BofA SECURITIES

Ocular Therapeutix

Inserting a new option for wAMD; Initiate at Buy

Initiating Coverage: BUY | PO: 15.00 USD | Price: 5.03 USD

Axpaxli's infrequent dosing is differentiated in wAMD

We initiate coverage of Ocular Therapeutix (OCUL) with a Buy rating and $15 PO. OCUL is developing a pipeline of sustained release drug therapies leveraging their proprietary Elutyx platform with potential in ophthalmology indications. We think that Axpaxli, the company's lead asset, has the potential to provide a highly differentiated profile in the treatment of wet age-related macular degeneration (wAMD) offering infrequent dosing (~9 months) vs current SoC (6-8wks), which is a key area of unmet need. In our view, the wAMD market is well-established and large enough to support multiple players. wAMD could represent an attractive commercial opportunity for OCUL.

Axpaxli early data support initiation of pivotal trials in 1Q

Axpaxli, an extended-release axitinib insert, showed encouraging signs of clinical durability and a favorable safety profile in ph 1 with 60% of pts being anti-VEGF rescue-free for up to 12 months and no reported drug-related ocular or systemic SAEs. On the heels of this data, OCUL recently initiated their first pivotal trial (SOL) of Axpaxli in wAMD in 1Q and is preparing initiate a second pivotal trial in 2H24.

Axpaxli in wAMD is the key value driver

We model risk-adjusted peak sales for Axpaxli in wAMD of $870mn (50% LoS, 5% peak penetration) contributing $11/sh. In our view, Axpaxli's initial data is supportive of a competitive profile over current standard of care, but we note further clinical validation is needed given a small sample size. Additionally, we think other extended-release inserts in development and gene therapy could represent additional competition down the line. We view Dextenza, which is approved for post-surgical ocular pain and ocular itching, as a modest commercial opportunity (peak sales: $191mn) contributing $3/sh to our PO and look for additional validation for the rest of the pipeline.

Pipeline could provide additional upside

OCUL has three additional product candidates in development for other ophthalmic conditions, including Paxtrava in glaucoma and ocular hypertension, and OTX-DED and -CSI in dry eye. Additional near-term catalysts include: 1) **Axpaxli**: topline ph 2 HELIOS data in NPDR in 2Q24, initiating second wAMD pivotal trial in 2H24, 2) **Paxtrava**: reporting ph 2 data at ASCRS (April 5-8), and 3) **OTX-DED** and **OTX-CSI**: completing enrollment for and determining placebo comparator for potential pivotal trial in 1H24. We think positive results providing clinical validation to the pipeline could represent additional upside.

Estimates (Dec) (US$)	2021A	2022A	2023E	2024E	2025E
EPS	(0.08)	(0.86)	(0.81)	(0.83)	(0.83)
GAAP EPS	(0.09)	(0.92)	(0.83)	(0.83)	(0.83)
EPS Change (YoY)	96.9%	-975.0%	5.8%	-2.5%	0%
Consensus EPS (Bloomberg)			(1.02)	(1.00)	(0.81)
DPS	0	0	0	0	0
Valuation (Dec)					
EV / EBITDA*	NM	NM	NM	NM	0.3x
Free Cash Flow Yield*	-10.4%	1.3%	3.1%	3.5%	3.8%

* For full definitions of *iQmethod*℠ measures, see page 20.

09 February 2024

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Stock Data

Price	5.03 USD
Price Objective	15.00 USD
Date Established	8-Feb-2024
Investment Opinion	C-1-9
52-Week Range	2.00 USD - 7.96 USD
Mrkt Val (mn) / Shares Out (mn)	578 USD / 114.8
Free Float	96.6%
Average Daily Value (mn)	6.44 USD
BofA Ticker / Exchange	OCUL / NAS
Bloomberg / Reuters	OCUL US / OCUL.OQ
ROE (2023E)	-115.2%
Net Dbt to Eqty (Dec-2022A)	-264.6%

Abbreviations

1Q/2Q: first/ second quarter
1H/2H: first-second half
ASCRS: American Society of Cataract and Refractive Surgery
BCVA: best corrected visual acuity
NPDR: non-proliferative diabetic retinopathy
Ph: phase
Pts: patients
VEGF: vascular endothelial growth receptor

See page 17 for a complete list of abbreviations

iQprofile℠ Ocular Therapeutix

iQmethod℠ **– Bus Performance***

(US$ Millions)	2021A	2022A	2023E	2024E	2025E
Return on Capital Employed	-33.9%	-47.3%	-49.2%	-61.8%	-144.1%
Return on Equity	-8.0%	-115.2%	-115.2%	-188.0%	NM
Operating Margin	-179.3%	-152.7%	-137.4%	-134.2%	-112.6%
Free Cash Flow	(60)	8	18	20	22

iQmethod℠ **– Quality of Earnings***

(US$ Millions)	2021A	2022A	2023E	2024E	2025E
Cash Realization Ratio	NM	NM	NM	NM	NM
Asset Replacement Ratio	0.5x	1.8x	1.9x	2.1x	0x
Tax Rate	NM	NM	NM	NM	NM
Net Debt-to-Equity Ratio	-179.8%	-264.6%	-163.0%	-517.6%	NM
Interest Cover	-11.7x	-11.2x	-8.4x	-9.4x	-9.2x

Income Statement Data (Dec)

(US$ Millions)	2021A	2022A	2023E	2024E	2025E
Sales	44	51	60	72	87
% Change	150.1%	18.3%	16.9%	19.0%	21.4%
Gross Profit	39	47	54	65	78
% Change	155.3%	20.0%	15.6%	19.0%	21.4%
EBITDA	(76)	(77)	(81)	(94)	2,011
% Change	-25.9%	-1.2%	-5.3%	-16.6%	NM
Net Interest & Other Income	71	8	10	(1)	(2)
Net Income (Adjusted)	**(7)**	**(71)**	**(72)**	**(97)**	**(100)**
% Change	**95.8%**	**-984.1%**	**-1.9%**	**-34.6%**	**-2.1%**

Free Cash Flow Data (Dec)

(US$ Millions)	2021A	2022A	2023E	2024E	2025E
Net Income from Cont Operations (GAAP)	(78)	(79)	(83)	(96)	(98)
Depreciation & Amortization	2	2	2	2	2,109
Change in Working Capital	(3)	1	2	2	2
Deferred Taxation Charge	NA	NA	NA	NA	NA
Other Adjustments, Net	20	87	101	116	(1,987)
Capital Expenditure	(1)	(4)	(4)	(4)	(5)
Free Cash Flow	**-60**	**8**	**18**	**20**	**22**
% Change	**NM**	**NM**	**129.2%**	**12.8%**	**10.1%**
Share / Issue Repurchase	NA	NA	NA	NA	NA
Cost of Dividends Paid	0	0	0	0	0
Change in Debt	0	0	0	0	0

Balance Sheet Data (Dec)

(US$ Millions)	2021A	2022A	2023E	2024E	2025E
Cash & Equivalents	164	102	156	79	1
Trade Receivables	21	21	22	22	22
Other Current Assets	6	6	6	6	6
Property, Plant & Equipment	7	10	12	14	17
Other Non-Current Assets	7	10	10	10	10
Total Assets	**205**	**149**	**206**	**131**	**57**
Short-Term Debt	0	0	0	0	0
Other Current Liabilities	26	31	33	34	36
Long-Term Debt	6	9	9	10	10
Other Non-Current Liabilities	85	74	74	74	75
Total Liabilities	**117**	**114**	**115**	**118**	**120**
Total Equity	**88**	**35**	**90**	**13**	**(64)**
Total Equity & Liabilities	**205**	**149**	**206**	**131**	**57**

* For full definitions of ***iQ***method℠ measures, see page 20.

Company Sector

Biotechnology

Company Description

Ocular Therapeutix is a commercial-stage biotechnology company focusing on developing extended-release therapies for ophthalmic indications. Its lead asset is Axpaxli, an intravitreal insert for long-term sustained delivery of axitinib, with potential in wet age-related macular degeneration (wAMD) currently in phase 3. The company also has an approved product, Dextenza, and has programs in diabetic retinopathy, glaucoma and dry eye disease.

Investment Rationale

We rate OCUL at Buy. We think the extended-release delivery platform in different ophthalmic indication has potential to be differentiated. View Axpaxli's data in wAMD as differentiated and suggesting potential to decrease high treatment burden, which could represent an attractive commercial opportunity given this wAMD is a large market. The company also has an FDA-approved product, Dextenza, which represents a modest commercial opportunity and additional shots on goal in other eye indications.

Stock Data

Average Daily Volume	1,280,668

Quarterly Earnings Estimates

	2022	2023
Q1	-0.15A	-0.39A
Q2	-0.23A	-0.26A
Q3	-0.31A	-0.01A
Q4	-0.19A	-0.19E

Initiating OCUL at Buy with $15 PO

We initiate coverage of Ocular Therapeutix (OCUL) with a Buy rating and a price objective (PO) of $15. OCUL is a commercial-stage biotechnology company focusing on developing novel therapies for ophthalmic indications leveraging their proprietary bioabsorbable hydrogel technology, Elutyx™, for long-term, sustained drug delivery. The company has one approved product, Dextenza, an intravitreal implant for sustained dexamethasone delivery, for post-operative ophthalmic surgery pain and itching associated with allergic conjunctivitis. The company is also developing its lead asset, Axpaxli, an axitinib intravitreal implant, for wet age-related macular degeneration (wAMD) and diabetic retinopathy. Additional assets in the pipeline include Paxtrava for glaucoma and ocular hypertension, OTX-ED for episodic dry eye disease and OTX-CSI for dry eye disease.

Axpaxli in wAMD contributes $11/sh

We model launch of Axpaxli in wAMD in 2027. We assume a 50% likelihood of success (LoS) in US/ex-US and model worldwide risk-adjusted peak sales of $869mn in 2034. We estimate ~1.2mn US wAMD patients and ~1.2mn ex-US wAMD patients and assume a 5% peak penetration in US/ex-US. We assume a $15K/implant price (30% ex-US discount) based on management commentary and current cost for wAMD treatments, re-dosing every 9 months, and 20% gross-to-net (GtN). We apply a 10% discount rate (WACC), 10% cost of goods sold (COGS) and no terminal value.

Dextenza in post-cataract surgery pain contributes $3/sh

We assume use in post-cataract surgery as the main driver of Dextenza revenues based on management commentary. We estimate ~4.5mn cataract surgeries in the US per year and peak penetration of 8%. We model a price of $550/treatment with 15% GtN and no price increase. We apply a 9% WACC, 10% COGS and no terminal value for Dextenza.

Pipeline and cash contribute $1/sh

We model $400mn for gross pipeline value for Axpaxli in diabetic retinopathy, Paxtrava, OTC-ED, OTX-CSI and other early-stage assets in development, which could represent additional upside if clinically validated. OCUL reported ~$218mn in cash and cash equivalents after the latest public offering. We apply 14% WACC for pipeline and corporate expenses.

Exhibit 1: BofA estimates and assumptions in OCUL valuation
Summary of our model estimates and assumptions

Name	NPV	$/sh	LoS	Peak penetration	Risk Adj. peak sales
Dextenza	$333,629	$3	100%	8% US	$191,687
Axpaxli in wAMD	$1,294,094	$11	50%	5%/5% Us/ex-US	$869,829
Pipeline	-$81,120	-$1			
Net cash	$218,250	$2			
Total	$1,764,853	$15			

Source: BofA Global Research

BofA GLOBAL RESEARCH

Investment positives

Infrequent dosing and differentiated mechanism of action may set Axpaxli apart
OCUL's Axpaxli is a preformed, bioresorbable hydrogel fiber implant, inserted intravitreally to provide a long-lasting treatment for patients with wet age-related macular degeneration (wAMD). Current standard of care requires intravitreal injections of anti-VEGF antibodies every 1-3 months. These treatments have been shown to be effective, but the high frequency of dosing poses a large burden on elderly patients. Axpaxli appears to be differentiated in two ways: 1) initial phase 1 data supports sustained efficacy for 6+months, which could significantly reduce the treatment burden associated with anti-VEGF injections, and 2) Axpaxli has a differentiated mechanism of action using axitinib, a tyrosine kinase inhibitor (TKI) with high selectivity and affinity for VEGF receptors, as the active component as opposed to traditional anti-VEGF antibodies. Given initial data suggesting a potentially differentiated profile in the highly competitive wAMD space, we see Axpaxli as an attractive commercial opportunity.

wAMD provides a large and established market for lead product candidate
wAMD is one of the leading causes of vision impairment among elderly patients in developed countries and presents one of the largest market opportunities in retinal disease. The current wAMD patient population of ~1.5 million in the US continues to grow – with approximately 200k new diagnoses yearly – and estimates project an addressable population of greater than ~4 million patients in major markets by 2028. The wAMD market is well established and our KOLs have highlighted the need for novel therapies that could reduce the treatment burden. Despite the long-standing prominence of certain commercial anti-VEGF products like Eylea and Lucentis, the wAMD has been receptive to new entrants with a differentiated profile and we believe there is potential for Axpaxli to enter this market.

Current longer-acting agents have shown disappointing real-world durability
Newer therapies like 8mg Eylea High-Dose (Eylea HD; approved by FDA in 2023 for 8 to 16-week dosing intervals) and 6mg Vabysmo (approved by FDA in 2022 for up to four-month dosing intervals) are marketed to extend anti-VEGF durability and reduce injection frequency without sacrificing efficacy. However, our KOLs have commented that so far neither Eylea HD nor Vabysmo have shown a consistent ability to replicate the extended durability seen in clinical trials in real-world use. Thus, we believe Axpaxli still has the potential to be first to meet a key unmet in wAMD.

Early clinical data indicates a potentially favorable safety profile
Safety data from OCUL's two phase 1 trials investigating the proof-of-concept and durability of Axpaxli showed that the implant was generally well tolerated. In the 45 patients dosed with Axpaxli, there were no drug-related ocular or systemic serious adverse events (SAEs) reported. While this requires further validation in OCUL's upcoming pivotal trials, we view this as a favorable sign for Axpaxli and highlight this is a key requirement given current treatments have minimal side effects.

Intravitreal implants in wAMD could also reduce physician burden
Current standard of care requires that physicians inject patients every ~6-8 weeks on average, with upwards of 10+ injections often needed during the first year. By extending the time between doses, we note that Axpaxli could also significantly alleviate the burden that wAMD patients place on clinicians and the healthcare system.

Axpaxli's design may render it less costly to produce than competition
Given Axpaxli's design as a small-molecule tyrosine kinase inhibitor (TKI) encapsulated into a single implant, it may be less costly to produce than larger anti-VEGF antibody treatments. This could provide the asset with significant upside as the company moves towards commercialization and distribution in later years.

Investment risks

The current treatment landscape in wAMD is crowded

OCUL's main indication – wAMD – has several established competitors in the space, many of which have established reputations among the retina community. Currently, there are 6 notable anti-VEGF injections on the market, with two already indicated for long-lasting treatment. Most of these therapies have been on the market for several years and have robust clinical validation and safety databases, making them trusted by both physicians and wAMD patients. Further, KOLs have observed that well-controlled patients may be less likely to switch treatments.

Pace of pivotal trial enrollment will be near term driver of stock performance

OCUL plans to initiate the pivotal SOL trial evaluating Axpaxli in approximately 300 treatment-naïve wAMD patients in 1Q24. SOL is a superiority trial that will compare a single implant of Axpaxli to a single injection of 2mg aflibercept (Eylea). Patients will be followed monthly and rescued as needed with supplemental anti-VEGF treatment upon the loss from baseline of 15 or more letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart or at the discretion of investigators. In our conversations, KOLs warned that risk associated with this study design may be unappealing to wAMD patients, possibly hindering enrollment. We note that, with Axpaxli in wAMD being the key driver of the company's valuation, issues with enrollment could have significant negative implications on stock performance in the near term. As such, we will continue to monitor the cadence of enrollment and study progress overall.

Axpaxli has a direct competitor in EYP-1901

Eyepoint Pharmaceuticals (EYPT; not covered) is currently developing an intravitreal implant for the treatment of wAMD. EYP-1901 employs vorolanib – a tyrosine kinase inhibitor (TKI) with VEGF inhibition capabilities – in the form of a bio-erodible implant. To date, 160+ patients have been dosed in phase 1 and 2 studies. In the phase 2 DAVIO-2, '1901 was statistically non-inferior to the current standard of care (2mg aflibercept; Eylea) and stable over 6 months. Our KOLs have indicated that they find the mechanism of action of both '1901 and Axpaxli to be similarly favorable. We note that '1901 has been studied in a larger patient population and our KOLs do not see a clear differentiation between Axpaxli and '1901 at this point, which could represent additional competition if both therapies are approved.

Gene therapy approaches have began to shown long-term durability

Gene therapy approaches in wAMD are also moving into pivotal studies following recent positive results in phase 2 trials. 4D Molecular Therapeutics (FDMT) recently reported up to 89% annualized injection rate reduction and 63% of patients remaining injection free in phase 2, and has shown durability for up to 2 years in a small number of patients. We think the possibility of a one-and-done therapy could represent a competitive threat to Axpaxli's commercial opportunity. However, we note long-term safety concerns with gene therapy will likely impact initial uptake and we think there would be a place for extended-release inserts in certain wAMD patient populations.

OCUL is highly levered to a single indication

Currently, we see Axpaxli in wAMD as the key value driver and primary focus for OCUL in the near term. While we do see potential in the company's lead product candidate, we acknowledge the risk associated with the company being highly levered to the outcome of Axpaxli in wAMD. We think there is risk associated with moving into pivotal studies given a limited number of patients studied so far and a negative outcome from the pivotal trial could represent significant downside to the company.

Company will need to raise additional cash going forward

Despite a recent public offering with gross proceeds of $115.1mn, we believe that OCUL will likely need to raise additional cash going forward. With two pivotal trials for Axpaxli initiating in 2024 and the anticipated commercialization of Axpaxli thereafter (we estimate a 2027 launch), along with several early pipeline assets that may be advancing in the coming years, we expect operating expenses to increase to meet the needs of the growing company.

Company Overview

Ocular Therapeutics (OCUL) is a commercial-stage biotechnology company focusing on developing extended-release therapies for ophthalmic indications using their proprietary bioabsorbable hydrogel technology, Elutyx™. The company has one FDA-approved product, Dextenza, an intraocular insert for long-term delivery of dexamethasone. Dextenza is approved for ocular inflammation and pain following ophthalmic surgery and ocular itching associated with allergic conjunctivitis. However, near-term focus is on the development of Axpaxli, an intravitreal insert for long-term sustained delivery of axitinib, with potential wet age-related macular degeneration (wAMD). wAMD is a large market and could represent a significant commercial opportunity for OCUL. Axpaxli is also being evaluated in non-proliferative diabetic retinopathy. OCUL is also developing additional assets in different ophthalmic indications including Paxtrava for glaucoma and ocular hypertension, OTX-DED for episodic dry eye disease and OTX-CSI for dry eye disease. Below we provide an overview of the platform, highlight the company's pipeline and key catalysts in 2024 (Exhibit 2).

Elutyx technology is highly flexible

The Elutyx platform is based on a bioresorbable hydrogel-based formulation technology consisting of proprietary PEG (polyethylene glycol) polymers. PEG-based hydrogels form matrixes that encapsulate the active ingredient (small molecules, peptides, biologics) and can be modified to control the drug release rate by adjusting different parameters. The Elutyx technology uses branched PEG molecules that contain 4 to 8 branches with a reactive site at each end that can be used to cross-link with a secondary molecule to spontaneously form the hydrogel matrix. These hydrogels slowly degrade in the presence of water and can be modified to have different mechanical properties and bioabsorption rates. Importantly, hydrogels tend to be highly biocompatible and elicit little to no immune responses.

Axpaxli's initial data supports moving to pivotal studies in wAMD

Axpaxli has shown initial positive data suggesting significant anti-VEGF injection rate reduction in wAMD patients as well as high rates of injections freedom after 10 months. In a phase 1 trial, 73% of patients (N=15) were injection free after a single treatment with Axpaxli and had an injection rate reduction of 89% at 9 months. At 12 months, 33% of patients remained injection free. Importantly, patients in the study had a mean of 8 anti-VEGF injections per year at baseline. These improvements also correlated with preservation of visual acuity based on BCVA as well as stable central subfield thickness (CSFT). Axpaxli was generally well tolerated with no serious adverse events reported. Based on these initial results, OCUL is moving to pivotal studies for Axpaxli in wAMD. The company received approval from FDA for a special protocol assessment (SPA) to expand the eligibility criteria for the trial. The phase 3 trial design involves a superiority trial design comparing Axpaxli to a single dose of aflibercept evaluating the proportion of patients who maintain visual acuity based on 15 letter loss at week 36. The phase 3 SOL trial is expected to initiate patient screening in 1Q, and the company is preparing to a second phase 3 trial in 2H (as early as 3Q).

Diabetic retinopathy could expand the commercial opportunity for Axpaxli

Axpaxli is also being investigated in diabetic retinopathy (DR). The company estimates the total market opportunity in moderate to severe non-proliferative diabetic retinopathy (NPDR) represents ~3.3mn patients in the US. Anti-VEGF treatment has been shown to be effective in NPDR providing clinical validation for the mechanism of action of Axpaxli in this indication. Axpaxli is currently being evaluated in the phase 1 HELIOS trial in moderate-to-severe NPDR patients versus sham injection. The study will enroll 21 patients randomized 2:1 to either 600 µg Axpaxli or sham. Topline data at 9 months is expected in 2Q24.

Phase 2 data for Paxtrava in glaucoma in April

Paxtrava is being evaluated as a potential therapy for the treatment of glaucoma. The company estimates glaucoma or ocular hypertension affect ~172mn worldwide representing a ~6.8bn and ~3.7bn markets in the US, respectively. Paxtrava is an intracameral implant designed to deliver travopost, an FDA-approved prostaglandin analog designed to treat elevated intraocular pressure (IOP), directly in the eye for up to 6 months. Paxtrava was evaluated in a phase 1 study in 19 glaucoma subjects and demonstrated clinically meaningful decrease in IOP comparable to topical therapy. Paxtrava demonstrated a tolerable safety profile. Paxtrava is currently being evaluated in a phase 2 trial comparing Paxtrava 26 µg vs Durysta (bimatoprost intracameral implant). The trial is evaluating diurnal IOP changes from baseline at 2, 6 and 12 weeks as well as safety and tolerability. Topline data from the phase 2 trial is expected at the American Society of Cataract and Refractive Surgery (ASCRS) meeting in April (April 5-8).

Assessment of next steps for dry eye programs is ongoing

OCUL is also exploring the dry eye market, which they estimate to be ~$5.7bn globally, with two different products. The first product is OTX-DED, an intracanalicular insert designed to deliver 0.2mg or 0.3mg of dexamethasone, for short-term treatment of dry eye disease. The second product is OTX-CSI, an intracanalicular insert loaded with cyclosporine, for moderate to severe dry eye disease. OTX-DED demonstrated positive results in a phase 2 trial evaluating both formulations. OTX-CSI did not show separation from a vehicle insert in phase 2 studies but showed trending signs of benefit. OCUL is currently running a small trial to determine the appropriate placebo comparator arm for both programs and determine next steps for the program.

Dextenza represents a modest commercial opportunity

Dextenza is OCUL's first commercial product and was approved in 2018. Dextenza is an intracanalicular insert to deliver dexamethasone for up to 30 days. Dextenza is approved for the treatment of post-surgical ocular inflammation and pain and ocular itching associated with allergic conjunctivitis. However, management has commented that ocular itching is a small commercial opportunity and the vast majority of Dextenza use is in the post-surgical setting. Dextenza revenues in 2022 were $50.2mn and reported $43.2mn in the first 3 quarters of 2023. The company has commented they have captured less than 5% of the post-cataract surgery market and they believe this is the biggest opportunity for growth in 2024.

Exhibit 2: Key upcoming catalysts for OCUL
Summary of near-term catalysts

Program	Indication	Catalyst	Timeline
	wAMD	Screen first patient in ph 3 SOL trial	1Q24
Axpaxli (OTX-TKI)	wAMD	Initiate second phase 3 trial	2H24
	Diabetic Retinopathy	Interim phase 1 HELIOS data	1Q24
Paxtrava (OTX-TIC)	Glaucoma	Topline phase 2 data	April 5-8 (ASCRS meeting)
OTX-DED	Episodic dry eye disease	Comparator arm trial enrollment completion	1H24
OTXCSI	Dry eye disease	Comparator arm trial enrollment completion	1H24

Source: BofA Global Research

BofA GLOBAL RESEARCH

Axpaxli (OTX-TKI) in wAMD

OCUL's most advanced product candidate, Axpaxli (OTX-TKI; axitinib intravitreal implant), utilizes axitinib, a tyrosine kinase inhibitor (TKI), in the form of an intravitreal implant to target wet age-related macular degeneration (wAMD). The extended and sustained release of Axpaxli could provide significant competitive upside over current therapies, most of which require frequent intravitreal injections every 4-8 weeks. The implant is also bioresorbable and is absorbed into the body after 8-9 months. One phase 3 pivotal trial in wet AMD is currently enrolling and a second is expected to initiate in 3Q24.

Overview of wAMD

wAMD is a disease characterized by growth of abnormal, leaky blood vessels into the central part of the retina known as the macula (choroidal neovascularization, CNV). If untreated, this neovascularization can lead to a scar forming under the macular region of the retina, resulting in distortion and loss of central vision. It is generally accepted that one of the underlying causes of the disease is overexpression of the cell signaling molecule, vascular endothelial growth factor (VEGF), which drives formation of new blood vessels.

Diagnosis and prevalence of wAMD

wAMD symptoms (distortion and/or blurring of central vision, etc.) usually appear suddenly and progress quickly. Patients suspected of having wAMD are sent to a retinal specialist to receive further eye examinations including optical coherence tomography (OCT) scans – which can detect subretinal fluid, hemorrhaging and scarring – and Fluorescein dye angiography imaging. Notably, while OCT is the most frequent imaging modality used to identify wAMD, studies note that it may lead to overdiagnosis. It is recommended that patients begin treatment within two weeks of initial detection, as prolonged delay of treatment is likely to result in severe vision loss. If left untreated for over 2 years, over half of eyes with wAMD and sub-foveal CNV will lose 6 or more lines of vision.

In developed countries, wAMD is one of the leading causes of impaired vision in elderly patients. In 2022, there were an estimated 1.6 million people living with wAMD in the United States. With approximately 200K new cases of wAMD annually in the US, the addressable population is expected to grow at a 3% compound annual growth rate through 2027.

ETDRS BCVA is the most relevant clinical measure in wAMD studies

The primary endpoint in most ophthalmic trials, including wet AMD, is Early Treatment Diabetic Retinopathy Study (ETDRS) Best Corrected Visual Acuity (BCVA). The ETDRS BCVA protocol offers a standardized visual acuity measurement and a calculated visual acuity score that can be used as a continuous variable for statistical analysis. BCVA is defined as the best possible vision an eye can see with corrective lenses, measured with an eye chart. The ETDRS employs a standardized chart (14 lines of five letters per line in a logarithmic progression) to measure visual acuity.

If 20 or more chart letters can be correctly read from 4 meters away, the ETDRS letter score can be calculated as the total number of letters correctly read plus 30. Therefore, the maximum possible ETDRS BCVA letter score is 100. A gain or loss of 3 lines (15 letters) is routinely used as an outcome in clinical trials, as this is considered a moderate degree of change in visual acuity. For wet AMD, the FDA recommends that studies show one of the following: 1) a statistically significant smaller percentage of patients in the treatment group with 15 ETDRS letters lost in BCVA at 9+ months than in the control group, 2) a statistically significant larger percentage of patients in the treatment group with 15 ETDRS letters gain in BCVA at 9+ months than in the control group, or 3) a statistically significant difference between groups in mean BCVA of 15 ETDRS letters or more.

Current treatments focused on anti-VEGF

wAMD is currently treated with chronic intravitreal injections of anti-VEGF antibodies to inhibit growth of new blood vessels and prevent fluid leakage. Current treatments (Exhibit 1) are typically administered several times within the first few months and then every 1-3 months thereafter. These treatments can stabilize visual acuity or lead to minor improvements if patients comply with the treatment regimen. We note that the safety profile of anti-VEGF drugs is very favorable, with them being very well tolerated in general.

Exhibit 3: Current wAMD treatments
wAMD patients have several treatment options to stabilize visual acuity

	Developer	Delivery	Molecule	Initial Dosing	Follow-up Dosing	Mechanism of Action
Eylea	Regeneron	Injection	Recombinant fusion protein (VEGFR-1 & 2) fused to FC region of human IgG1	2mg Q4W (First 3 months)	2mg Q8W	VEGF inhibitor
Eylea High-Dose	Regeneron	Injection	Recombinant fusion protein (VEGFR-1 & 2) fused to FC region of human IgG1	8mg Q4W (First 3 months)	8mg Q8-16W	VEGF inhibitor
Vabysmo	Roche	Injection	Bispecific IgG1 Antibody	6mg Q4W (First 4 Doses)	6mg on one of the following schedules: Weeks 28 and 44 Weeks 24, 36, 48 Weeks 20, 28, 36, 44	Blocks VEGF-A & Angiopoietin 2 (ang-2)
Avastin	Roche	Injection	Recombinant monoclonal IgG1 antibody	1.25mg Q4W (Monthly)	N/A	VEGF inhibitor
Lucentis	Roche	Injection	IgG1 monoclonal antibody fragment (Fab)	0.5mg Q4W (Monthly)	N/A	VEGF inhibitor
Beovu	Novartis	Injection	Monoclonal single-chain Fv (scFv) antibody	6mg ~Q4W (First 3 months)	6mg Q8-12W	VEGF-A inhibitor

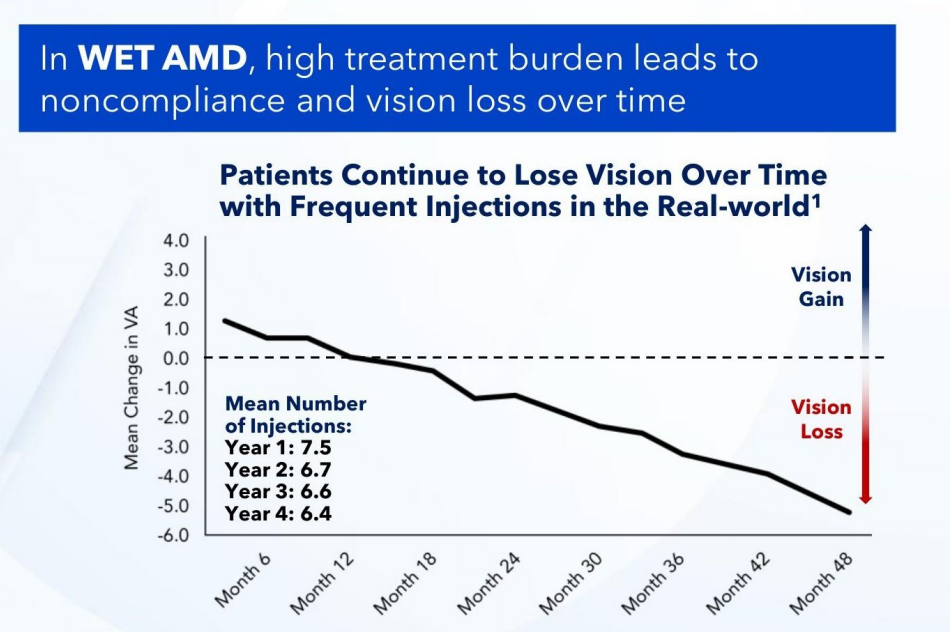
Abbreviations: Ang-2: Angiopoietin 2; Fab: Antibody fragment; FC: Fragment crystallizable region; IgG1: Immunoglobulin G1 antibody; Q4W: Every 4 weeks; Q8W: Every 8 week; Q12W: Every 12 weeks; Mg: milligrams; VEGF(R): Vascular endothelial growth factor (receptor) scFv: single-chain Fv;
Source: BofA Global Research

BofA GLOBAL RESEARCH

High treatment burden for wAMD patients remains an issue

Despite the numerous options that exist for wAMD patients, there remains a high unmet need for therapies with a lower treatment burden. With such frequent dosing required (KOLs note up to 10 injections may be needed in first year), such an elderly patient population – often with concurrent medical problems – can find it difficult adhering to the treatment protocol. These compliance issues ultimately lead to further vision impairment and even loss due to wet AMD progression over time (Exhibit 4).

Exhibit 4: Noncompliance is a major issue for wAMD patients
Lowering the treatment burden for elderly patients is key for new therapies



Source: Company filing

BofA GLOBAL RESEARCH

Eylea HD and VABYSMO approvals mark a shift to longer acting agents

Newer therapies and developing pipeline products typically employ anti-VEGF therapy but aim to extend dosing frequency to reduce the treatment burden and potentially provide more durable vision preservation. In July 2023, the FDA approved Eylea High-Dose (Eylea HD; 8 mg aflibercept injection – Regeneron), making it the first treatment approved for immediate dosing at 8-week to 16-week dosing intervals (following three initial monthly doses) in wAMD. FDA approval was based on the 48-week results of PULSAR– a double-masked, active-controlled pivotal trial evaluating Eylea HD compared to 2mg Eylea injection for the treatment of wAMD. PULSAR (N=1,009) met its primary endpoint, with Eylea HD demonstrating non-inferior and clinically equivalent vision gains to Q8W 2mg Eylea at 48 weeks with both 12 and 16-week dosing regimens after 3 initial monthly doses.

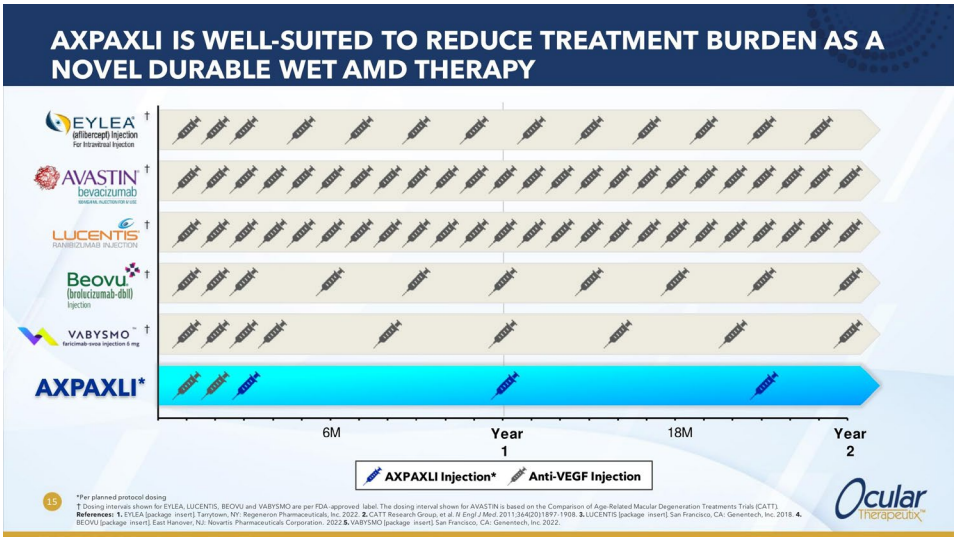
Vabysmo (6mg faricimab-svoa injection – Roche), a bispecific (two-target) antibody, was also approved by the FDA in 2022 for dosing at up to four-month intervals after four initial monthly treatments. Vabysmo works slightly differently to traditional anti-VEGFs, as it targets and inhibits both VEGF-A and angiopoietin-2 (Ang-2), and their respective pathways. When overproduced, VEGF-A and Ang-2 are both responsible for the abnormal growth of new blood vessels and vascular leakage. The FDA approval of Vabysmo for wAMD was based on two identically designed phase 3 studies (TENAYA and LUCERNE) comparing Vabysmo to aflibercept injection. Both TENAYA and LUCERNE met their primary endpoint (average change in BCVA score from baseline at weeks 40, 44 and 48), with +5.8 and +6.6 letters change from baseline, respectively, at one year, compared to +5.1 and +6.6 letters for patients receiving aflibercept.

AXPAXLI targets a sustained release of 6+ months

OCUL is developing an intravitreal implant with the goal of providing a long-lasting treatment for patients with wAMD. Axpaxli (axitinib intravitreal implant) is a preformed, bioresorbable hydrogel fiber implant that combines axitinib, a potent TKI that inhibits the cellular processes necessary for blood vessel formation (angiogenesis), with OCUL's proprietary ELUTYX technology. The implant is delivered into the eye via a 25-gauge (or narrower) needle. OCUL has designed Axpaxli for 6+ months of sustained drug delivery, including a small re-treatment window during which an effective dose of axitinib can still

reach therapeutic targets after full bio-resorption of the implant. This window ensures that patients are never required to have two implants simultaneously, while also providing patients timing flexibility for receiving subsequent implants without sacrificing retinal health.

Exhibit 5: Axpaxli significantly reduces treatment burden in wAMD
Axpaxli injection frequency as compared to anti-VEGF injections



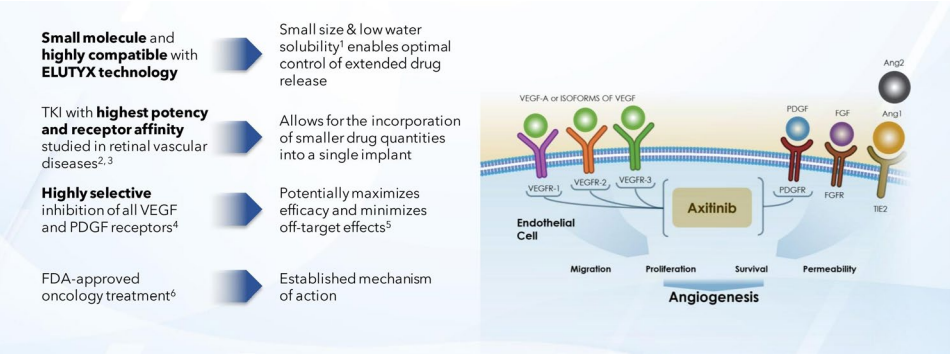
Source: Company filing

BofA GLOBAL RESEARCH

Axpaxli uses a differentiated mechanism of action in wAMD

As a tyrosine kinase inhibitor (TKI), Axpaxli has a differentiated therapeutic approach to traditional antibody anti-VEGF treatments. TKIs are a class of drugs that can bind to portions of tyrosine kinase receptors (TKRs) that lie inside the cell (intracellular domains) and prevent them from activating various signaling pathways. This differs from current anti-VEGF drugs, which bind TKRs outside the cell (extracellular space). Vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) receptors are two TKRs that play key roles in the formation of blood vessels (angiogenesis). Axitinib is a selective inhibitor of all VEGF and PDGF receptors, preventing them from kicking off the cascade that results in blood vessel formation. We note that studies have shown that axitinib has the highest affinity for VEGF receptors of the TKIs currently being evaluated for retinal diseases. This increased affinity allows Axpaxli to achieve similar clinical effects to other treatments with less drug, allowing for a more extended release and smaller implant size.

Exhibit 6: Axpaxli is differentiated from current anti-VEGF treatments
Axitinib is a TKI with high affinity for the receptors that cause wAMD



Abbreviations: FDA: Food and Drug Administration; PDGF(R): Platelet-derived growth factor (receptor); TKI: Tyrosine kinase inhibitor VEGF(R): Vascular endothelial growth factor (receptor)
Source: Company filing

BofA GLOBAL RESEARCH

Axitinib is also a small molecule designed to be highly compatible with OCUL's Elutyx platform, which should enable optimal control of extended drug release from a single implant. Intravitreal implants like Axpaxli have the potential to treat retinal neovascular diseases chronically with many fewer injections than anti-VEGF therapies, and OCUL believes they can achieve superior efficacy with their proprietary approach. We note that axitinib is an FDA-approved oncology treatment for kidney cancer (Inlyta – Pfizer), but still requires validation in retinal diseases. We are encouraged by the potential of Axpaxli in wet AMD but will continue to look for further validation in the clinic.

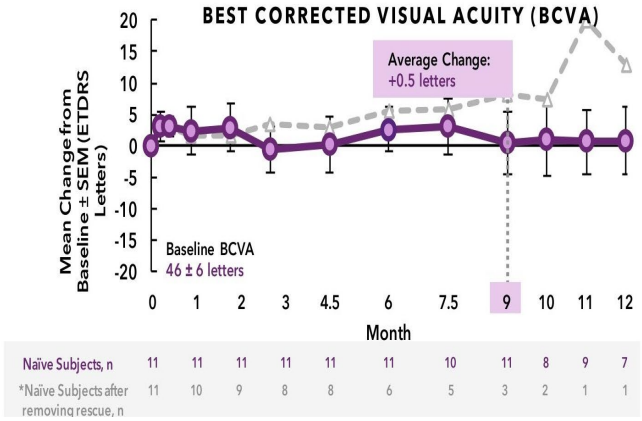
Overview of Axpaxli clinical data

OCUL has completed two phase 1 trials of Axpaxli in wet AMD, dosing 45 patients to investigate proof-of-concept (Australia trial) and durability (US trial). The randomized, masked and controlled US trial compared a treatment arm (N=16) receiving a single Axpaxli implant (600 micrograms axitinib) and an anti-VEGF injection at one month, to a 5-subject arm receiving on-label 2mg aflibercept injections every 8 weeks. All 21 subjects had been previously treated with, and responsive to, standard-of-care (SOC) anti-VEGF therapy.

Data from the Australia dose-escalation trial

In the phase 1 trial conducted in Australia, 29 treatment-naïve or previously treated active wet AMD patients were dosed with Axpaxli in an open-label, dose escalation trial. Data from this cohort showed a clinically meaningful reduction in retinal fluid among treatment naïve subjects (n=11), with an average of +0.5 letters change in best corrected visual acuity (BCVA) at 9 months (Exhibit 7) and an average of -197 microns change in central subfield thickness (CSFT) (Exhibit 8). Safety data from the comprehensive phase 1 program showed that Axpaxli was generally well tolerated, with no drug-related ocular or systemic serious adverse events reported.

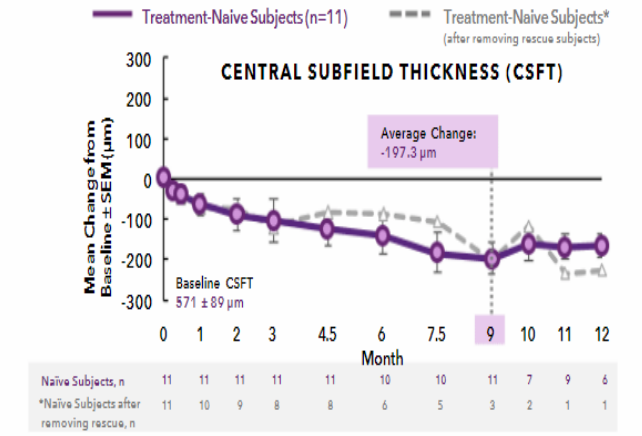
Exhibit 7: Axpaxli improved visual acuity in treatment naïve subjects
Average change in BCVA was +0.5 letters at 9 months



Source: Company filing

BofA GLOBAL RESEARCH

Exhibit 8: Axpaxli had a clinically meaningful reduction in retinal fluid
Treatment naïve patients saw an average of -197.3 microns at 9 months



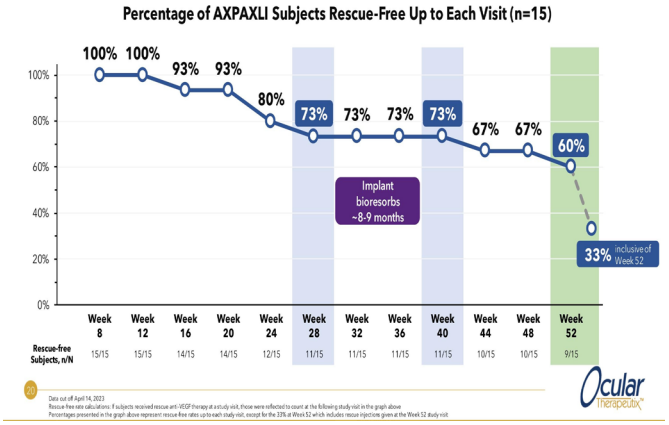
Source: Company filing

BofA GLOBAL RESEARCH

12-month data from the US phase 1 trial

Data from the US cohort also showed 73% and 60% of patients were rescue-free up to 10 and 12 months (Exhibit 9), respectively, and a clinically meaningful 89% reduction in treatment burden as compared to aflibercept injection. Notably, at 12 months, the 16 US trial subjects treated with a single Axpaxli implant demonstrated maintenance of vision, as measured by BCVA (mean change from baseline of -1.0 letters) and retinal fluid, as measured by central subfield thickness (CSFT; mean change from baseline of +20.2 microns)(Exhibit 10). This was compared to the aflibercept arm which saw changes from baseline of +2.0 letters in BCVA and -2.2 microns in CSFT at 12 months. We view the durability and reduction in treatment burden exhibited by the Axpaxli implant in phase 1 as quite promising. However, we will be looking to see a clinical benefit (mean baseline change in both BCVA and CSFT) that closer matches the aflibercept arm in future trials.

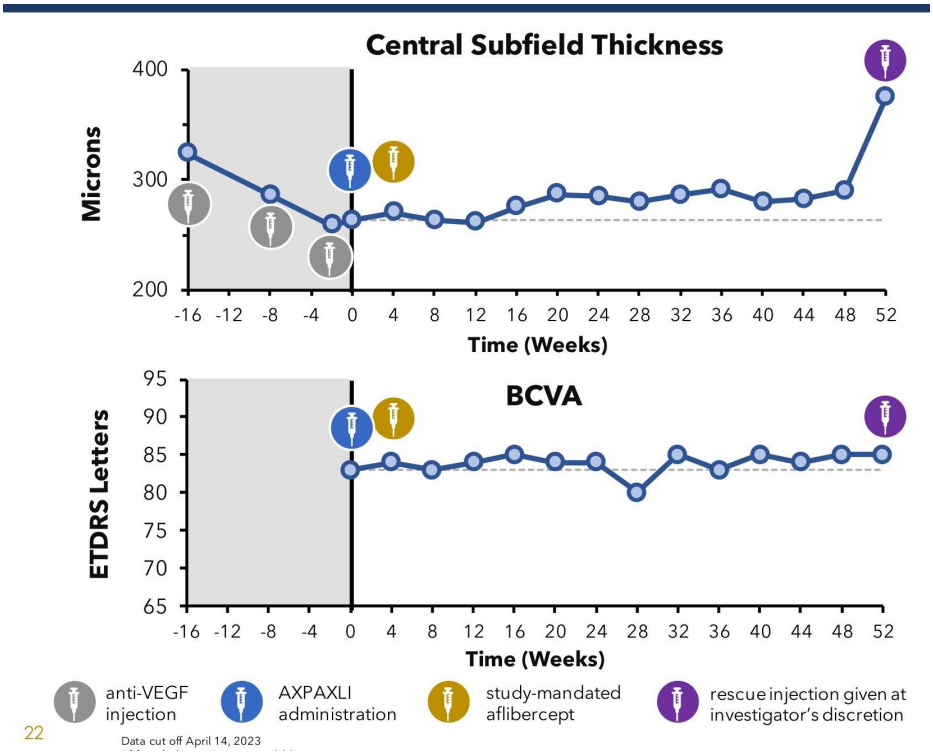
Exhibit 9: Axpaxli demonstrated extended duration of action
60% of patients were rescue free up to 12 months



Source: Company filing

BofA GLOBAL RESEARCH

Exhibit 10: Axpaxli showed sustained efficacy in US phase 1 study
Patients with controlled fluid experienced BCVA and CSFT maintenance up to 12 months



Source: Company filing

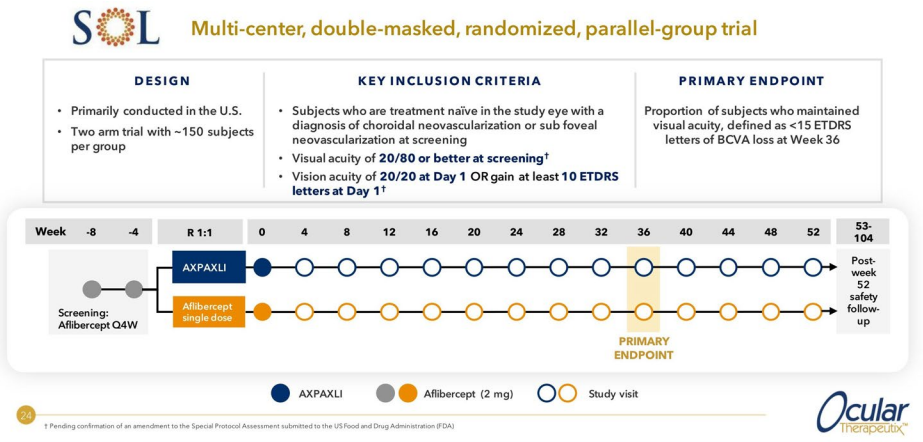
BofA GLOBAL RESEARCH

Ongoing phase 3 trial design

OCUL will begin the multi-center, randomized, parallel-group phase 3 SOL trial in 1Q24, evaluating Axpaxli in wet AMD patients who are treatment naïve in the study eye (Exhibit 11). The company anticipates enrolling approximately 300 evaluable wet AMD subjects with good visual acuity and a diagnosis of choroidal neovascularization or sub-foveal neovascularization at screening. SOL is designed as a superiority trial comparing a single implant of Axpaxli to a single injection of aflibercept and assessing the safety and efficacy of Axpaxli by measuring BCVA and CSFT. After randomization, every patient will receive either one implant of Axpaxli in the investigational arm, or one injection of

aflibercept in the control arm. Patients will be followed every month and rescued as needed with supplemental anti-VEGF treatment. The trial's pre-specified rescue criteria include either a loss from baseline of 15 or more letters on the ETDRS chart, or the emergence of a new hemorrhage that is deemed to be likely to cause irreversible vision loss. The primary endpoint of the study will be the proportion of subjects who maintained visual acuity, defined as a BCVA loss of less than 15 letters on the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart at week 36.

Exhibit 11: Trial design for phase 3 SOL study
OCUL anticipates screening the first subject in 1Q24



Source: Company filing

BofA GLOBAL RESEARCH

After reaching SPA agreement with FDA, SOL is anticipated to begin in 1Q

In January 2024, the company announced the FDA's agreement to amend their initial (October 2023) Special Protocol Assessment (SPA) for the pivotal SOL trial of Axpaxli in wet AMD. The amendment proposed broadening the inclusion criteria for SOL to include treatment-naïve patients with visual acuity of 20/80 or better at the initial screening visit. Between screening and Day 1 of the study (after receiving two aflibercept injections), eligible participants would need to either gain at least 10 ETDRS letters or achieve visual acuity of ~20/20. The SPA amendment also included a change to an Axpaxli implant containing 450 micrograms of axitinib Form IV, which is more soluble and allows for an increase in daily delivered dose and better synchronization with the implant's resorption. OCUL anticipates screening the first study subject in 1Q24. The company is also preparing to initiate a second pivotal wet AMD trial in 2H24 (as early as 3Q). We will continue to look for more color from management on the timing of future data updates for the SOL trial.

Takeaways from our discussions with Key Opinion Leaders

From our conversations with key opinion leaders (KOLs), over half of their wet AMD patients are being treated with 2 mg Eylea (aflibercept injection – Regeneron) followed by a significant portion (~10-25%) on 6mg Vabysmo (faricimab-svoa injection – Roche). KOLs named insurance coverage as a critical factor in dictating an initial treatment regimen, as some plans may require other drugs (e.g. avastin, lucentis or biosimilars) before moving on to the preferred Eylea and Vabysmo. Notably, traditional anti-VEGF treatments have begun to face generic competition, with Lucentis (ranibizumab injection – Roche) already losing revenue due to multiple approved biosimilars entering the market. Biosimilars for Eylea (2 mg aflibercept injection – Regeneron) are also expected to enter the market soon, which would likely cause a massive shift in the landscape for wet AMD treatment.

KOLs believe longer-acting agents still need to live up to potential

On longer-acting agents, KOLs have noted a marked disappointment in their real-life efficacy, with the small number of patients on these drugs still requiring injections every

8-10 weeks or so. Notably, our KOLs have found the clinical durability and efficacy of Vabysmo to be particularly underwhelming, with patients not seeing the same lengthy extensions between injections, or the improved efficacy over 2 mg Eylea that were observed in registrational trials. However, KOLs believe that these approvals still do signal a shift in the treatment paradigm towards longer acting agents and – as patients achieve access – they will begin to opt for treatments with lower burdens. Yet, there remains a segment of the elderly wAMD population – especially those considering themselves well controlled on their current regimen – that is hesitant to switch to newer therapies, despite this promise of a lower treatment burden. Given these factors, we will continue to monitor the shifting treatment landscape in wet AMD as it evolves.

KOLs view Axpaxli and EYP-1901 similarly, but question OCUL's trial design

On the competitive landscape among pipeline implants, our KOLs note that it remains difficult to draw comparison between OCUL's Axpaxli and EyePoint's EYP-1901 at this stage. The basic science underlying the mechanism of both implants is sound and the safety and efficacy profiles observed from both of their respective phase 1 programs were favorable. However, KOLs did mention that OCUL's decision to move Axpaxli directly from phase 1 to phase 3 as a cautionary point, as EYP-1901 has significantly more data entering its pivotal trial after completing a phase 2 study.

On the SOL pivotal trial design, KOLs warned that the study design could be unattractive to wAMD patients and their providers, making it difficult to enroll. Recall, under the pre-specified rescue criteria, patients can only receive a rescue anti-VEGF injection upon either a 15-letter loss from baseline or the emergence of a potentially blinding hemorrhage. KOLs transparently noted that this may not be a risk some wAMD patients are willing to take. OCUL plans to enroll 300 evaluable wAMD patients to initiate SOL in 1Q24. We will continue to look to management for color on the cadence of enrollment and the timeline for upcoming study updates.

Our thoughts on Axpaxli in wet AMD

We are encouraged by early clinical data from Axpaxli durable responses after up to 9 months with a significant decrease in annualized injection rates and a significant proportion of patients remaining injection free. We think the extended-release profile of Axpaxli supporting infrequent redosing could be a key point of differentiation in the wAMD space and meet a key unmet need in reducing treatment burden for this elderly population. We think the superiority trial design for the pivotal program could differentiate Axpaxli from similar approaches but highlight that our KOLs noted there could be enrollment challenges as patients in the placebo arm would be off treatment for an extended period of time. While we think EyePoint could represent additional competition in the wAMD space, we view the wAMD market as being large enough to support multiple players. Based on our conversations with KOLs, we think uptake of extended release could be positive given the high unmet need and even a modest marker share would represent an attractive commercial opportunity. We also view gene therapy as a potential additional competitor down the line, but we expect this approach could be reserved for more severe patients as the physician and patient community becomes more comfortable with the safety and durability. We await future phase 3 clinical data and will continue to follow the developing treatment landscape in wet AMD to inform our estimates.

Management

Antony Mattessich is OCUL's CEO and president. Mattessich joined the company in August of 2017. Prior to joining OCUL, he previously held leadership roles at Mundipharma International and Novartis. He has also held several positions at Bristol-Myers Squibb, including Head of Operations for the International Medicines Group. He received a BA from UC Berkeley and a Masters in International Affairs from Columbia University.

Donald Notman is the CFO of OCUL. Prior to joining OCUL, Mr. Notman served as Senior Vice President and CFO of Thrasos Therapeutics Inc. He has also served as Managing Director and Head of Private Capital Markets for Leerink Partners. Mr. Notman received his BA from Middlebury College and earned an MBA from the Tuck School of Business at Dartmouth College.

Christopher White is OCUL's Chief Business Officer. Mr. White previously served as the Chief Operating Officer of Silver Creek Pharmaceuticals, and prior to that held various senior leadership positions in the biotechnology industry including Chief Business Officer at both Entasis Therapeutics and AMAG Pharmaceuticals. He has also worked as a partner in management consulting, advising biopharma clients at Accenture and A.T. Kearney. Mr. White received a BS from Tufts University and an MBA from Columbia University.

Peter Jarrett, Ph.D., is OCUL's Chief Scientific Officer. Prior to his current role, Dr. Jarrett served as Vice President of R&D at Focal and was subsequently named VP of Biomaterials R&D at Genzyme when they acquired Focal. Throughout his career, Dr. Jarrett has had a successful track record of developing bioresorbable polymers for medical devices and drug delivery systems. He received his BA from Connecticut College and his Ph.D. from the University of Connecticut Institute of Materials Science.

Rabia Gurses Ozden, M.D., is the CMO of OCUL. Dr. Ozden previously served as Chief Development Officer at Akouos, Inc. and before that was the CMO of Nightstar, a gene therapy company focused on rare inherited retinal diseases. She has also held leadership roles at Applied Genetic Technologies Corporation and GlaxoSmithKline. She received her MD from Hacettepe University School of Medicine, completed her ophthalmology residency at Ankara University School of Medicine and her clinical fellowship in Glaucoma at the New York Eye and Ear Infirmary.

Abbreviations

1Q: first quarter
1H: first half
Ang-2: angiopoietin 2
ASCRS: American Society of Cataract and Refractive surgery
BCVA: best-corrected visual acuity
COGS: cost of goods sold
CNV: choroidal neovascularization
CSFT: central subfield thickness
ETDRS: Early Treatment Diabetic Retinopathy Study
Fab: antibody fragment
FC: fragment crystallizable region
FDA: Food and Drug Administration
GtN: gross-to-net
IgG1: Immunoglobulin G1 antibody
IOP: intraocular pressure
KOL: key opinion leader
LoS: likelihood of success
Mg: milligram
NPDR: non-proliferative diabetic retinopathy
OCT: optical coherence tomography

PDGF®: platelet-derived growth factor (receptor)
PEG: polyethylene glycol
Ph: phase
PO: price objective
Pts: patients
Q4W: every four weeks
SAE: serious adverse event
ScFv: single-chain Fv
SoC: standard-of-care
SPA: Special Protocol Assessment
TKI: tyrosine kinase inhibitor
TKR: tyrosine kinase receptor
VEGF(R): vascular endothelial growth factor (receptor)
WACC: weighted average cost of capital
wAMD: wet age-related macular degeneration

Price objective basis & risk

Ocular Therapeutix (OCUL)
Our $15 PO is based on a probability adjusted net present value analysis. Our valuation consists of $11/sh for Axpaxli in wAMD, $3/sh for Dextenza in post-cataract surgery pain and $1/sh for pipeline and cash. Our DCF-based model goes out to 2040. We assume 9% WACC for Dextenza, 10% WCC for Axpaxli and 14% WACC for pipeline. We assume no terminal value.

Upside risks to our PO are: 1) positive clinical data from the phase 3 program of Axpaxli, 2) positive clinical data for programs in the pipeline, and 3) better than expected market penetration of Dextenza.

Downside risks to our PO are: 1) slow than expected enrollment in the phase 3 program of Axpaxli, 2) negative results from ongoing clinical trials, 3) unexpected safety signals resulting from the use of intraocular inserts, and 4) increasing competitive pressure from other extended-release inserts or gene therapies in wAMD.

Analyst Certification

I, Tazeen Ahmad, hereby certify that the views expressed in this research report accurately reflect my personal views about the subject securities and issuers. I also certify that no part of my compensation was, is, or will be, directly or indirectly, related to the specific recommendations or view expressed in this research report.

US - Biotechnology Coverage Cluster

Investment rating	Company	BofA Ticker	Bloomberg symbol	Analyst
BUY				
	4D Molecular Therapeutics, Inc.	FDMT	FDMT US	Tazeen Ahmad
	Alnylam Pharmaceuticals	ALNY	ALNY US	Tazeen Ahmad
	Amicus Therapeutics	FOLD	FOLD US	Tazeen Ahmad
	Annexon Biosciences	ANNX	ANNX US	Tazeen Ahmad
	Apellis Pharmaceuticals	APLS	APLS US	Tazeen Ahmad
	Argenx SE	ARGX	ARGX US	Tazeen Ahmad
	Arvinas	ARVN	ARVN US	Tazeen Ahmad
	Ascendis Pharma	ASND	ASND US	Tazeen Ahmad
	Biocryst Pharmaceuticals Inc	BCRX	BCRX US	Tazeen Ahmad
	BioNTech	BNTX	BNTX US	Tazeen Ahmad
	Denali Therapeutics	DNLI	DNLI US	Tazeen Ahmad
	Inozyme Pharma, Inc.	INZY	INZY US	Tazeen Ahmad
	Merus	MRUS	MRUS US	Tazeen Ahmad
	Neurocrine Biosciences	NBIX	NBIX US	Tazeen Ahmad
	Ocular Therapeutix	OCUL	OCUL US	Tazeen Ahmad
	PepGen Inc	PEPG	PEPG US	Tazeen Ahmad
	Rhythm Pharmaceuticals	RYTM	RYTM US	Tazeen Ahmad
	Sarepta Therapeutics	SRPT	SRPT US	Tazeen Ahmad
	Ultragenyx Pharmaceuticals	RARE	RARE US	Tazeen Ahmad
NEUTRAL				
	Acadia Pharmaceuticals	ACAD	ACAD US	Tazeen Ahmad
	Incyte Corporation	INCY	INCY US	Tazeen Ahmad
	Prothena Corporation	PRTA	PRTA US	Tazeen Ahmad
	SAGE Therapeutics	SAGE	SAGE US	Tazeen Ahmad
UNDERPERFORM				
	Achilles Therapeutics	ACHL	ACHL US	Tazeen Ahmad
	Fate Therapeutics	FATE	FATE US	Tazeen Ahmad
	Fulcrum Therapeutics	FULC	FULC US	Tazeen Ahmad
	Pharvaris	PHVS	PHVS US	Tazeen Ahmad
	PTC Therapeutics	PTCT	PTCT US	Tazeen Ahmad

iQmethod℠ Measures Definitions

Business Performance	Numerator	Denominator
Return On Capital Employed	NOPAT = (EBIT + Interest Income) × (1 – Tax Rate) + Goodwill Amortization	Total Assets – Current Liabilities + ST Debt + Accumulated Goodwill Amortization
Return On Equity	Net Income	Shareholders' Equity
Operating Margin	Operating Profit	Sales
Earnings Growth	Expected 5 Year CAGR From Latest Actual	N/A
Free Cash Flow	Cash Flow From Operations – Total Capex	N/A

Quality of Earnings	Numerator	Denominator
Cash Realization Ratio	Cash Flow From Operations	Net Income
Asset Replacement Ratio	Capex	Depreciation
Tax Rate	Tax Charge	Pre-Tax Income
Net Debt-To-Equity Ratio	Net Debt = Total Debt – Cash & Equivalents	Total Equity
Interest Cover	EBIT	Interest Expense

Valuation Toolkit	Numerator	Denominator
Price / Earnings Ratio	Current Share Price	Diluted Earnings Per Share (Basis As Specified)
Price / Book Value	Current Share Price	Shareholders' Equity / Current Basic Shares
Dividend Yield	Annualised Declared Cash Dividend	Current Share Price
Free Cash Flow Yield	Cash Flow From Operations – Total Capex	Market Cap = Current Share Price × Current Basic Shares
Enterprise Value / Sales	EV = Current Share Price × Current Shares + Minority Equity + Net Debt + Other LT Liabilities	Sales
EV / EBITDA	Enterprise Value	Basic EBIT + Depreciation + Amortization

iQmethod℠ is the set of BofA Global Research standard measures that serve to maintain global consistency under three broad headings: Business Performance, Quality of Earnings, and validations. The key features of iQmethod are: A consistently structured, detailed, and transparent methodology. Guidelines to maximize the effectiveness of the comparative valuation process, and to identify some common pitfalls.

iQdatabase® is our real-time global research database that is sourced directly from our equity analysts' earnings models and includes forecasted as well as historical data for income statements, balance sheets, and cash flow statements for companies covered by BofA Global Research.

Disclosures

Important Disclosures

Equity Investment Rating Distribution: Health Care Group (as of 31 Dec 2023)

Coverage Universe	Count	Percent	Inv. Banking Relationships [R1]	Count	Percent
Buy	234	60.94%	Buy	115	49.15%
Hold	80	20.83%	Hold	36	45.00%
Sell	70	18.23%	Sell	29	41.43%

Equity Investment Rating Distribution: Global Group (as of 31 Dec 2023)

Coverage Universe	Count	Percent	Inv. Banking Relationships [R1]	Count	Percent
Buy	1895	53.62%	Buy	1083	57.15%
Hold	832	23.54%	Hold	454	54.57%
Sell	807	22.84%	Sell	383	47.46%

[R1] Issuers that were investment banking clients of BofA Securities or one of its affiliates within the past 12 months. For purposes of this Investment Rating Distribution, the coverage universe includes only stocks. A stock rated Neutral is included as a Hold, and a stock rated Underperform is included as a Sell.

FUNDAMENTAL EQUITY OPINION KEY: Opinions include a Volatility Risk Rating, an Investment Rating and an Income Rating. VOLATILITY RISK RATINGS, indicators of potential price fluctuation, are: A - Low, B - Medium and C - High. INVESTMENT RATINGS reflect the analyst's assessment of both a stock's absolute total return potential as well as its attractiveness for investment relative to other stocks within its Coverage Cluster (defined below). Our investment ratings are: 1 - Buy stocks are expected to have a total return of at least 10% and are the most attractive stocks in the coverage cluster; 2 - Neutral stocks are expected to remain flat or increase in value and are less attractive than Buy rated stocks and 3 - Underperform stocks are the least attractive stocks in a coverage cluster. An investment rating of 6 (No Rating) indicates that a stock is no longer trading on the basis of fundamentals. Analysts assign investment ratings considering, among other things, the 0-12 month total return expectation for a stock and the firm's guidelines for ratings dispersions (shown in the table below). The current price objective for a stock should be referenced to better understand the total return expectation at any given time. The price objective reflects the analyst's view of the potential price appreciation (depreciation).

Investment rating	Total return expectation (within 12-month period of date of initial rating)	Ratings dispersion guidelines for coverage cluster[R2]
Buy	≥ 10%	≤ 70%
Neutral	≥ 0%	≤ 30%
Underperform	N/A	≥ 20%

[R2]Ratings dispersions may vary from time to time where BofA Global Research believes it better reflects the investment prospects of stocks in a Coverage Cluster.

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