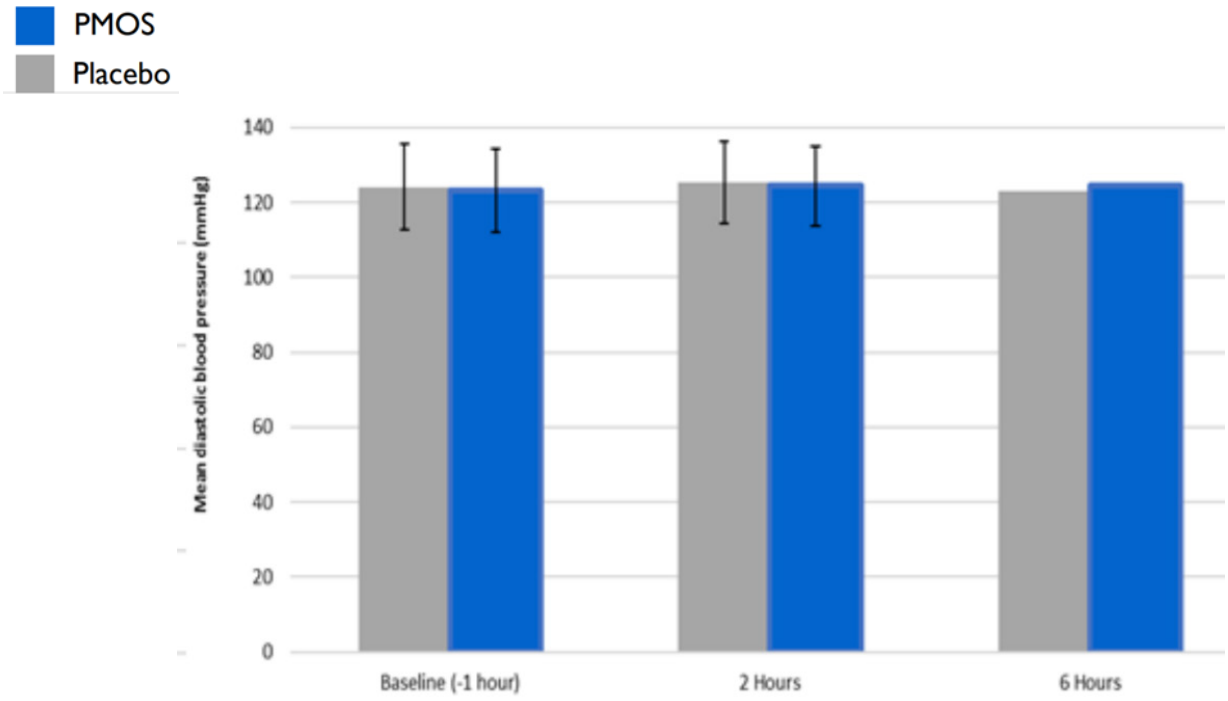
Nyxol had no significant impact on the patients systolic pressure (Figure 16), diastolic pressure (Figure 17) or heart rate (Figure 18).

Figure 16 Effect of Nyxol on Patients Systolic Pressure

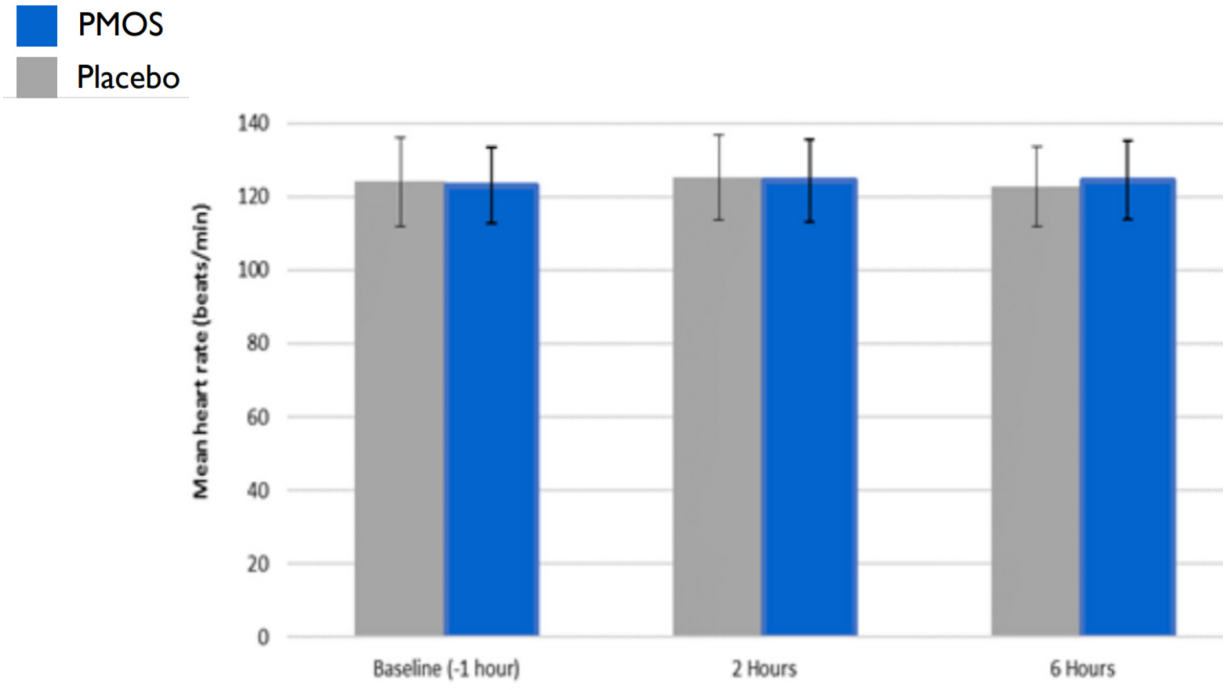


(Karpecki, 2020)

Figure 17 Effect of Nyxol on Patients Diastolic Pressure



(Karpecki, 2020)
Figure 18 Effect of Nyxol on Patients Heart Rate

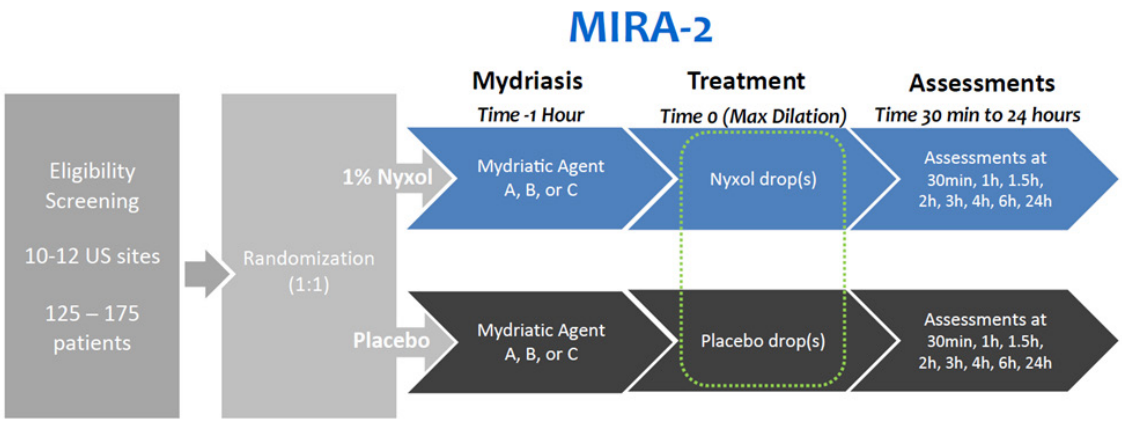


(Karpecki, 2020)

2.2.2 Planned Mydriasis Reversal Clinical Trial – MIRA-2

Ocuphire expects to initiate MIRA-2, a Phase 3, double-masked, randomized, placebo-controlled, multi-center trial in normal healthy patients in the second half of 2020 in the U.S. (Figure 19). The MIRA-2 trial is expected to evaluate the effect of 1% Nyxol to reverse pharmacologically induced mydriasis. The trial is expected to enroll approximately 125-175 healthy patients. Eligible patients are expected to be administered a mydriatic (either phenylephrine and tropicamide) and be given one or two drops of 1% Nyxol approximately one hour later after max pupil diameter, and then measured at multiple time points from 30 minutes to 6 hours and 24 hours.

Figure 19 Phase 3 Reversal of Mydriasis Clinical Trial Design (MIRA-2)



(Ocuphire Corporate Business Presentation)

An overview of clinical trial MIRA-2 can be found in Table 11.

Table 11 Overview of Clinical Trial MIRA-2

Overview of MIRA-2 Clinical Trial	
Title	MIRA-2
Condition	Reversal of Pharmacologically Induced Mydriasis
Type	Interventional
Phase	Phase 3
Design	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) Primary Purpose: Treatment
Intervention	Drug: Phentolamine Mesylate Ophthalmic Solution 1.0% Phentolamine mesylate (Nyxol) ophthalmic solution 1.0% is a non-selective alpha-1 and alpha-2 adrenergic antagonist Other Names: Nyxol® Nyxol Other: Phentolamine Mesylate Ophthalmic Solution Vehicle (Placebo) Placebo (vehicle) is a sterile, isotonic, buffered aqueous solution containing mannitol and sodium acetate
Arms	Placebo Comparator: Placebo Administered once daily Intervention: Other: Phentolamine Mesylate Ophthalmic Solution Vehicle (Placebo) Experimental: Phentolamine Mesylate Ophthalmic Solution 1.0% Administered once daily Intervention: Drug: Phentolamine Mesylate Ophthalmic Solution 1.0%
Primary Outcome	The primary endpoint is expected to be percent of patients who return to within 0.2 mm of their pupil diameter baseline at 90 minutes or less after receiving Nyxol.

Secondary Outcomes	Pupil diameter at all other timepoints Accommodation Time savings
Enrollment	125-175
Eligibility Criteria	Adults and pediatrics Otherwise healthy subjects with no pre-existing ocular conditions/procedures that achieve mydriatic pupil size 3:1:1 stratification for mydriatic agent: 2.5% phenylephrine, 1% tropicamide, and Paremyd® (combo) Balance stratification of dark and light irides
Location	United States
Sponsor	Ocuphire Pharma Inc.
Status	Not yet started

Patient safety is expected to be assessed by AE monitoring, conjunctival redness monitoring, visual acuity, IOP and vital sign assessments including heart rate and blood pressure.

The status of the MIRA-2 trial is that Ocuphire have selected their CRO but are still in the process of finalizing the protocol, budget and selecting the trial sites. Ocuphire expects to report top-line data for this acute indication Phase 3 registration trial in 2021.

2.3 Presbyopia

Presbyopia is a physiological condition wherein there is a progressive functional decline in the accommodative capacity of the crystalline lens. Clinically, it manifests as a progressive difficulty in reading at the usual reading distance (Singh and Tripathy, 2020) (Figure 20).

Normally, the nucleus is stiffer than the cortex in the older lens, whereas, among young individuals, the cortex is stiffer than the nucleus (Heys et al., 2004). However, the stiffness of both nucleus and cortex equalizes between 35 to 40 years; and this is probably the cause of the onset of presbyopic symptoms around 40 years of age (Weeber et al., 2007).

Another important factor attributing to the presbyopia is a relative change in the shape of the lens with increasing age (increased thickness of lens), such that the vector forces exerted by zonules at the equator spread over a wider region around the equator. This results in a minimal effect on lens shape with zonular contraction and relaxation (Koretz et al., 2002).

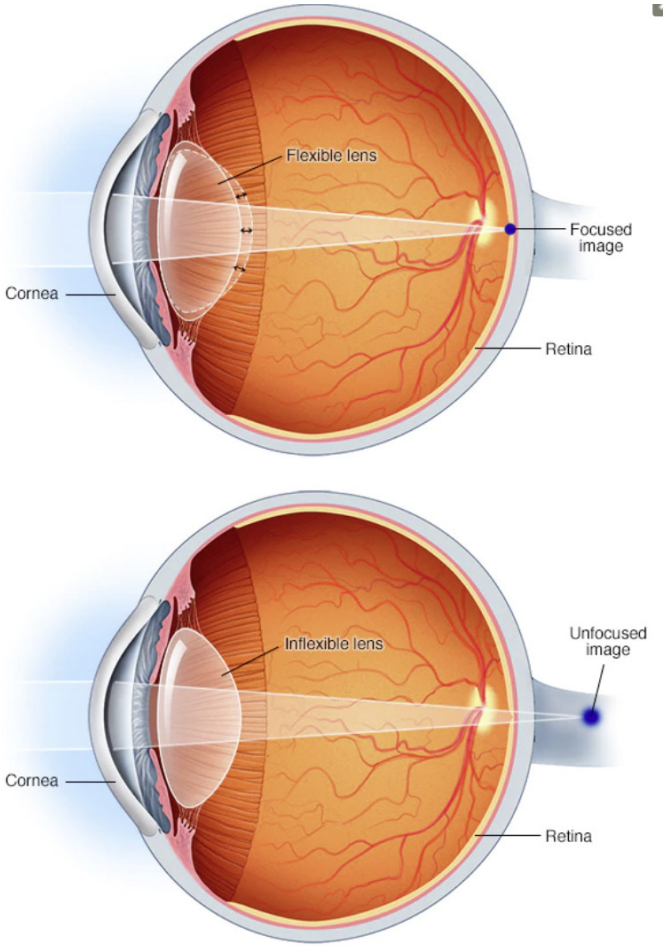
There are both non-surgical and surgical options for the treatment/management of presbyopia.

Non-surgical options include:
- Spectacles
    - Single vision lenses
    - Bifocal lenses and
    - Progressive lenses
- Contact Lenses
    - Monofocal
    - Multifocal

Surgical options include:
- Corneal procedures
- Scleral procedures
- Monovision with intraocular implant
- Phakic intraocular lenses
- Clear lens extraction followed by IOL implantation

(Singh and Tripathy, 2020)

Figure 20 Schematic Representation of Presbyopia



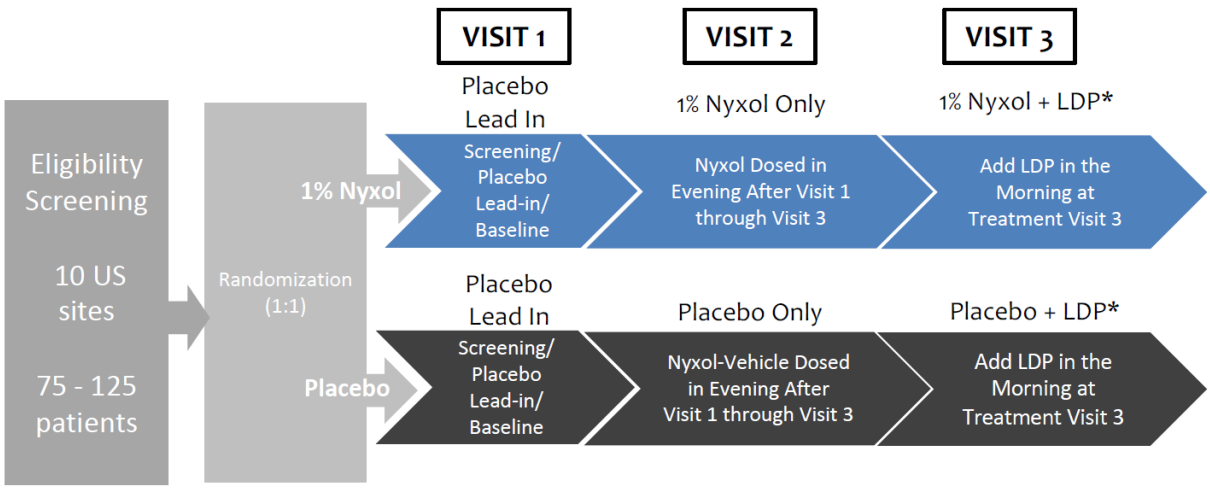
(Mayo Foundation for Clinical Education and Research, Presbyopia)

Presbyopia is an ever-increasing global problem affecting over a billion worldwide (Holden et al., 2008). The increase in the number of the aging population has prompted health care professionals to find ways to manage the situation with various non-surgical and surgical means effectively.

2.3.1 Planned Presbyopia Clinical Trial – VEGA-1

Ocuphire expects to initiate VEGA-1, a Phase 2 proof of concept, double-masked, randomized, placebo-controlled, multi-center trial in patients with presbyopia in the first quarter of 2021 (Figure 21). The VEGA-1 trial is expected to be designed to evaluate the effect of a kit combination with Nyxol and low dose pilocarpine for temporary treatment of presbyopia. The trial is expected to enroll approximately 75-125 patients with a clinical diagnosis of presbyopia (20/50 or worse near vision).

Figure 21 Phase 3 Presbyopia Clinical Trial Design (MIRA-2)



(Ocuphire Corporate Business Presentation)

An overview of the VEGA-1 study can be found in Table 12.
Table 12 Overview of Clinical Trial VEGA-1

Overview of VEGA-1 Clinical Trial	
Title	VEGA-1
Condition	Presbyopia
Type	Interventional
Phase	Phase 2
Design	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) Primary Purpose: Treatment
Intervention	Drug: Phentolamine Mesylate Ophthalmic Solution 1.0% plus low dose pilocarpine Other: Phentolamine Mesylate Ophthalmic Solution Vehicle (Placebo)
Arms	Placebo Comparator: Placebo Administered once daily Intervention: Other: Phentolamine Mesylate Ophthalmic Solution Vehicle (Placebo) Experimental: Phentolamine Mesylate Ophthalmic Solution 1.0% plus low dose pilocarpine Administered once daily Intervention: Drug: Phentolamine Mesylate Ophthalmic Solution 1.0% plus low dose pilocarpine
Primary Outcome	The primary endpoint is expected to be percent of patients with at least 3 lines (15 letters or more) of binocular distance corrected near visual acuity (DCNVA) improvement on a standard near vision eye chart.
Secondary Outcomes	Pupil diameter and percent of patients with improvements in DCNVA at 1 and 2 lines of the combination compared to placebo and each component.
Enrollment	75-125
Eligibility Criteria	- Clinical diagnosis of Presbyopia (20/50 or worse) - 40 to 60 years old - Otherwise healthy subjects with no pre-existing ocular conditions/procedures
Location	United States
Sponsor	Ocuphire Pharma Inc.
Status	Not yet started
DCNVA = Distance Corrected Near Visual Acuity	

Patient safety is expected to be assessed by AE monitoring, conjunctival redness monitoring, distance visual acuity, IOP and vital sign assessments (heart rate and blood pressure).

The status of the VEGA-1 trial is that Ocuphire is finalizing the protocol and budget and is in the process of selecting their CRO and trial sites. Ocuphire expects to report top-line data for the Phase 2 trial in the second quarter of 2021.

2.4 Glaucoma

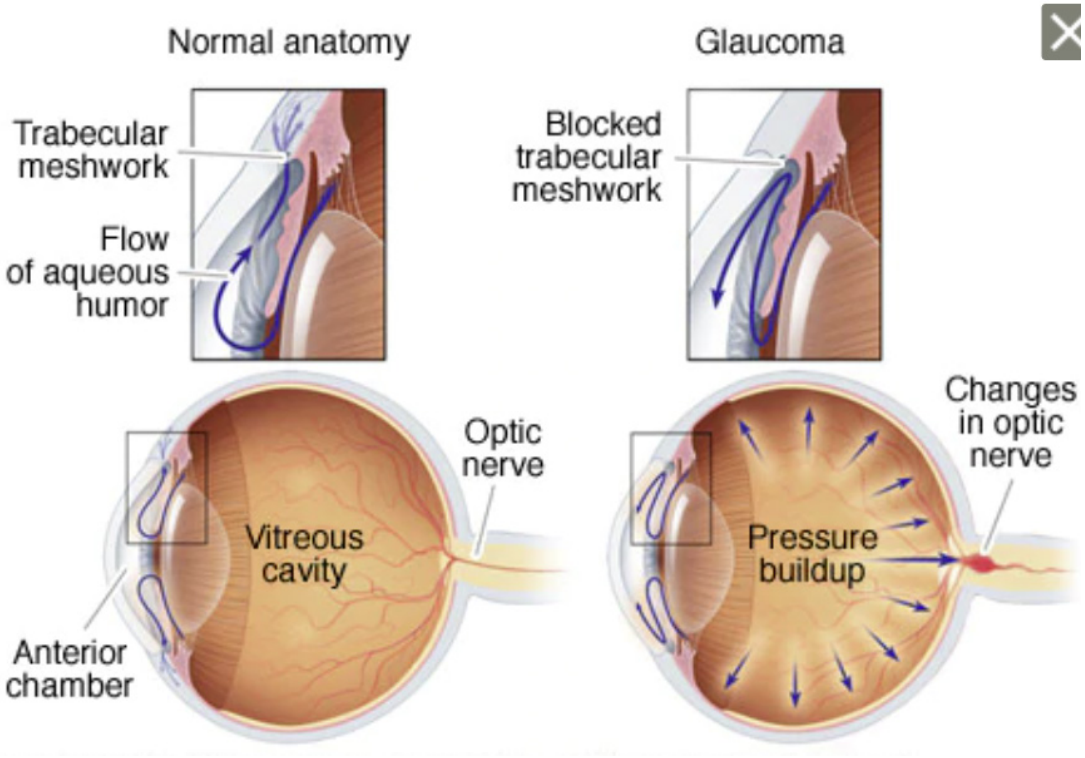
Glaucoma refers to a collection of diseases whereby increased intraocular pressure adversely impacts the optic nerve, and subsequently, the visual field. Glaucoma is defined as an acquired loss of retinal ganglion cells and axons within the optic nerve or optic neuropathy that results in a characteristic optic nerve head appearance and a corresponding progressive loss of vision. This pattern of peripheral loss of vision can be a distinguishing characteristic from other forms of vision loss (Jonas et al., 2017).

There are four general categories of glaucoma:

- Primary open-angle glaucoma - typically manifests as slow, painless damage to the optic nerve that is thought to be due to the drainage system in the eye becoming ineffective.
- Primary angle-closure glaucoma - the drainage system of the eye becomes blocked abruptly due to the closure of the angle formed between the cornea and the iris.
- Secondary open-angle glaucoma - due to injury, eye disease, and rarely eye surgery causing increased intraocular pressure and, therefore, optic nerve damage like the open-angle form of glaucoma
- Secondary angle-closure glaucoma - the lens can displace into the pupil or anterior chamber, causing an acute pupillary block.

(Dietze et al., 2020)

The most common type of glaucoma in the U.S. is primary open-angle glaucoma (Cook et al., 2012) (Figure 22).
Figure 22 Schematic Representation of Open-angle Glaucoma



(Mayo Foundation for Cinical Education and Research, Glaucoma)

Glaucoma management is tailored to the specific type and severity. However, there is no treatment at this time that can reverse any of the vision loss that has occurred, it can only help to prevent further damage and vision loss. Visual field testing and mapping of vision loss are helpful in monitoring disease progression (Dietze et al., 2020). Open-angle glaucoma is generally managed initially with medications to lower eye pressure. Medication classes include prostaglandin analogs, beta-blockers, carbonic anhydrase inhibitors, an alpha-2 agonist, miotic agents, and more recently rho-kinase inhibitors and nitric-oxide donating medications (Dietze et al., 2020).

Angle-closure glaucoma is an emergency and must be treated as such. This is because pressures can be high enough to cause glaucomatous optic nerve damage, ischemic nerve damage, or retinal vascular occlusion (Wright et al., 2016). Patients take medication to reduce eye pressure as quickly as possible but usually require a laser procedure called laser peripheral iridotomy.

Secondary glaucoma should be treated for the underlying cause of glaucoma with the possible addition of medications to lower intraocular pressure depending on the underlying cause (Bai et al., 2009).

2.4.1 Completed Glaucoma Clinical Trial NCT03960866

2.4.1.1 NCT03960866 Design

Clinical trial NCT03960866 (ORION-1) was a placebo-controlled double-masked, multiple dose, Phase 2 study in 40 patients with intraocular pressure ≥ 22 and ≤ 30 mmHg, evaluating ocular and systemic safety and efficacy following administration of phentolamine mesylate 1.0% once daily at 8:00 am to 10:00 pm in both eyes for 14 days.

The objectives of this study were to:

- Evaluate the efficacy of phentolamine mesylate to lower IOP in the treatment of Open-Angle Glaucoma (OAG) and Ocular Hypertension (OHT).
- Evaluate the ocular and systemic safety of phentolamine mesylate compared to its vehicle.
- Evaluate additional efficacy of phentolamine mesylate to improve visual performance.

A brief overview of study NCT03960866 can be found in Table 13.
Table 13 Overview of Clinical Trial NCT03960866

Overview of Clinical Trial NCT03960866 (ClinicalTrials.gov)	
Title	Safety and Efficacy of Ophthalmic Phentolamine Mesylate in Glaucoma
Condition	Open Angle Glaucoma Ocular Hypertension
Type	Interventional
Phase	Phase 2
Design	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Investigator, Outcomes Assessor) Primary Purpose: Treatment
Intervention	Drug: Phentolamine Mesylate Ophthalmic Solution 1% Topical Sterile Ophthalmic Solution Other Name: Nyxol® Other: Phentolamine Mesylate Ophthalmic Solution Vehicle (Placebo) Topical Sterile Ophthalmic Solution
Arms	Experimental: Nyxol Ophthalmic Solution 1% One drop in each eye daily (QD) at or before bedtime (8pm to 10pm) for 14 days Intervention: Drug: Phentolamine Mesylate Ophthalmic Solution 1% Placebo Comparator: Nyxol Ophthalmic Solution Vehicle One drop in each eye daily (QD) at or before bedtime (8pm to 10pm) for 14 days Intervention: Other: Phentolamine Mesylate Ophthalmic Solution Vehicle (Placebo)
Primary Outcome	Intraocular Pressure [Time Frame: 14 days] Change from Baseline in mean diurnal IOP in the study eye

Secondary Outcomes	Distance Visual Acuity [Time Frame: 14 days] Change in Distance Visual Acuity from Baseline measured at 4 meters (photopic and mesopic) Near Visual Acuity [Time Frame: 14 days] Change in Near Visual Acuity from Baseline measured at 16 inches (photopic and mesopic) Pupil Diameter [Time Frame: 14 days] Change and percent change from Baseline in Pupil Diameter (mesopic and photopic) Conjunctival Hyperemia [Time Frame: 14 days] Change in Conjunctival Hyperemia score
Enrollment	40 (39 actual)
Eligibility Criteria	Inclusion Criteria: - 18 years of age or greater - Diagnosis of open angle glaucoma (OAG) or ocular hypertension (OHT). A reported history of untreated OHT with IOP ≥22mmHg and ≤ 30mmHg is preferred. - Untreated or treated OAG/OHT with 2 or fewer ocular hypotensive medications. - Untreated (post-washout) mean IOP ≥ 22mmHg and ≤30mmHg in the study eye at the Qualification Visit (8AM). - Corrected visual acuity in each eye +1.0 logMAR or better by Early Treatment Diabetic Retinopathy Study (ETDRS) in each eye (equivalent to 20/200 or better) at the Screening Visit and Qualification Visit. - Otherwise healthy and well-controlled subjects. - Able and willing to give signed informed consent and follow study instructions. - Able to self-administer study medication or to have study medication administered by a caregiver throughout the study period. Exclusion Criteria: - Closed or very narrow angles (Grade 0-1, Shaffer) - Glaucoma: pseudo-exfoliation or pigment dispersion component - Known hypersensitivity to any alpha-adrenoceptor antagonists - Previous laser and/or non-laser glaucoma surgery or procedure in either eye - Refractive surgery in either eye - Ocular trauma in either eye within the six months prior to Screening, or ocular surgery or non-refractive laser treatment within the 3 months prior to Screening - Recent or current evidence of ocular infection or inflammation in either eye - Ocular medication in either eye of any kind within 30 days of Screening - Clinically significant ocular disease in either eye - History of diabetic retinopathy - Contact lens wear within three days prior to and for the duration of the study - Central corneal thickness in either eye >600 µm at Screening - Any abnormality in either eye preventing reliable applanation tonometry - Known hypersensitivity or contraindication to alpha- and/or beta-adrenoceptor antagonists - Clinically significant systemic disease that might interfere with the study - Participation in any investigational study within 30 days prior to Screening - Use of any topical or systemic adrenergic or cholinergic drugs up to 30 days prior to Screening, or during the study - Changes in systemic medication that could have an effect on IOP within 30 days prior to Screening - Women of childbearing potential who are pregnant, nursing, planning a pregnancy, or not using a medically acceptable form of birth control - Resting heart rate outside the normal range (50-110 beats per minute) at Screening or Qualification Visit - Hypertension with resting diastolic blood pressure (BP) > 105 mmHg or systolic BP > 160 mmHg at the Screening or Qualification Visit

Investigators	Not provided
Location	United States
Sponsor	Ocuphire Pharma, Inc.
Status	Completed
BP = Blood Pressure; ETDRS = Early Treatment Diabetic Retinopathy Study; IOP = Intraocular Pressure; OAG = Open Angle Glaucoma; OHT = Ocular Hypertension.	

2.4.1.2 NCT03960866 Demographics

A summary of the demographic information for glaucoma patients in Clinical Trial NCT03960866 can be found in Table 14.

Table 14 Demographic Information from Clinical Trial NCT03960866

Parameter	Treatment Group	
	Placebo	1% PM
n	20	19
Age (years) mean	63.2	58.1
Gender (female) n (%)	13 (65%)	9 (47%)
Race (white) n (%)	14 (70%)	11 (58%)

(Pepose, 2020)

A summary of the characteristics of the glaucoma patients in Clinical Trial NCT03960866 can be found in Table 15.
Table 15 Characteristic Information from Clinical Trial NCT03960866

Characteristics		Treatment Group	
		Placebo	Placebo
Study Eye N (%)	OD	10 (50%)	11 (58%)
	OS	10 (50%)	8 (42%)
Baseline Mean Diurnal IOP mean (SD)	Study Eyes	24.38 (2.097)	24.43 (1.675)
	All Eyes	23.75 (2.244)	23.07 (1662)
Baseline IOP Category N (%)	≥ 25 mmHg	13 (65%)	10 (53%)
	< 25 mmHg	7 (35%)	9 (47%)
Baseline BCDVA N (SD)	Photopic LogMAR	0.05 (0.11)	0.05 (0.14)
	Mesopic LogMAR	0.17 (0.12)	0.19 (0.13)
BCDVA = Best-Corrected Distance Visual Acuity; IOP = Intraocular Pressure; mmHg = Millimeters of Mercury; OD = Oculus Dexter (right eye); OS = Oculus Sinister (left eye); SD = Standard Deviation			

(Pepose, 2020)

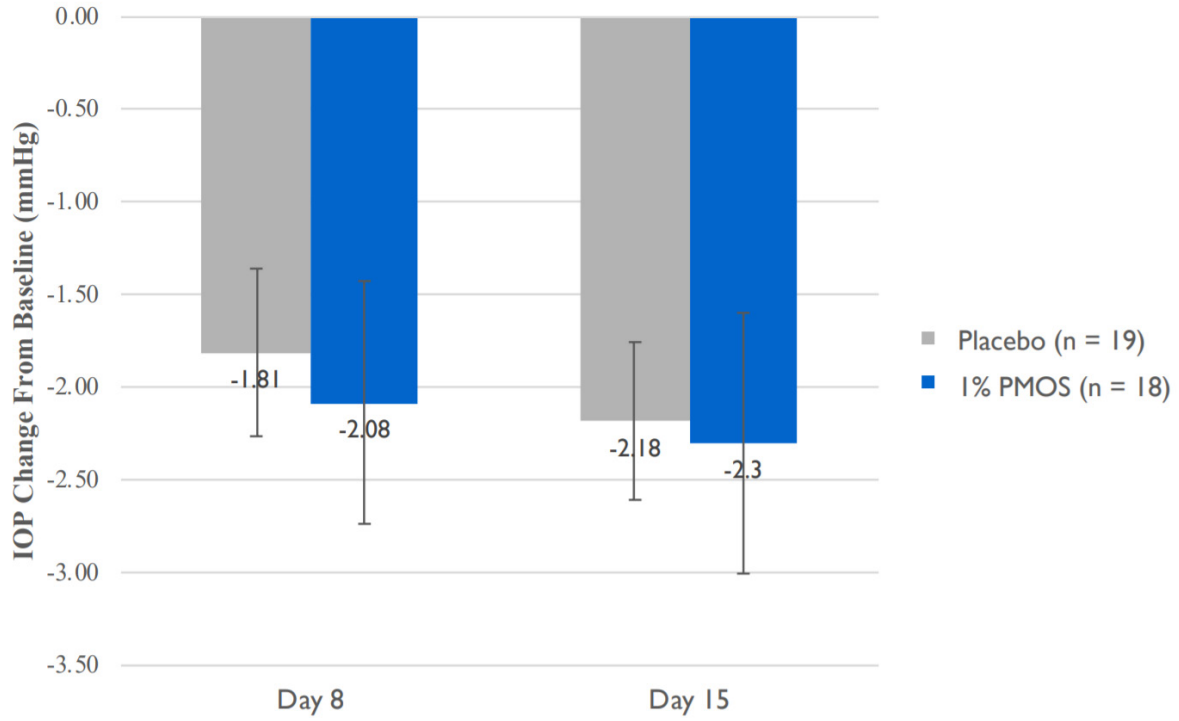
The demographics and characteristics of the placebo and phentolamine mesylate groups were similar.

2.4.1.3 NCT03960866 Efficacy

Intraocular Pressure

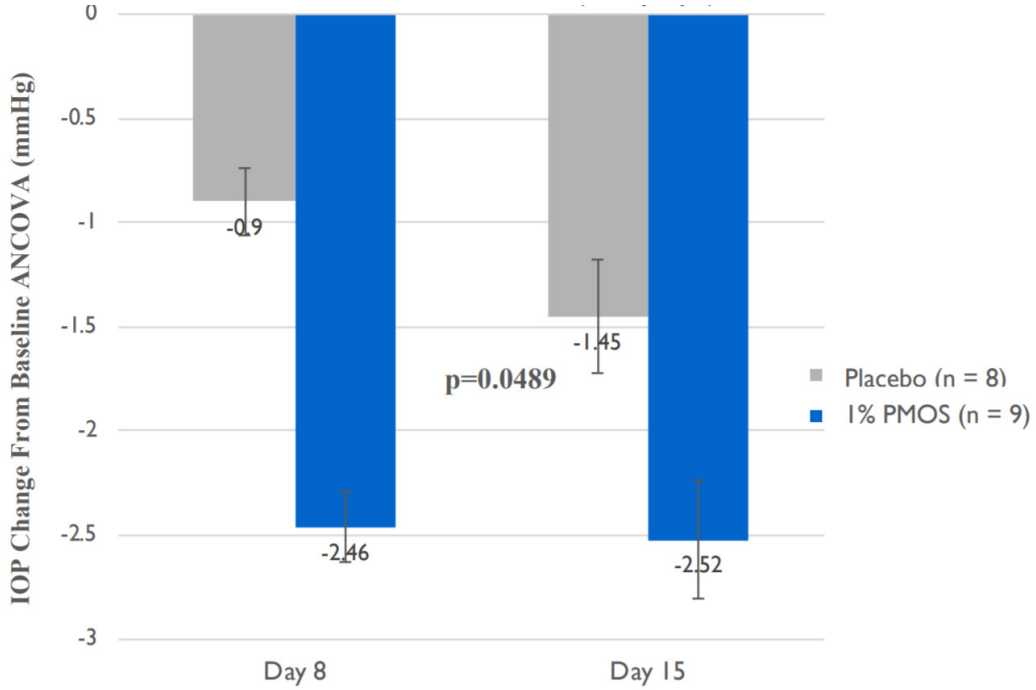
Phentolamine mesylate ophthalmic solution did not show a significant decrease in IOP after day 15 (Figure 23) but did demonstrate a significant decrease in patients with baseline IOP < 24 mmHg (Figure 24).

Figure 23 Mean Change in Diurnal IOP at Day 8 and Day15 - All Patients



(Pepose, 2020)

Figure 24 Mean Change in Diurnal IOP at Day 8 and Day 15 - Patients with Baseline IOP < 24 mmHg

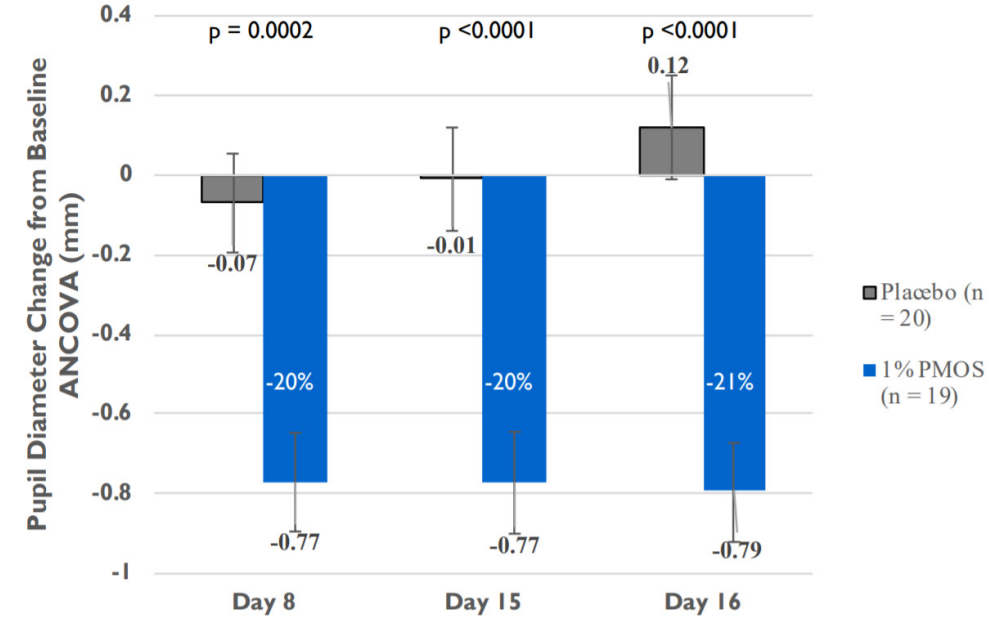


(Pepose, 2020)

Pupil Diameter

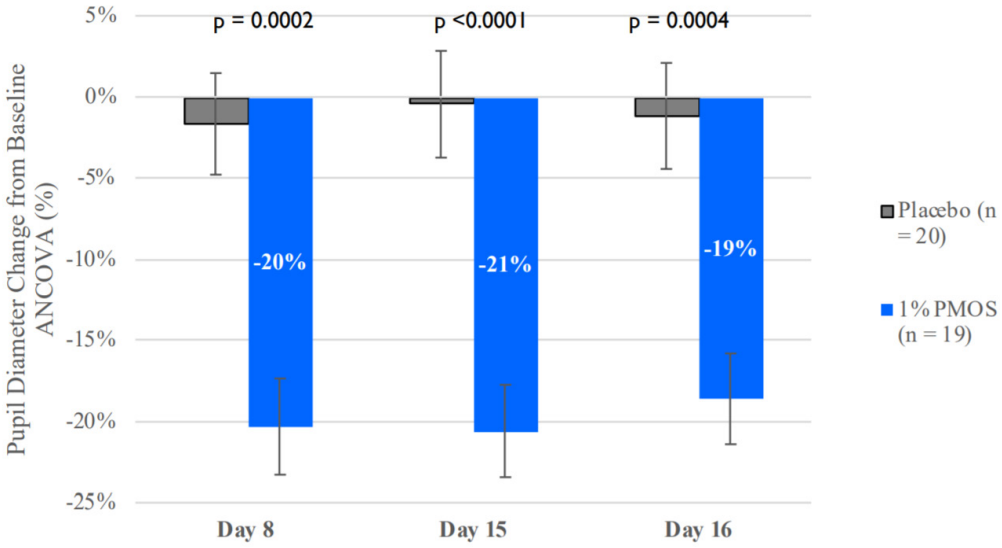
Phentolamine mesylate ophthalmic solution showed a consistent 20% mean reduction (~1mm) in pupil diameter from baseline in both photopic (Figure 25) and mesopic (Figure 26) conditions that is sustained over 24 hours with bedtime daily dosing.

Figure 25 Reduction in Pupil Diameter under Photopic Conditions



(Pepose, 2020)

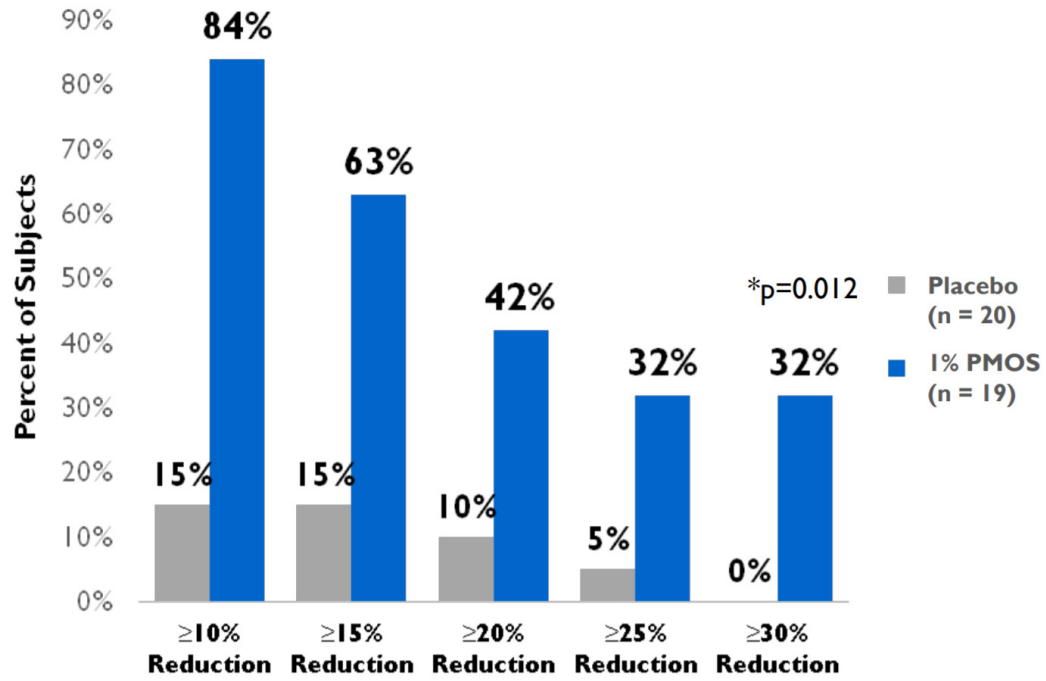
Figure 26 Reduction in Pupil Diameter under Mesopic Conditions



(Pepose, 2020)

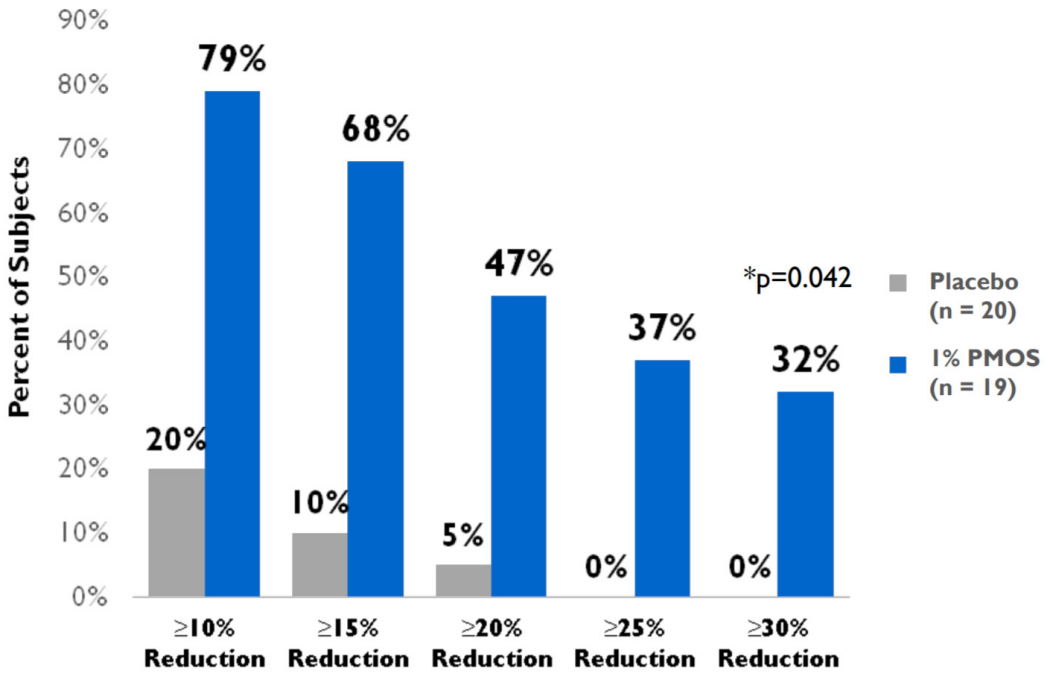
One-third of subjects who were given phentolamine mesylate ophthalmic solution had ≥ 30% reduction in pupil diameter under both photopic (Figure 27) and mesopic (Figure 28) conditions.

Figure 27 Percent of Patients Achieving Reductions in Pupil Diameter in Photopic Conditions



(Pepose, 2020)

Figure 28 Percent of Patients Achieving Reductions in Pupil Diameter in Mesopic Conditions

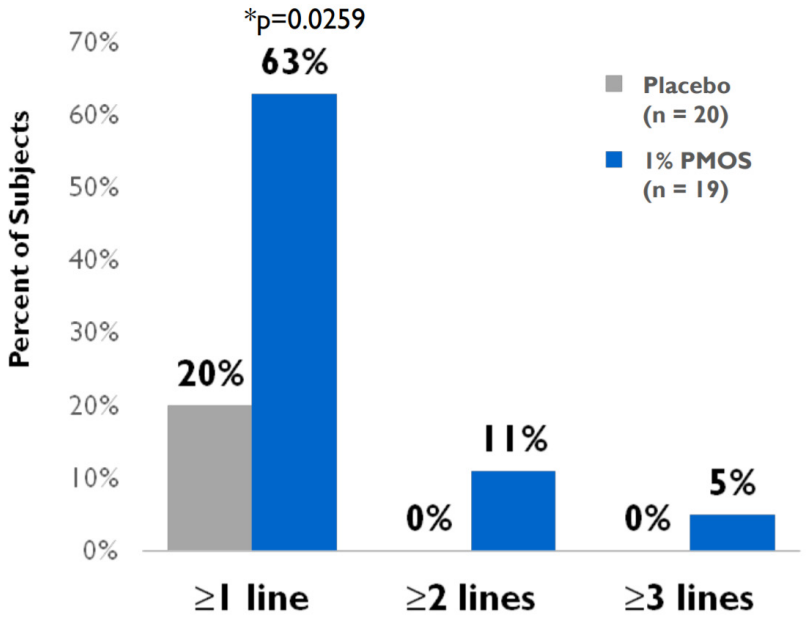


(Pepose, 2020)

Visual Acuity

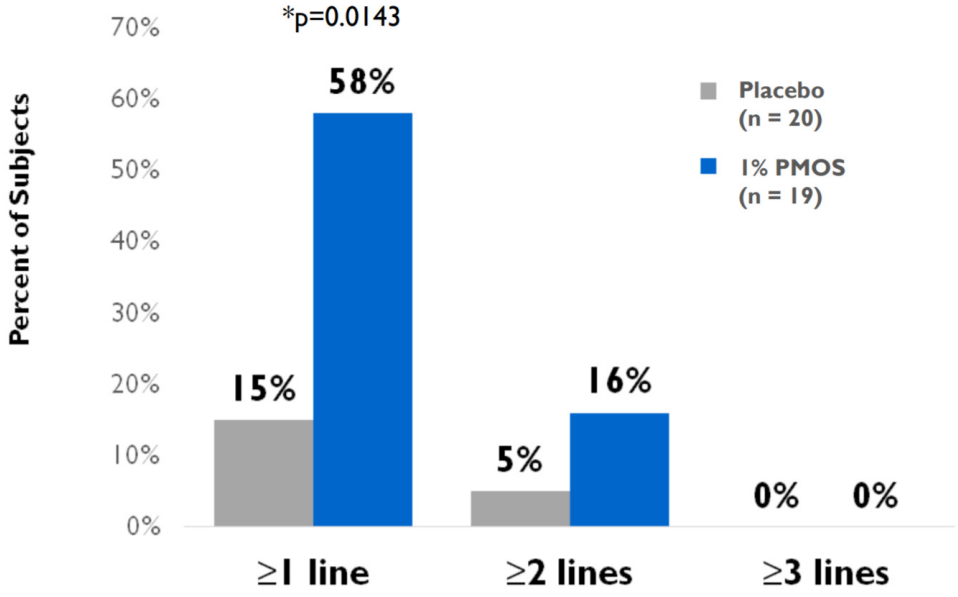
Approximately 60% of subjects who were given phentolamine mesylate ophthalmic solution had ≥ 1-line of improvement in distance-corrected near visual acuity at day 15 in both photopic (Figure 29) and mesopic (Figure 30) conditions.

Figure 29 Percent of Patients with DCNVA Line Improvement under Photopic Conditions



(Pepose, 2020)

Figure 30 Percent of Patients with DCNVA Line Improvement under Mesopic Conditions



(Pepose, 2020)

In conclusion, although the IOP endpoint related to glaucoma was not met in this clinical trial, many prespecified endpoints for other indications were successfully met with daily dosing of 1% phentolamine mesylate eye drops in the evening, including pupil diameter reduction and visual acuity performance. This information is therefore clinically relevant to the other potential indications for 1% phentolamine mesylate such as NVD and Presbyopia.

2.4.1.4 NCT03960866 Safety

The incidence of TEAEs were higher in the 1% phentolamine mesylate arm compared with the placebo arm (31.6% vs 5.0%) but all TEAEs were mild in severity, with no serious TEAEs or TEAEs leading to withdrawal or study medication discontinuation (Table 16).

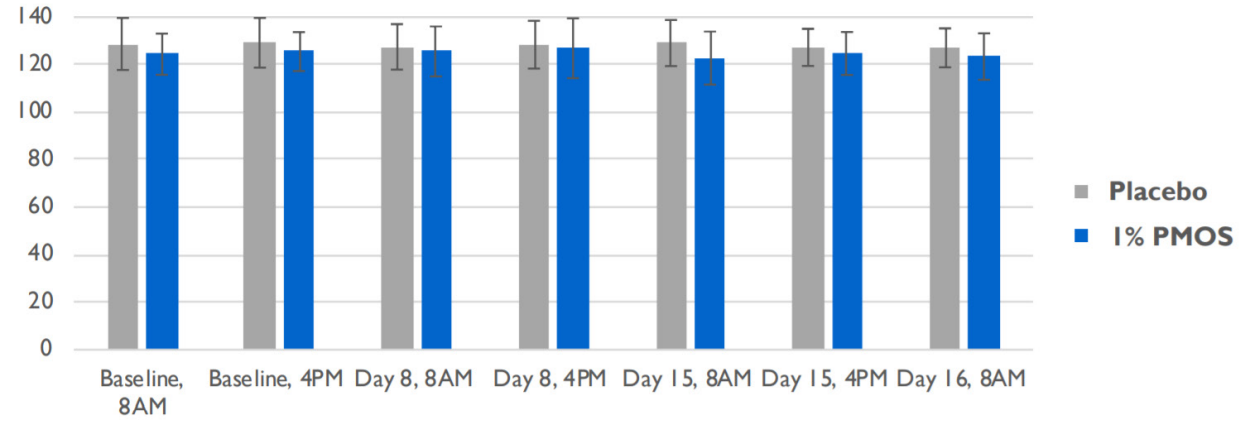
Table 16 Adverse Effects following Treatment with either 1% Phentolamine Mesylate or Placebo

System Organ Class Preferred Term	Treatment Group	
	1% PM (n=19) n (%)	Placebo (n=20) n (%)
Total number of TEAEs	16	2
Eye Disorders	3 (15.8)	1 (5.0)
Conjunctival hyperemia	3 (15.8)	1 (5.0)
Eye pruritus	1 (5.3)	0
Vision blurred	0	0
Conjunctival hemorrhage	0	0
Corneal deposits	0	0
Erythema of eyelid	0	0
Eye irritation	0	0
Eyelid edema	0	0
Lacrimation increased	0	0
Eye pain	0	0
Visual acuity reduced	0	0
Conjunctival edema	0	0
Foreign body sensation in eyes	0	0
Punctate keratitis	0	0
General disorders and administration site conditions	3 (15.8)	0
Instillation site burn	2 (10.5)	0
Instillation site pain	1 (5.3)	0
Infections and infestations	1 (5.3)	0
Instillation site pain	1 (5.3)	0
Upper respiratory tract infection	1 (5.3)	0
Nervous system disorders	0	0
Headache	0	0
Skin and subcutaneous tissue disorders	0	0
Injury, poisoning and procedural complication	0	0
Respiratory, thoracic, and mediastinal disorders	0	0
Cardiac disorders	0	0
Vascular disorders	0	0
PM = Phentolamine Mesylate; TEAE = Treatment Emergent Adverse Event		

(Ocuphire Corporation Business Document)

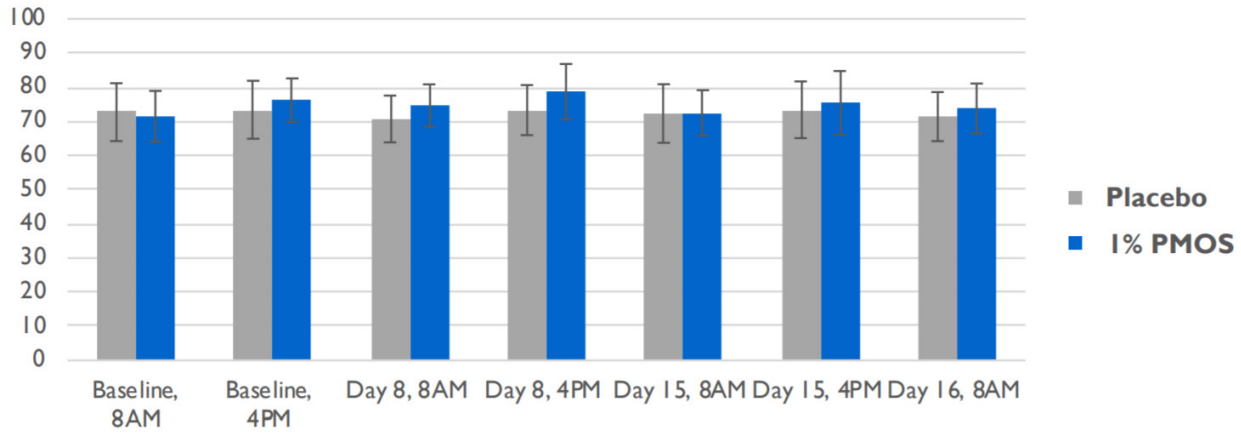
There were no changes in systolic blood pressure (Figure 31) and heart rate (Figure 32) were observed with treatment of patients with phentolamine mesylate ophthalmic solution.

Figure 31 Blood Pressure following Treatment with either 1% Phentolamine Mesylate or Placebo



(Pepose, 2020)

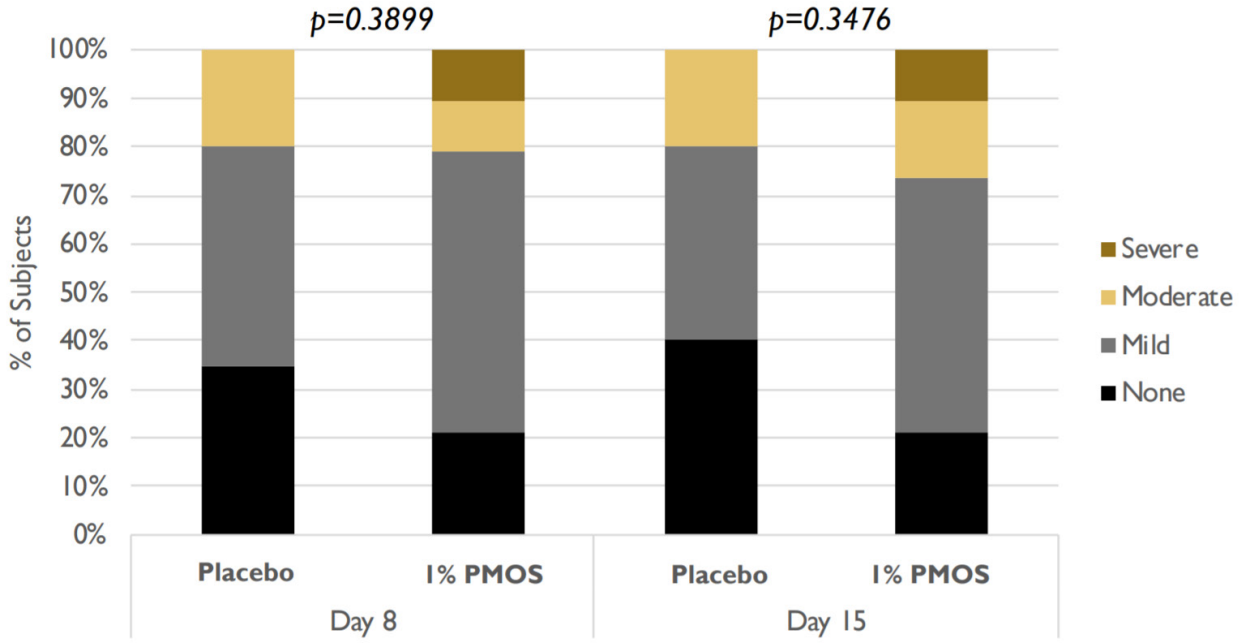
Figure 32 Heart Rate following Treatment with either 1% Phentolamine Mesylate or Placebo



(Pepose, 2020)

Phentolamine mesylate ophthalmic solution dosed at bedtime did not demonstrate a statistically significant difference from placebo for redness at Day 8 and Day 15 (Figure 33).

Figure 33 Percent of Subjects with Conjunctival Hyperemia at 8am in the Study Eye



(Pepose, 2020)

In conclusion, 1% phentolamine mesylate was well tolerated and there were no major ocular or systemic safety issues. An evening dose regimen minimized eye redness during daytime while benefiting near visual acuity in an elderly population.

3 APX3330

3.1 Diabetic Retinopathy and Diabetic Macular Edema

Diabetic retinopathy is one of the major neurovascular complications of diabetes and is a leading cause of blindness in working age adults. In people with diabetes, too much blood sugar can damage the tiny blood vessels at the back inner wall of the eye (retina) or block them completely (diabetic retinopathy). Sometimes, tiny bulges (microaneurysms) protrude from the vessel walls, leaking or oozing fluid and blood into the retina. This fluid can cause swelling (edema) in the central part of the retina (macula). This is a serious eye complication called diabetic macular edema that can cause vision problems or blindness.

According to the recent epidemiological data shared by the American Academy of Ophthalmology, the global burden of diabetes mellitus is 387 million, which is estimated to increase to 592 million by 2035. Ninety-three million people are globally affected by diabetic retinopathy. The prevalence of diabetic retinopathy is 77.3% in type 1 diabetes patients and 25.1% in type 2 diabetes patients, out of which approximately 25% to 30% are expected to develop vision-threatening diabetic macular edema (Wilkinson-Berka et al., 2008). Between 5% and 8% of patients with diabetic retinopathy need laser treatment (Moutray et al., 2018). As many as 0.5% of patients will require vitrectomy surgery (Gupta et al., 2013).

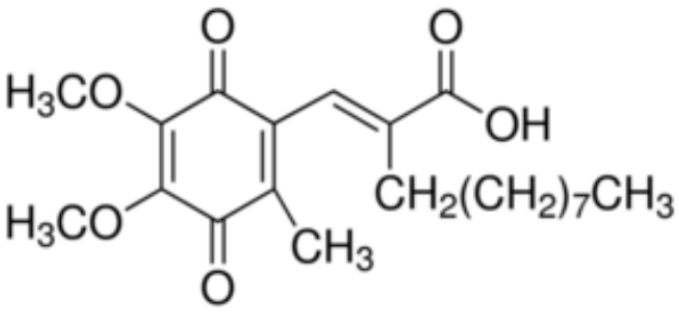
Anti-VEGF agents have become the first line of treatment for center involving diabetic macular edema. Bevacizumab, Ranibizumab, and aflibercept have shown to have beneficial effects in patients with baseline better visual acuity. Aflibercept is shown to have better visual outcomes in patients with worse baseline visual acuity on presentation (Cai et al., 2017). Recently, Aflibercept and Ranibizumab have received FDA approval for use in diabetic retinopathy associated with macular edema (Vaziri et al., 2015). Intravitreal steroid implants also are used in recalcitrant cases (Lattanzio et al., 2017). In the era of anti-VEGF medications, laser treatment is usually avoided in the center involving macular edema. It may be added as adjuvant therapy in patients not responding to anti-VEGF therapy alone.

3.2 Mechanism of Action

APX3330 is a small molecule that specifically targets Apurinic/Apyrimidinic Endonuclease 1/Redox Factor-1 (APE-1/Ref-1). APE-1/Ref-1 is a multifunctional protein that plays a central role in the cellular response to DNA damage and redox regulation against oxidative stress (Tell et al., 2005, Xanthoudakis et al., 1994). APE-1/Ref-1 functions in the DNA base excision repair pathway, the redox regulation of several transcription factors, and the control of intracellular redox status through the inhibition of reactive oxygen species (ROS) production (Choi et al., 2016). APE-1/Ref-1 is predominantly localized in the nucleus; however, its subcellular localization is dynamically regulated and it may be found in the mitochondria or elsewhere in the cytoplasm.

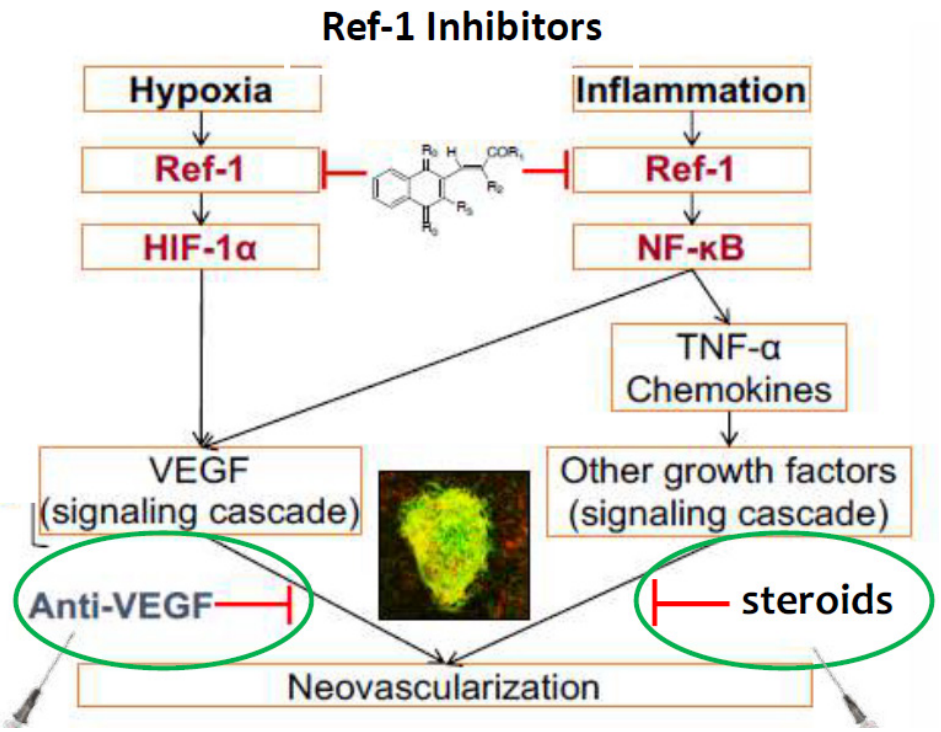
APX3330 ([(2E)-3-[5-(2,3dimethoxy-6-methyl-1,4-benzoquinolyl)]-2-nonyl-2-propenoic acid]) (Figure 34) is a quinone compound that functions as a redox inhibitor of APE-1/Ref-1 by increasing disulfide bond formation with Cys 65 and Cys 93 residues of APE-1/Ref-1 (Su et al., 2011). APX3330 suppresses the inflammatory response in activated macrophages and in tumor-associated macrophages (Jedinak et al., 2011). APX3330 also inhibits the in vitro growth of endothelial progenitor cells and VEGF secretion (Zou et al., 2009; Jiang et al., 2011). Recently, Jiang et al. (2015) reported that APE-1/Ref-1 regulated tumor angiogenesis through a transforming growth factor-beta (TGF-β)-dependent pathway (Jiang et al., 2015; Ren et al., 2014).

Figure 34 APX3330 Molecular Structure



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-κB and HIF-1α and its downstream target, VEGF (Figure 35). These transcription factors are implicated in multiple pathways relevant to the pathophysiology of retinal and choroidal vascular diseases, including diabetic retinopathy, diabetic macular edema, and wet age-related macular degeneration (wAMD). Moreover, data from 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.

Figure 35 APX3330 Mechanism of Action



(Ocuphire Corporate Business Presentation)

APE-1/Ref-1 is highly expressed within many cells in the diseased retina. Studies have demonstrated that it is upregulated 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 oxidized low-density lipoprotein (oxLDL), an agent that upregulates factors involved in inflammation and angiogenesis, APX3330 reduced transcriptional activity of many of these key factors, namely HIF-1α and NF-κB. This reduces the activity of their downstream targets, VEGF, and that of inflammatory mediators.

3.3 Clinical Information

3.3.1 Completed Clinical Trials

To date APX3330 has been dosed in over 340 patients across six Phase 1 and five Phase 2 trials. A summary of these completed trials has been provided in Table 17.

Table 17 Summary of Completed APX3330 Clinical Trials

Trial Name	Patient Population	Trial Phase	Trial Description
APX_CLN_0001	Healthy Volunteers	Phase 1	A randomized, single-dose, placebo-controlled trial of APX3330 to investigate the safety and pharmacokinetics (PK) during oral dosing of APX3330 to healthy adult males. A total of 18 patients were treated with single oral doses of APX3330 (10 mg, 30 mg, 60 mg, 120 mg, 180 mg or 240 mg) or the placebo in a blind manner.

APX_CLN_0002	Healthy Volunteers	Phase 1	An 8-day, randomized, repeat-dose, placebo-controlled trial to investigate the safety and PK of orally dosed APX3330 in healthy adult male patients. A total of 18 patients were treated with oral dosing of APX3330 (120 mg or 240 mg) or the placebo in a blind manner once or twice a day for 8 successive days.
APX_CLN_0003	Healthy Volunteers	Phase 1	A 7-day repeat-dose trial (120 mg) in 6 healthy patients to determine the effects of food on orally administered APX3330.
APX_CLN_0004	Healthy Volunteers	Phase 1	A single-dose trial (120 mg) in 6 healthy patients to determine the effect of meals on the pharmacokinetics of APX3330.
APX_CLN_0005	Chronic Hepatitis B Patients	Phase 2	A 12-week dose-escalation trial (20 mg, 60 mg, 120 mg, 240 mg) in 40 chronic hepatitis B patients. Patients received oral administration of one tablet per dose (2 tablets in the case of the administration of 240 mg) twice a day, after breakfast and after dinner.
APX_CLN_0006	Chronic Hepatitis C Patients	Phase 2	A 12-week dose-escalation trial (20 mg, 60 mg, 120 mg, 240 mg) in 51 chronic hepatitis C patients. The objective of the trial was to investigate the safety, efficacy and utility of APX3330 in treating patients with chronic hepatitis C.
APX_CLN_0007	Chronic Hepatitis C Patients	Phase 2	A 12-week double-masked, randomized placebo-controlled trial (0 mg, 120 mg, 240 mg) in chronic hepatitis C patients that had failed previous interferon treatment. Safety was evaluated in 196 completed patients. The mean treatment period in each group was 82 days in the placebo group, 79 days in the 120 mg group and 78 days in the 240 mg group. The primary endpoints of this trial were measurement of the rate of change in the glutamic pyruvate transaminase (GPT) level, degree of improvement in liver function and assessment of general performance status.
APX_CLN_0008	Healthy Volunteers	Phase 1	A 3-step, single-dose, single-blind trial (300 mg, 420 mg, 600 mg) in 27 healthy patients to investigate the safety and PK of higher doses.
APX_CLN_0009	Advanced Liver Cirrhosis Patients	Phase 2	A 2-week repeated-dose trial (120 mg) in 30 patients with acute severe hepatitis, including patients with advanced liver cirrhosis. Efficacy endpoints included objective measures of liver function and subjective improvement of patient functional status. Safety measures included the assessment of the general tolerability of the drug (i.e., changes in vital signs) and changes in clinical laboratory values.

APX_CLN_0010	Advanced Liver Cirrhosis Patients	Phase 2	A 4-week repeated-dose trial (120 mg) in 30 patients with alcoholic hepatitis, including patients with liver cirrhosis. Efficacy endpoints included objective measures of liver function and subjective improvement of patient functional status. Safety measures included the assessment of the general tolerability of the product candidate (i.e., changes in vital signs) and changes in clinical laboratory values.
APX_CLN_0011	Advanced Solid Tumor Patients	Phase 1	A multi-center, open-label, dose-escalation 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.
GPT = Glutamic Pyruvate Transaminase; PK = Pharmacokinetics			

APX3330 exhibits predictable pharmacokinetics (PK) that were consistent with the PK data obtained in preclinical studies. Moreover, in two studies it was found that meals had no impact on the product candidate's PK.

3.3.2 Safety Information

Safety data were collected from the five Phase 1 and five Phase 2 trials run by Eisai as well as a Phase 1 trial run by Apexian. In the 75 patients receiving either placebo or treatment in the five Phase 1 trials (CLN_0001, 2, 3, 4, and 8), five patients in the treatment arms experienced AEs (mild diarrhea at doses of 120 mg, 180 mg, or 240 mg per day). In the five Phase 2 trials, of the 279 patients given APX3330, 40 (14%) had AEs, the majority of which were mild. The specific AEs for the five Phase 2 trials are listed in the Table 18.

Table 18 Adverse Effects following Treatment with either APX3330 or Placebo

System Organ Class Preferred Term	APX3330		Placebo	
	n (%)	# events	n (%)	# Events
Adverse Events	40 (14.3)	52	11 (16.2)	15
Blood and Lymphatic System	1 (0.4)	1	0	0
Anemia	1 (0.4)	1	0	0
Cardiac Disorders	1 (0.4)	1	0	0
Palpitations	1 (0.4)	1	0	0
Gastrointestinal Disorders	12 (4.3)	14	2 (2.9)	2
Abdominal discomfort	1 (0.4)	1	1(1.5)	1
Abdominal pain	1 (0.4)	1	0	0
Abdominal pain lower	1 (0.4)	1	0	0
Cheilitis	1 (0.4)	1	0	0
Diarrhea	3 (1.1)	3	00	00
Feces soft	1 (0.4)	1	0	0
Gastric ulcer	2 (0.7)	2	0	0
Hypo aesthesia oral	1 (0.4)	1	0	0
Mouth Swelling	1 (0.4)	1	0	0
Stomatitis	0	0	1 (1.5)	1
Tongue dry	1 (0.4)	1	0	0
General Disorders and Administration Site Conditions	6 (2.2)	6	3 (4.4)	3
Chest discomfort	1 (0.4)	1	0	0
Feeling abnormal	0	0	1 (1.5)	1
Malaise	3 (1.1)	3	1 (1.5)	1
Peripheral edema	1 (0.4)	1	0	0
Peripheral swelling	0	0	1 (1.5)	1
Pyrexia	1 (0.4)	1	0	0

Infection and Infestations Nasopharyngitis Upper respiratory tract infection	3 (1.1) 1 (0.4) 2 (0.7)	3 1 2	0 0 0	0 0 0
Investigations Blood urea increased Urobilinogen urine increased	2 (0.7) 1 (0.4) 1 (0.4)	2 1 1	0 0 0	0 0 0
Musculoskeletal and Connective Tissue Limb discomfort Musculoskeletal pain Pain in extremity	0 0 0 0	0 0 0 0	3(2.9) 1 (1.5) 1 (1.5) 1 (1.5)	3 1 1 1
Nervous System Disorders Ageusia Burning sensation Dizziness Headache Hypoaesthesia Hypoglycemic coma Parosmia Subarachnoid hemorrhage	4 (1.4) 0 1 (0.4) 1 (0.4) 2 (0.7) 1 (0.4) 1 (0.4) 0 0	6 0 1 1 2 1 1 0 0	4 (5.9) 1 (1.5) 0 0 1 (1.5) 1 (1.5) 0 1 (1.5) 1 (1.5)	5 1 0 0 1 1 0 1 1
Eye Disorders Ocular discomfort	1 (0.4) 1 (0.4)	1 1	0 0	0 0
Psychiatric disorders Insomnia	1 (0.4) 1 (0.4)	1 1	0 0	0 0
Renal and Urinary Disorders Hematuria	1 (0.4) 1 (0.4)	1 1	0 0	0 0Re
Respiratory, Thoracic and Mediastinal Disorders Alopecia Drug eruption Dry skin Eczema Papule Pruritus Rash Urticaria	12 (4.3) 1 (0.4) 1 (0.4) 1 (0.4) 2 (0.7) 1 (0.4) 5 (1.8) 2 (0.7) 1 (0.4)	14 1 1 1 2 1 5 2 1	1 (1.5) 0 0 0 0 0 1 (1.5) 0 0	1 0 0 0 0 0 1 0 0

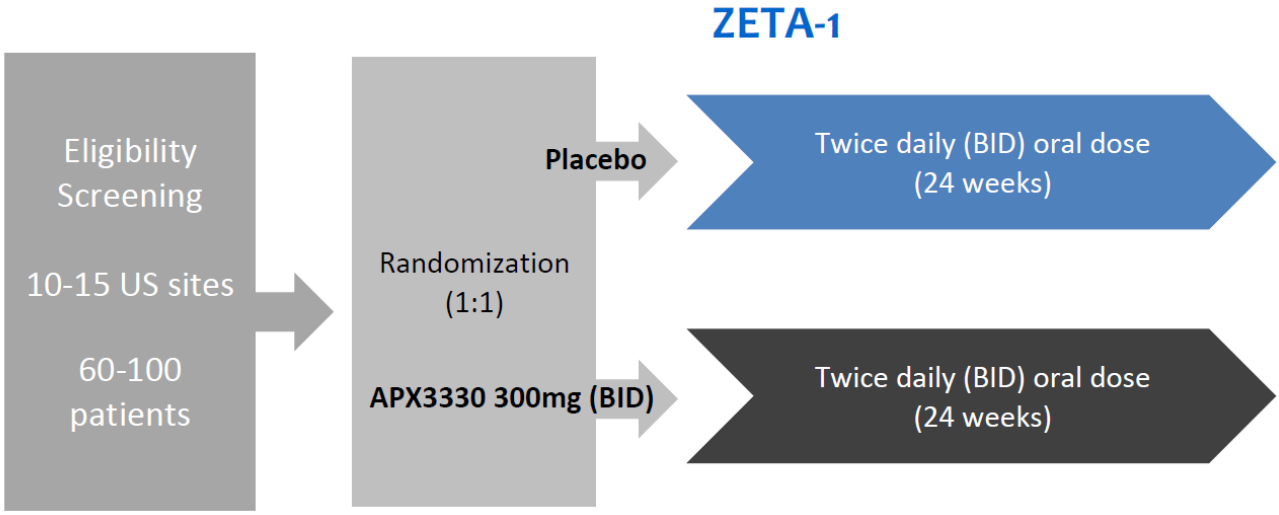
(Ocuphire Corporate Business Document)

In the Phase 1 trial, APX_CLN_0011, patients received higher doses of APX3330, up to 720 mg/day. Two patients who received 720 mg/day had a diffuse, macular rash that was spontaneously reversible. Of note, patients who had been taking doses up to 600 mg/day did not have any signs of acute toxicity. Moreover, of the 19 patients in the APX_CLN_0011 Phase 1 trial described above, four patients had over six months of exposure, and three patients (at a dose of 600 mg/day) had over 300 days of exposure without an AE.

3.3.3 Planned Diabetic Retinopathy Clinical Trial – ZETA-1

Ocuphire expects to initiate ZETA-1, a Phase 2 double-masked, randomized, placebo-controlled, multi-center trial in patients with DR and DME in first quarter 2021 (Figure 36). The ZETA-1 trial is expected to enroll 60-100 patients to evaluate the effect of 600 mg of APX3330 (300 mg twice a day) in treating patients with moderately severe nonproliferative diabetic retinopathy (NPDR) to mild proliferative diabetic retinopathy (PDR), as well as patients with DME without loss of central vision.

Figure 36 Phase 2 Diabetic Retinopathy/Diabetic Macular Edema Clinical Trial Design (ZETA-1)



(Ocuphire Corporate Business Presentation)

A brief overview of study ZETA-1 can be found in Table 19.
Table 19 Overview of Clinical Trial ZETA-1

Overview of ZETA-1 Clinical Trial	
Title	ZETA-1
Condition	Diabetic Retinopathy and Diabetic Macular Edema
Type	Interventional
Phase	Phase 2
Design	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) Primary Purpose: Treatment
Intervention	Drug: APX3330 Other: Placebo
Arms	Placebo Comparator: Placebo Administered twice daily (BID) Experimental: APX3330 Administered twice daily
Primary Outcome	The primary endpoint is expected to be percent of patients with a ≥2 step improvement on the Diabetic Retinopathy Screening Score (DRSS) at week 24.
Secondary Outcomes	Secondary endpoints at multiple timepoints are expected to include: central subfield thickness low luminance high contrast distance visual acuity, and leakage area / nonperfusion / neovascularization on fluorescein angiogram.
Enrollment	60-100

Eligibility Criteria	- At least 18 years of age - Patients with Diabetic Retinopathy Severity Score (DRSS) showing moderately severe NPDR to mild PDR - Patients with evidence of DME without loss of central vision (clinical exam, FA and OCT) - BCDVA ETDRS criteria - Diabetic patients with no other pre-existing ocular conditions
Location	United States
Sponsor	Ocuphire Pharma Inc.
Status	Not yet started
BCDVA = Best-Corrected Distance Visual Acuity; BID = Twice per Day; DME = Diabetic Macular Edema; DRSS = Diabetic Retinopathy Severity Score; ETDRS = Early Treatment Diabetic Retinopathy Study; FA = Fluorescein Angiography; NPDR = Nonproliferative Diabetic Retinopathy; OCT = Optical Coherence Tomography; PDR = Proliferative Diabetic Retinopathy	

Patient safety is expected to be assessed by AE monitoring, clinical laboratory evaluations, IOP and vital sign assessments.

The status of the ZETA-1 trial is the FDA has accepted the protocol and Ocuphire is working on finalizing the budget and drug manufacturing. Ocuphire is also in the process of selecting their CRO and clinical sites. Ocuphire expects to report top-line data for the Phase 2 trial in the fourth quarter of 2021.

4 Summary

Ocuphire is developing two ophthalmic drugs, Nyxol and APX3330, for multiple eye related indications. Nyxol a once-daily preservative-free eye drop formulation of phentolamine mesylate, is a non-selective alpha-1 and alpha-2 adrenergic antagonist designed to reduce pupil size and improve visual acuity. The results of the Nyxol clinical trials support the following key points:

- Nyxol reduces pupil diameter with durable effects. In multiple Phase 2 trials, Nyxol reduced pupil diameter by approximately 20% (~1 – 1.5 mm) in both dim and bright conditions, and the reductions were sustained over 24 hours.
- Nyxol improves low contrast visual acuity. When studied in patients with night vision disturbances 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.
- Nyxol has a promising safety profile. To date, Nyxol has been observed to be well tolerated, with unchanged or decreased intraocular pressure, in the seven completed Phase 1 and Phase 2 clinical trials conducted. Nyxol produces a transient, mild hyperemia (eye redness) effect that disappears within four to eight 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.
- Nyxol is designed for convenient, once-daily administration. Nyxol is being evaluated for chronic use with once-daily administration before bedtime. Nyxol has shown in multiple Phase 2 trials to have an over 24-hour durable effect, which could allow for better patient compliance.
- Nyxol is a stable, cost-effective ophthalmic formulation. Nyxol is a single-use, preservative-free, proprietary eye drop formulation with good stability for eventual commercialization. Its active pharmaceutical ingredient, phentolamine mesylate USP grade, is a small molecule with advantages of standardized, scalable, lower-cost manufacturing processes.

Ocuphire plans to initiate two Phase 3 studies of Nyxol (LYNX-1 in NVD and MIRA-2 in RM) in Q4 of 2020. Top-line results are expected starting in Q1 of 2021 and continuing throughout the remainder of the year. In addition, Ocuphire also intends to initiate a Phase 2 study of Nyxol (VEGA-1 in presbyopia) in Q1 of 2021.

APX3330 a twice-a-day oral tablet, is designed to inhibit angiogenesis and inflammation pathways relevant to retinal and choroidal vascular diseases. The results of the APX3330 preclinical and clinical studies support the following key points:

- APX3330 has the potential to be an oral therapy. Compared to intravitreal anti-VEGF injections, associated with systemic adverse events and ocular complications, twice a day oral administration of APX3330 could be a convenient alternative treatment for retinal disease, if approved.
- APX3330's upstream target is 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 by working upstream of the current anti-VEGF therapies, thus Ocuphire believes it could complement anti-VEGF therapies and potentially reduce frequency of doctor visits.

- APX3330 has a promising tolerability profile. In eleven completed Phase 1 and Phase 2 clinical trials, APX3330 was well tolerated with no significant acute neurologic, cardiovascular, liver, or pulmonary events.
- APX3330 is a stable, cost-effective oral tablet. APX3330 is formulated as an oral tablet with stability suitable for eventual commercialization, and its active pharmaceutical ingredient is a small molecule with the advantages of standardized, scalable lower-cost manufacturing processes.

Ocuphire plans to initiate one Phase 2 study of APX3330 (ZETA-1 in DR and DME) in Q1 of 2021.
In conclusion, Ocuphire have developed a comprehensive clinical development plan for Nyxol eye drops and APX3330 oral tablets which if successful should allow them to submit several NDAs to the FDA in the coming years.

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