

The next wave in AMD

A spotlight on next-generation therapies

Age-related macular degeneration (AMD) is the leading cause of blindness in older adults in western countries. Even though neovascular AMD (NVAMD, or wet-AMD) can be controlled in most cases with recurring anti-vascular endothelial growth factor A (VEGF-A) intravitreal injections (IVT), there is a substantial unmet need for those with the dry form of the disease (whose prevalence is over five times higher), particularly those who develop geographic atrophy (GA). There is also a need to improve NVAMD treatments, as recurring IVT injections are burdensome, and about a third of patients will become refractory to anti-VEGF-A over time. This report provides an overview of most of the leading candidates and technologies that will shape the AMD market in the coming decade. Not all of these products will be successful, but those that are could potentially generate outsized returns for investors.

A huge market opportunity

The NVAMD market size is already substantial, at over \$5.25bn worldwide revenue, and growing in double-digits, as ranibizumab and aflibercept (the current leading treatments) had 13–14% revenue growth in the past year. NVAMD reflects roughly only half of late-stage AMD patients. Late-stage AMD (defined as those patients with GA or NVAMD) affects roughly five million people across the US and Europe, and most of these patients will become legally blind without treatment. Another approximately fifteen to 20 million people in these regions have early-to-intermediate forms of dry-AMD and could be at risk of developing late-AMD, but there is no widely accepted and approved treatment for this stage of the condition. Altogether, approved and effective GA or dry-AMD treatments could add billions of dollars to an already huge AMD market.

Likely winners...

- **Treatments** that gain regulatory approval and can be shown to either require less frequent, invasive dosing than current approved IVT drugs or provide stronger or more sustained improvements in vision compared to or added to current NVAMD standard-of-care.
- **NVAMD treatments** that can be self-administered by patients or administered non-invasively.
- **Products** that can be shown to stabilize vision in dry-AMD or GA patients.
- **Patients** who will benefit from potentially more effective treatments, and/or may require less frequent invasive dosing.

Likely losers...

- **Companies** currently marketing anti-VEGF IVT drugs in NVAMD, but which lack follow-on candidates in their pipeline to compete with emerging new competition.

Winners and losers: the companies shown above do not translate into buys and sells as other themes (and valuation parameters) may conflict with this one.

Edison themes



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Viewpoint

AMD is the leading cause of blindness among older adults in western countries and falls into two categories, dry-AMD and NVAMD. NVAMD can be controlled in most cases with recurring anti-VEGF-A intravitreal injections, and this market is already worth more than \$5.25bn worldwide. There is a need to improve NVAMD therapy, as recurring injections are burdensome, and about a third of patients will become refractory to anti-VEGF-A over time. Many emerging candidates may potentially provide options for refractory NVAMD patients in the next half-decade, and/or result in meaningfully reduced invasive dosing frequencies. Beyond this, there is a substantial unmet need for those with dry-AMD (representing >80% of AMD patients), particularly those who develop GA, as there is no widely accepted and approved treatment. Approved and effective GA or dry-AMD treatments could thus foster a multi-billion dollar industry, and we highlight recent promising data from both drug candidates targeting oxidative stress and/or inflammation, as well as from light-based therapies.

Edison themes

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Analyst

Pooya Hemami, OD, CFA +1 646-653-7026

healthcare@edisongroup.com

Opportunities abound in the NVAMD space

Firms are looking at ways to extend NVAMD treatment durability to reduce the frequency of IVT instillations. Roche and Novartis are working on late-stage follow-on mAB drugs that are more efficient or effective in targeting the angiogenesis factors in NVAMD. Novartis recently filed a biologics license application (BLA) for brolocizumab and Roche started Phase III studies on faricimab. We also review alternate mechanisms including gene therapies that can provide extended treatment durations of potentially up to a year, as well as candidates targeting non-VEGF-A mechanisms to provide options for those refractory to current treatments. Topical (non-invasive) treatments are an exciting prospect as well.

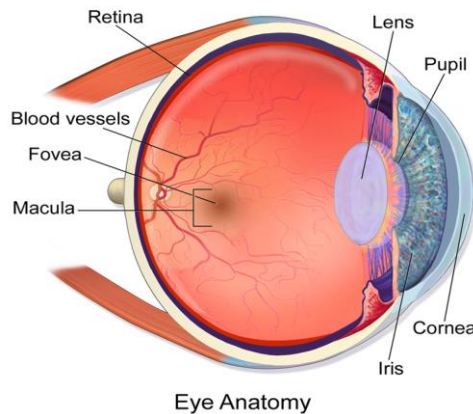
Dry-AMD represents an untapped frontier

Firms are developing treatments targeting inflammation and/or oxidative stress, and there is finally some promising Phase II data for Apellis's APL-2 and Allegro's risuteganib, in particular, which along with other candidates hold real potential for this huge untapped market. Recent trials show that proprietary light-based therapy (Ellex's 2RT and LumiThera's Valeda) may potentially decelerate progression of early-to-intermediate stage Dry-AMD patients. Altogether, we expect the next five to 10 years to be potentially revolutionary in a segment that until now has had little to offer to patients beyond dietary supplements and lifestyle modifications.

Overview

Age-related macular degeneration (AMD) is the leading cause of blindness in adults over the age of 55 in western countries, and is characterised by damage to the macular¹ region of the retina, leading to central vision loss. Prevalence increases with age, as about 2% of the population have the condition at age 40, rising to c 25% by age 80.² AMD patients generally maintain their peripheral vision but the damage to central vision can be so severe in advanced cases as to restrict a patient's ability to work, read, recognise faces or independently perform other habitual tasks.

Exhibit 1: Diagram of an eyeball including the location of macula



Source: Wikimedia Commons

- ¹ The macula is the central region of the retina, containing the highest density of photoreceptors compared to other regions, thus accounting for the high level of resolution and colour perception associated with the central vision. Photoreceptor cells in the retina absorb light photons, resulting in a biochemical reaction that leads to the generation of an electrical signal that stimulates downstream neurons (retinal ganglion cells) which then travel through the optic nerve and into the visual pathway leading to the occipital cortex of the brain.
- ² Friedman DS, O'Colmain BJ, Muñoz B, Tomany SC, McCarty C, de Jong PT, Nemesure B, Mitchell P, Kempen J, Eye Diseases Prevalence Research Group. *Arch Ophthalmol*. 2004 Apr; 122(4):564-72

While the exact pathophysiology is not fully understood, AMD is believed to be caused by oxidative stress, mitochondrial dysfunction, inflammatory processes and/or cardiovascular (lipid-cholesterol pathway) factors. Genetic and environmental factors (such as smoking history or prolonged exposure to ultraviolet light) may also play a role in pathogenesis. There are two forms of AMD: dry (non-exudative) and wet (exudative).

The dry form of AMD accounts for about 80–90% of cases (all AMD cases start as dry-AMD) and cellular atrophy is the primary cause of vision loss and photoreceptor damage in this form. This condition often evolves relatively slowly but currently has no proven broadly approved treatment, although lifestyle factors and dietary or nutritional supplement changes may help decelerate progression. As the dry form of the condition advances, it can lead to geographic atrophy (GA), where there are irreversible scattered or confluent areas of degeneration of the retinal pigment epithelium (RPE) cells, damaging the overlying photoreceptors and resulting in a loss of visual function. While some patients with GA may have near-normal visual acuity (VA) levels, most will at minimum have reductions in contrast sensitivity, and in many cases, GA patients will have sharp reductions in VA (20/80, or 25% of normal vision, or lower).

The wet form (also called NVAMD) is characterised by exudative and neovascular changes, such as the formation of choroidal neovascularisation (CNV). CNV refers to newly immature blood vessels from the eye's choroid layer growing into the overlying retina, which often leaks fluid, compromising the function of photoreceptors and connecting neurons, leading to central vision loss. The loss can be reversible if the excess fluid is eliminated in a timely manner, such as through the use of injection treatments to suppress vascular endothelial growth factor (VEGF), the current standard of care (SoC). However, without timely treatment, the excess fluid can lead to macular scarring/fibrosis, damaging photoreceptors and resulting in more permanent central vision loss. Further, for many treated NVAMD patients, the factors leading to CNV formation are ongoing and chronic, and persistent and recurrent fluid accumulation can still lead to fibrosis and permanent vision loss if anti-VEGF therapy is not adequately maintained (thus patients require ongoing and repeated IVT injections to control the condition).

The wet form of AMD is always preceded by the dry form, and it accounts for about 10–20% of AMD cases. Prior to the usage of anti-VEGF (vascular endothelial factor) injection treatments, the current standard of care for NVAMD, it accounted for over 80% of AMD patients with legal blindness.³

Early-stage AMD is mostly asymptomatic and characterised by drusen (deposits below the retinal pigment epithelium, or RPE, level), reticular pseudodrusen (RPD, deposits above the RPE), and pigmentary changes. Late-stage AMD is often defined as patients who develop NVAMD and/or GA. In general, RPE dysfunction and atrophy precedes the late stages of AMD (GA or CNV).

Globally, the prevalence of AMD (all stages) in adults above age 45 is estimated at 8.0%,⁴ affecting about 13 million people across western Europe, and the US prevalence of all-stage AMD was approximately 7.2 million in 2008.⁵ However, under the currently accepted treatment patterns, the primary target market for medical therapy are those with late stages of the disease (NVAMD or GA), as most earlier-stage patients are asymptomatic and may never evolve to vision-threatening, later disease stages. It is effectively the late-AMD population that is the primary target market for medical therapies, most particularly the NVAMD market (whereby prompt medical treatment is generally

³ Legal blindness refers to patients with a central VA of 20/200 (10%) or worse in the better eye when a patient is wearing their best-corrected prescription lenses, or those with a visual field of less than 20 degrees.

⁴ Wong WL, Su X, Li X et al. *Lancet Glob Health*. 2014 Feb;2(2):e106-16.

⁵ Klein R, Chou CF, Klein BEK, et al. *Arch Ophthalmol*. 2011;129(1):75-80. doi:10.1001/archophthalmol.2010.318

needed upon CNV diagnosis, as permanent scarring and severe vision loss often result if untreated).

Individuals with Caucasian or European ancestry are believed to be more prone to developing AMD. The prevalence of Caucasians in the United States with NVAMD, GA, and Late-stage AMD has been estimated at 1.1 million, 1.0 million and 2.0 million,⁶ respectively. Based on US National Institutes of Health (NIH) data⁷ that estimates that Caucasians account for 89% of all US AMD cases, we estimate that the US prevalence of NVAMD, GA and Late-stage AMD would be approximately 1.2 million, 1.1 million and 2.2 million, respectively.

In Europe, it has been estimated that the number of people with Late-stage AMD was 2.7 million in 2013, and that it will rise to 3.9 million by 2040 (a 1.4% CAGR).⁸

NVAMD treatments exist, but room for improvement

The current standard-of-care (SoC) for NVAMD is to reduce angiogenesis (blood vessel proliferation) by blocking vascular endothelial growth factor A (VEGF-A) binding and activity. VEGF-A is a biochemical signal protein that promotes angiogenesis throughout the body and in the eye, and tends to be over-expressed in hypoxic environments. Currently, the only effective reliable mechanism to block VEGF-A in the retina is through intravitreal injection (IVT) of monoclonal antibodies (mABs) targeting this protein.

The first FDA-approved therapy of CNV/NVAMD was pegaptanib sodium (Macugen, sold by Bausch (BHC, TSX) and Pfizer (PFE, NYSE)) in 2004, but its uptake was relatively limited compared to off-label bevacizumab (Avastin, Novartis (NOVN, SIX)) and then ranibizumab (Lucentis, marketed by Roche (ROG, SIX) in the US and Novartis in ex-US markets; approved in 2006) and most recently, aflibercept (Eylea, marketed by Regeneron (REGN, Nasdaq) and Bayer (BAYN, Xetra); approved in 2011). Both ranibizumab and aflibercept work by inhibiting VEGF-A thus blocking angiogenesis (the growth of new blood vessels). Aflibercept is a soluble decoy receptor that in addition to binding VEGF-A also inhibits placental growth factor (PLGF), which itself is another growth factor involved in promoting angiogenesis. All of these products currently must be delivered through IVT.

Today, anti-VEGF-A therapy for CNV (typically, ranibizumab or aflibercept) dramatically improves or stabilises vision in the large majority of NVAMD patients. For instance, when ranibizumab was approved by the FDA, the two pivotal Phase III (MARINA and ANCHOR) trials showed that 95% of treated NVAMD patients maintained their baseline VA at 12 months, and up to 40% improved (defined as a gain of 15 letters or more vs baseline) their vision at one year. At two years, patients in the MARINA pivotal study experienced an average improvement of 6.6 letters vs baseline, compared to a loss of 14.9 letters in the sham (control) arm. Up to 40% of ranibizumab-treated patients achieved VA of 20/40 (50%) or better.

The success of VEGF-A blockers in NVAMD also resulted in their use and approvals in other retinal conditions involving unwanted angiogenesis or vascular leakage in a hypoxic environment, such as diabetic retinopathy (DR) related conditions such as diabetic macular edema (DME), retinal vein occlusions (RVO), etc. These conditions generally also involve a VEGF-A dependent pathogenesis pathway.

⁶ Rudnicka AR, Kapetanakis VV, Jarrar Z et al. *Am J Ophthalmol*. 2015 Jul;160(1):85-93.e3. doi: 10.1016/j.ajo.2015.04.003. Epub 2015 Apr 6.

⁷ US National Institutes of Health. <https://nei.nih.gov/eyedata/amd> Accessed 22 February 2019.

⁸ Colijn JM, Buitendijk GHS, Prokofyeva E, et al. *Ophthalmology*. 2017 Dec;124(12):1753-1763. doi: 10.1016/j.ophtha.2017.05.035. Epub 2017 Jul 14.

Chronic nature of therapy provides a recurring revenue stream

Under the current SoC, NVAMD patients require recurring (often every four to eight weeks) IVT injections of anti-VEGF-A treatments (typically ranibizumab or aflibercept) in NVAMD-affected eyes, primarily to prevent the recurrence of new areas of CNV. This has led to significant revenue generation for the leading drugs, as Eylea recorded 2018 global sales of \$6.75bn (+14% y-o-y) and global Lucentis sales were \$3.74bn (c +13% y-o-y). Wet-AMD and diabetic retinopathy (including DME) were the primary sources of revenue for both products and we estimate that NVAMD represents approximately 50% of the total anti-VEGF-A retinal drug market (with DR including DME accounting for most of the other half).⁹ Contributions also occur from other medical retina indications associated with angiogenesis and/or hypoxia (such as macular edema following RVO). Both Eylea and Lucentis are administered through injections (often administered every four to eight weeks) and each dose costs about \$2,000 in the US.

While VEGF-A IVT therapy is often effective, it has several drawbacks for the patient; it requires patients (who are senior citizens and may have other comorbidities or mobility restrictions) to have a regular visit to their eye care practitioner (ECP) to receive IVT injections, which may not be comfortable or convenient for the patient. Any IVT injection carries a small but nonzero risk of endophthalmitis (intraocular inflammation), a potentially devastating condition that often leads to total blindness. A recent multicentre longitudinal study involving over 88,000 injections between January 2006 and November 2016 found that the cumulative risk of developing infectious endophthalmitis after 60 IVT injections was 0.84% and the cumulative risk of non-infectious endophthalmitis was approximately 0.23%.¹⁰ These factors provide incentives for firms to develop new therapies for NVAMD to improve convenience, efficacy and/or reduce the frequency of invasive¹¹ procedures.

Further, it has been estimated that 20–37%^{12, 13} of NVAMD patients' vision continues to worsen and they ultimately become legally blind (20/200 or worse VA) despite anti-VEGF therapy, further prompting the need to develop new treatment for patients refractory to current NVAMD SoC.

Below we classify different approaches under clinical investigation for ameliorating NVAMD in the market, which is already worth in excess of \$5.25bn worldwide (excluding the use of VEGF-A drugs for non-NVAMD indications such as DR/DME).

Evolutionary pipeline of emerging anti-VEGF NVAMD therapies

The evolutionary (lower-risk and more conventional) approach, currently taken by big pharma participants such as Roche and Novartis, is to develop follow-on mAB drugs that are more efficient or effective in targeting the angiogenesis factors in NVAMD, which can reduce the frequency of IVT instillations for patients and improve compliance. The leading advanced (Phase III or later) stage drugs in this category are Roche's faricimab and Novartis's brolucizumab. Both drugs are being investigated in NVAMD and DME:

Novartis filed a biologics licence application (BLA) for brolucizumab in NVAMD, using a priority review voucher, and could potentially obtain approval before YE19. The regulatory application is largely based on Phase III data from the [HAWK](#) and [HARRIER](#) studies, which both met their primary endpoints of non-inferiority to aflibercept in mean change in best-corrected visual acuity

⁹ Taking into consideration market research prepared by Global Market Insights and Prescient & Strategic Intelligence.

¹⁰ Daien V, Nguyen V, Essex RW et al. *Ophthalmology*. 2018 Jan;125(1):66-74. doi: 10.1016/j.ophtha.2017.07.005. Epub 2017 Aug 8.

¹¹ Each individual procedure carrying a nonzero risk of endophthalmitis.

¹² Maguire, MG et al. *Ophthalmology* 2016, 123(8), 1751 – 61

¹³ Rofagha, S. et al. *Ophthalmology* 2013, 120(11):2292-9.

(BCVA) from baseline to week 48. Novartis also stated that secondary endpoint assessments in both studies showed that significantly fewer brolocizumab-treated patients (vs aflibercept) had disease activity or (excessive) retinal fluid at week 48. The firm states that these are the first and only global head-to-head trials in patients with NVAMD that prospectively demonstrated 48-week efficacy starting with a 12-week dosing regimen. In contrast, aflibercept is typically dosed in NVAMD patients at every four weeks for three injections, and then at either every four weeks or every eight weeks (depending on patient response) thereafter for the first year.

Roche's faricimab is a bispecific mAB that targets both VEGF-A and angiopoietin-2 (Ang-2); Ang-2 is also believed to play an important role in NVAMD (relating to inflammation and vascular permeability). Phase II [STAIRWAY](#) data (n=76) in NVAMD showed that at week 52, faricimab patients dosed either every 12 or 16 weeks demonstrated sustained vision outcomes comparable to ranibizumab dosed every four weeks. The Phase III pivotal NVAMD studies [TENAYA](#) and [LUCERNE](#) (both started in H119; n=640 for each) will compare faricimab (dosed every 16 weeks, with an option to increase frequency if needed) to aflibercept dosed every eight weeks.

Allergan (AGN, NYSE) and Molecular Partners (MOLN, SIX) are developing abicipar pegol, a DARPIn (designed ankyrin repeat protein) designed to bind and inhibit VEGF-A. DARPins are small-protein therapeutic agents intended to bind targets with high potency and specificity. In Q318, results from two head-to-head Phase III trials against ranibizumab ([SEQUOIA](#) and [CEDAR](#)) were reported and showed that both the eight-week and 12-week treatment abicipar pegol regimens met the pre-specified primary endpoint of BCVA non-inferiority to ranibizumab (dosed at every four weeks). However, in both the SEQUOIA and CEDAR studies, the incidence of intraocular inflammation was c 15% in the abicipar pegol arms, compared to <1% in ranibizumab. In April 2019 the companies reported results from the [MAPLE](#) study evaluating the safety of abicipar produced via a modified manufacturing process, and showed a reduced (8.9%) incidence of intraocular inflammation. This level is still higher than that seen with competing approved anti-VEGF drugs, and may affect the product's likelihood of obtaining approval (in addition to its competitiveness among anti-VEGF treatments), although Allergan expects to file a BLA with the FDA in or around mid-2019.

A related approach also undertaken by Roche is to develop an improved drug delivery system that can reduce the number of patient visits or need for IVT injections of an existing anti-VEGF-A drug, ranibizumab. It has developed a Port Delivery System (PDS), which is a small, refillable device (indicated as slightly longer than a grain of rice), designed to continuously deliver a specialised formulation of ranibizumab over time. The PDS is implanted into an eye in a c 30-minute surgical procedure.

Each of these four approaches involve using an established primary mechanism of action (blocking angiogenesis by targeting VEGF-A) and, in our view, carry relatively lower regulatory risk (thus a higher chance of obtaining approval) than some of the more experimental approaches described later in this report. Provided they obtain regulatory approval, they are expected to be follow-on products to (and eventually extract the bulk of market share from) current mAB treatments like IVT ranibizumab or aflibercept. In particular, in our view brolocizumab has a high likelihood of obtaining FDA approval and we estimate that faricimab also appears to have a strong likelihood of reaching the market if its Phase III results are in line with trends reported STAIRWAY trial. Roche's PDS-ranibizumab could be a potential game-changer for patients who have mobility issues or restrictions or those located in rural areas (not within close driving distance to a treating ECP or ophthalmologist).

Exhibit 2: Later-stage injection or invasive anti-VEGF-A product candidates for NVAMD and/or DME

Product candidate	Company	Development stage	Mechanism	Notes	Next milestones
Brolocizumab	Novartis	BLA filed with FDA	Humanised single-chain antibody fragment (scFv) against VEGF-A, that may provide enhanced drug delivery characteristics compared to existing approved anti-VEGF mABs	Met primary endpoint (non-inferiority vs aflibercept) in two Phase III NVAMD studies reported in 2017 and confirmatory two-year data in H218; BLA application for NVAMD filed with FDA in April 2019.	FDA approval in 2019–20
Faricimab	Roche	Phase III	Bispecific antibody (biMab) binding simultaneously to VEGF-A and Angiopoietin2 (Ang2); Ang2 inhibition believed to potentially improve blood retinal barrier stability and reduce retinal vascular inflammation	229-pt Phase II (BOULEVARD) DME study showed statistically significant improvements in VA vs ranibizumab; two 900-pt Phase III trials (YOSEMITE and RHINE) in DME started Q318; two 640-pt Phase III NVAMD studies (TENAYA, LUCERNE) started in H119.	Top-line data in 2021
Abicipar pegol	Allergan / Molecular Partners	Phase III	DARPin (designed ankyrin repeat protein) designed to bind and inhibit VEGF-A	SEQUOIA and CEDAR Phase III trials showed that both 8-week and 12-week arms were non-inferior to ranibizumab (4-week dosage). Higher incidence of intraocular inflammation (15% in Phase III and 9% with modified manufacturing process).	File BLA in mid-2019
Port Delivery System (ranibizumab)	Roche	Phase III	Sustained delivery system of ranibizumab (implanted)	80% of patients in 179-pt Phase II study went six months or longer between device implant and first required refill; high dose group (100mg/mL) had similar vision outcomes to monthly ranibizumab injections; 360-pt Phase III efficacy (ARCHWAY) and 500-pt long-term safety study (PORTAL) started in H218.	Top-line data (ARCHWAY) in 2021 or 2022

Source: Company reports

Next-generation NVAMD therapies

Below we provide more detail on some of the more novel treatment approaches being investigated for NVAMD. In our view, these may have not yet demonstrated as comprehensive indications of safety and efficacy as the previously listed product candidates (which are in Phase III or registration stages), but they have more novel mechanisms of action or approaches, that can fit into one of the following three criteria:

- unique treatment mechanistic pathway allowing for a potentially more effective treatment in NVAMD patients, particularly if used in combination with existing anti-VEGF-A therapy; this approach could potentially also be used on patients currently refractory or not optimally treated with anti-VEGF-A therapy alone
- novel pharmacological approaches enabling longer duration of action, resulting in less frequent IVT dosing, or
- employing potentially less invasive or even non-invasive drug delivery approaches, improving patient compliance and potentially enabling self-administration in some cases.

Below we review some of the leading pipeline developments in these categories.

Exhibit 3: Next-generation product candidates for NVAMD (or possibly also DME/DR)

Product candidate	Company	Development stage	Mechanism	Next milestones
Unique mechanistic pathway potentially providing more effective treatment and/or additive benefit to anti-VEGF-A therapy				
OPT-302	Opthea	Phase IIb	VEGF-C/D 'trap' that blocks VEGF-C and VEGF-D	Data expected in Q419
DE-122 (carotuximab)	Santen/Tracon	Phase II	Antibody to endoglin, a protein overexpressed on endothelium cells that is essential for angiogenesis	Data expected in H120
ICON-4	Iconic Therapeutics	Pre-IND	Immunoconjugate fusion protein that binds to Tissue Factor (TF), targeting inflammation and CNV formation	Investigational New Drug (IND) application submission in 2020
Candidates aiming to extend therapeutic doses and reduce dosing frequency				
KSI-301	Kodiak Sciences	Phase Ib	Targeting VEGF using proprietary antibody biopolymer conjugate (ABC) platform	Phase Ib data H219; start Phase II in Q319
GB-102 (sunitinib depot)	Graybug Vision	Phase II	Tyrosine kinase inhibitor (TKI) that blocks several receptors associated with NVAMD progression	Phase IIb study to start in H219
RGX-314	Regenxbio	Phase I/IIa	Gene therapy using AAV8 vector to deliver a gene encoding for a mAB/protein that neutralizes VEGF activity	Data in H219 and start Phase IIb in H219
OXB-201	Oxford Biomedica	Phase I	Gene therapy using lentiviral vector derived from the Equine Infectious Anemia Virus (EIAV), aiming to deliver two genes encoding the anti-angiogenic proteins endostatin and angiostatin	Phase I study complete; firm may seek partnership opportunities before proceeding with future trials
AVDM-022	Adverum	Phase I	Gene therapy using AAV capsid vector to deliver genetic cassette expressing the anti-VEGF aflibercept drug	Data expected from first cohort of study in H219
Topical or non-invasive treatment candidates				
PAN-90806	PanOptica	Phase I/II	Topically applied small molecule that blocks activation of VEGF receptor 2 through inhibition of the receptor's tyrosine kinase activity	Data expected in mid-2019
SF0166	SciFluor/Allied Minds	Phase I/II	Fluorinated small molecule topical Integrin $\alpha\beta 3$ antagonist, blocking angiogenesis and reducing vascular permeability	Start Phase II study in DME; funding required

Source: Edison Investment Research

Approaches for targeting NVAMD patients refractory to anti-VEGF-A

OPT-302. Rather than targeting VEGF-A, Opthea's (OPT, ASX) OPT-302 blocks two other proteins of the VEGF family, namely VEGF-C and VEGF-D (it is a VEGF-C/D 'trap'). OPT-302 is intended to be used in conjunction with existing SoC anti-VEGF-A therapies in NVAMD and DME patients who are treatment naïve and potentially also in patients who respond sub-optimally or become refractory to existing treatments. Combination therapy of OPT-302 and a VEGF-A inhibitor is expected to achieve a more complete blockage of the mechanistic pathways involved in disease progression. In a 51-patient [Phase I/IIa study](#) evaluating OPT-302 in NVAMD, the mean gain in BCVA in treatment-naïve patients receiving the drug in combination with ranibizumab, from baseline at week 12, was +10.8 letters (n=18). While early results are promising, there was no standalone ranibizumab control arm, which challenges the assessment of OPT-302's additive contribution. Recruitment for a ranibizumab plus sham-controlled [366-patient Phase IIb NVAMD study](#) was completed in November 2018. The study is designed to assess whether the addition of OPT-302 to ranibizumab over a six-month period improves outcomes, including BCVA, in NVAMD patients. Top-line data is expected in Q419.

DE-122 (carotuximab). Santen Pharma (4536, Tokyo) is developing DE-122 (carotuximab), in-licensed from Tracon Pharma, for refractory NVAMD. Carotuximab is a novel antibody to endoglin, a protein overexpressed on endothelium cells that is essential for angiogenesis, and that is upregulated by anti-VEGF drugs. [Top-line Phase I/II results](#) of DE-122 for refractory NVAMD presented in 2018 showed that in addition to a lack of serious adverse events (SAE), among the 12 treated subjects, there were also signs of treatment activity as shown by mean change in central retinal subfield thickness (CST) as shown by spectral domain optical coherence tomography (SD-OCT). A [76-patient Phase II study](#) (AVANTE) is underway and will evaluate IVT injections in combination with ranibizumab vs ranibizumab monotherapy, with results expected in H120.

ICON-4. Privately held Iconic Therapeutics believes that Tissue Factor (TF) plays an important role in inflammation and CNV formation and is advancing its next-generation antibody to TF, ICON-4, to target TF in NVAMD patients. TF is a naturally occurring protein in humans that plays an important role in the coagulation cascade, but when overexpressed, it provokes inflammation and

angiogenesis. TF overexpression plays a pivotal role in multiple diseases, including NVAMD and cancer. The firm states that many biopharma firms have attempted to target and inhibit TF overexpression, but have been unsuccessful due to safety concerns. Iconic has developed a suite of proprietary molecules that strongly bind and inhibit TF, and are expected to be free of the liabilities associated with prior approaches. The firm's initial molecule, ICON-1, a first-generation TF blocker, was tested in an 88-patient [Phase II study \(EMERGE\)](#), which assessed newly diagnosed NVAMD patients who were followed for six months. The trial showed favourable safety and tolerability as well as signs of durable biological activity on CNV lesions when administered in combination with ranibizumab. Iconic is developing a second-generation anti-TF mAb, ICON-4, which has shown in preclinical CNV lesions a stronger effect in both monotherapy and in combination therapy, as well as improved potency and the ability to be delivered in higher doses. This molecule will be advanced in further clinical trials for NVAMD, as an IND submission expected in 2020. The company believes ICON-4 can help generate more durable treatment outcomes than anti-VEGF therapy alone and may provide additional therapeutic benefit in patients who sub-optimally respond to anti-VEGF treatments.

Therapeutic candidates aiming to deliver longer treatment effects

KSI-301. Kodiak Sciences (KOD, NASDAQ) is developing KSI-301, a biologic therapy targeting VEGF-A based on the firm's proprietary antibody biopolymer conjugate (ABC) platform, which is intended to provide an extended ocular half-life, thereby potentially allowing the condition to be well-controlled with IVT treatments dosed as infrequently as every three, four or even five months. The firm initiated a first-in-human, single ascending dose KSI-301 US Phase Ia clinical study in nine patients with severe (pre-treated) DME in July 2018. The last visit (12-week) data demonstrated safety and durability of responses following the single dose of KSI-301. Notably, 12 weeks after a single dose, median vision improvement from baseline of almost two lines of vision (nine eye chart letters) and median improvement in retinal edema of 121 microns were achieved across all three dose levels tested. No dose-limiting toxicities, drug-related SAEs or intraocular inflammation were observed through each patient's last visit at 12 weeks.

In Q418, the firm initiated an open-label, multiple-dose [US Phase Ib study](#) of KSI-301 in patients with anti-VEGF treatment-naïve NVAMD, DME and RVO. The firm plans to recruit 90 patients in total; all patients receive three loading doses once a month and are then followed monthly with further KSI-301 treatments determined by disease-specific retreatment criteria. All patients will be evaluated through 36 weeks. The firm indicates that to date, it has observed bioactivity in all three diseases tested and has not observed signs of intraocular inflammation in the multiple-dose setting, with more than 75 doses administered in total. It expects complete enrolment of these cohorts of patients in 2019. The firm intends to present ongoing data from the Phase Ib study at medical and investor meetings starting in the second half of 2019.

Kodiak expects to be enrolling patients in a global Phase II study of KSI-301 in NVAMD in Q319. This study is intended to evaluate the non-inferiority of intravitreal KSI-301 dosed on an every 12-, 16- or 20-week regimen compared to standard of care aflibercept dosed every eight weeks. The FDA indicated that this study, if successful, can be supportive of a marketing application for KSI-301, and the firm is designing and intending to execute this Phase II study as a pivotal study, with an option for an interim analysis in 2020. A primary data readout is expected in 2021.

GB-102. Privately held Graybug Vision is advancing GB-102, a depot formulation of sunitinib intended for IVT implantation. The formulation consists of bioabsorbable microparticles made from poly-lactic-co-glycolic acid (PLGA) and methoxy-polyethylene glycol (mPEG)-PLGA. The firm indicates that the mPEG component is a proprietary hydrophilic, biocompatible surface treatment designed to eliminate inflammation typically associated with ocular PLGA administration. The proprietary formulation allows for the microparticles to aggregate into a single biodegradable depot in the vitreous situated away from the visual axis. The microparticles gradually release sunitinib

malate and biodegrade into lactic and glycolic acid, which are naturally cleared from the body. Sunitinib is a small molecule receptor tyrosine kinase inhibitor (TKI) that blocks several intracellular receptors known to be associated with NVAMD progression (angiogenesis, proliferation, vascular permeability and fibrosis), such as VEGF receptors 1, -2 and -3. The firm also suggests sunitinib has shown neuroprotective effects of retinal ganglion cells (RGCs) and photoreceptors in preclinical models of neuronal injury.

The candidate is designed to potentially provide a standalone control for NVAMD with potentially as little as twice-yearly dosing. Graybug believes that inhibition of multiple receptors associated with CNV may provide a more complete blockade of the angiogenesis process associated with NVAMD compared to currently available monotherapy agents (aflibercept, bevacizumab or ranibizumab) and without the need for co-administered IVT agents. However, we note that, despite having been approved to treat cancers since 2006 and a well-studied molecule, to date no sunitinib product has yet been approved in NVAMD.

In early 2019, the company announced positive top-line results for the [ADAGIO study](#), a Phase I/IIa study of IVT GB-102 (sunitinib malate) in NVAMD patients. In addition to meeting safety and tolerability endpoints without dose-limiting toxicities, SAEs or inflammation, there was evidence of maintenance of visual acuity and central retinal thickness over at least six months as measured by eye chart readings and OCT. 88% and 68% of evaluable patients were maintained only on a single dose of GB-102 at three and six months, respectively. Planning for the [GB-102 Phase IIb clinical study](#) is underway and enrolment is planned to start in H219.

Gene therapies for prolonging NVAMD treatment

Some companies are working on gene therapies to provide a self-sustaining anti-VEGF response following the instillation of the relevant genetic encoding materials. Adverum Biotechnologies (ADVM, Nasdaq) and RegenxBio (RGNX, Nasdaq) are developing separate clinical-stage gene therapy candidates for NVAMD, with the aim of delivering anti-VEGF genetic coding information for sustained treatment effects, through their proprietary adeno-associated virus (AAV) vector systems. Oxford Biomedica's (OXB, LSE) OXB-201 uses the firm's proprietary LentiVector technology (which uses the lentiviral vector derived from the Equine Infectious Anemia Virus), to deliver two genes encoding the anti-angiogenic proteins endostatin and angiostatin. The potential promise of any of these gene therapy approaches is to provide a single IVT treatment that can provide a lasting (such as over 12 months) adequate anti-VEGF effect in a large subset of NVAMD patients (without requiring additional treatment over such a period). Below we provide details on each of them.

RGX-314. Regenxbio is developing RGX-314 for the treatment of NVAMD. RGX-314 is being developed as a novel, one-time sub-retinal treatment for NVAMD that is based on the firm's proprietary NAV AAV gene delivery platform and includes applying an AAV8 vector containing a gene encoding for a monoclonal antibody fragment protein that is designed to neutralise VEGF activity. The sub-retinal treatment procedure is more invasive than IVT injection approaches. According to principal investigator Jeffrey Heier, MD, of Ophthalmic Consultants of Boston, the [sub-retinal treatment](#) involves a conventional three-port, small-gauge core vitrectomy procedure and if required, the inducement of a posterior vitreous detachment. The gene therapy product is then introduced into the subretinal space using a small-gauge, subretinal cannula. The procedure is similar to that used for other approved retinal gene therapies, such as voretigene neparvovec (Luxturna, Spark Therapeutics). Compared to intravitreal delivery, subretinal delivery is anticipated to provide broader retinal coverage and higher protein expression, potentially leading to higher and more durable gene expression.

In May 2019 Regenxbio announced that it completed dosing across all five cohorts in the eight-site, open-label [US Phase I/IIa clinical trial](#) of RGX-314 in NVAMD (in a patient population who were previously treated with anti-VEGF injections). The trial began in Q217 and includes 42 dosed subjects across five escalating-dose cohorts, and each subject received a single dose of RGX-314

administered by subretinal delivery. The trial design included doses of 3×10^9 (Cohort 1), 1×10^{10} (Cohort 2), 6×10^{10} (Cohort 3), 1.6×10^{11} (Cohort 4) and 2.5×10^{11} (Cohort 5) genome copies (GC)/eye.

Regenxbio reported interim data in April 2019 from the study (prior to full recruitment), which stated the product was well-tolerated across all cohorts to date, with no drug-related SAEs. In particular, the treatment showed a durable treatment response from Cohort 3 of the study, at 12 months. Sustained and durable RGX-314 intraocular protein expression was detected at one year in all subjects in cohort 3 as measured by electrochemiluminescence immunoassay (ECL).

Across all six subjects in cohort 3 there was a mean BCVA improvement of +5 letters and mean CRT decrease by $39 \mu\text{m}$ from baseline at one year. Cohort 3 subjects received a low number of anti-VEGF injections following the administration of RGX-314, with a mean of 2.3 injections over the 12-month period following RGX-314 instillation. 50% of subjects (3/6) in cohort 3 remained injection-free at 12 months (ie not requiring 'rescue' conventional anti-VEGF IVT therapy) and with durable protein and clinical effect observed on BCVA and central retinal thickness (CRT). Among these three patients, mean BCVA improved by +10 letters (vs baseline) and mean CRT decreased by $59 \mu\text{m}$ from baseline in these subjects at one year.

The firm expects to report top-line data from all five cohorts by YE19, and plans to initiate a Phase IIb study in NVAMD before YE19 (as well as file an IND to study RGX-314 in DR).

ADVM-022. Adverum Biotechnologies is developing a clinical gene therapy candidate ADVM-022 (AAV.7m8-aflibercept). ADVM-022 uses a proprietary AAV capsid vector (AAV.7m8) to deliver a proprietary expression genetic cassette, which expresses the aflibercept drug. ADVM-022 is administered as a single IVT injection and is intended to minimise the treatment burden of repeated anti-VEGF injections. The firm reports that in preclinical non-human primate (NHP) studies, a single IVT administration of ADVM-022 provided sustained expression of aflibercept for at least thirty months at levels comparable to those experienced three to four weeks post-injection of aflibercept protein.

In September 2018, Adverum received fast track designation for ADVM-022 in NVAMD from the FDA. The company is currently assessing ADVM-022 in a [Phase I study \(OPTIC\)](#), which started in H218. The OPTIC trial is designed to be a multi-centre, open-label, Phase I, dose-escalation safety trial in patients with NVAMD who previously demonstrated responsiveness to anti-VEGF treatment. The study was designed to evaluate three dose levels of ADVM-022 administered as a single IVT injection.

In April 2019 the firm announced it completed enrolment and dosing of patients (n=6) in the first cohort (6×10^{11} vg/eye) in the OPTIC trial. The independent data monitoring committee (DMC) determined that enrolment and dosing of patients in the second cohort could proceed, based on a review of the preliminary safety data from the first cohort, which showed no SAEs or dose-limiting toxicities (DLTs). The firm in April 2019 also received a notification from the FDA requesting additional chemistry, manufacturing and controls (CMC) information and requirements on the ADVM-022 manufacturing process, and placing the study and IND on clinical hold. In May 2019, the clinical hold was lifted for the second cohort of the study, allowing dose escalation to 2×10^{12} vg/eye, but the firm decided, based on a 'robust preliminary anatomical response observed to date in the first cohort', to begin dosing the second six-patient cohort at a lower dose of 2×10^{11} vg/eye, and dosed the first patient in the second cohort in June 2019. The firm indicates that it believes the dose of the first cohort (6×10^{11} vg/eye) has demonstrated the potential to provide sustained efficacy following a single IVT injection.

While the FDA has lifted the clinical hold on the second cohort, ADVM-022 remains on partial clinical hold for dosing patients in the third originally planned cohort (with the highest dose of 6×10^{12} vg/eye). Adverum indicates it no longer plans to dose at this highest level, based on the robust

preliminary anatomical response observed in the first cohort of patients. The firm plans to report data on the 24-week primary and secondary outcomes from this first cohort of patients on [12 September 2019](#), as part of the Annual Retina Society Meeting in London, UK

OXB-201. Rather than target VEGF-A directly, Oxford Biomedica's OXB-201 delivers two genes that encode for the anti-angiogenic proteins endostatin and angiostatin. The firm believes these proteins act as part of the body's own natural 'brakes' for physiological neovascularisation and preclinical studies showed that increased expression of them in animal models suppressed CNV. Results from a 21-patient [Phase I study](#) showed that OXB-201 met the primary endpoints of safety and tolerability and also demonstrated some signs of clinical benefit. There was a reduction in vascular leakage and a dose-dependent sustained increase in endostatin and angiostatin expression and secretion. For some subjects, therapeutic gene expression was maintained for up to four years. Little to no improvement in VA was expected, as patients had generally low incoming VA at baseline; three out of the four cohorts had baseline VA requirements of no better than 20/200, or 10%, in the study eye, and the final, maximum-tolerated-dose cohort required an incoming VA no better than 20/80, or 25%. For all 15 subjects in cohorts three and four (who received the highest vector doses), there was no mean change from baseline BCVA at week 48. Importantly, an ongoing long-term follow-up [study](#) has highlighted stable expression of both endostatin and angiostatin out to six years, which underlines an effective duration of response from the firm's platform. OXB is looking for options to advance OXB-201, which can include partnering or out-licensing.

Topical delivery for NVAMD – a potential holy grail

Given the risk of endophthalmitis associated with IVT treatments, a real breakthrough would be if regularly recurring NVAMD therapy could be performed through non-invasive means, thereby eliminating endophthalmitis risks. Since a non-invasive topical delivery process could be self-administered, there could also be savings in medical procedure costs and improved patient compliance. If effective and somewhat comparable to the efficacy of current leading IVT Anti-VEGF-A treatments, topical therapy could capture a chunk of the market, by reducing the burden of IVT treatments in a sizeable segment of the NVAMD population. We estimate it is unlikely that topical therapies can exceed the efficacy of current (and upcoming) IVT treatments, but it is foreseeable that if a topical treatment obtains approval, potentially up to 25–50% of NVAMD patients (who are currently well-managed by periodic IVT treatments) could switch to a topical treatment and then either potentially be adequately managed without requiring further IVT treatments, or more likely, could reduce the need for IVT therapy to a once-yearly (or even more infrequent) basis. Two topical candidates having already shown some early human data are PAN-90806 and SF0166.

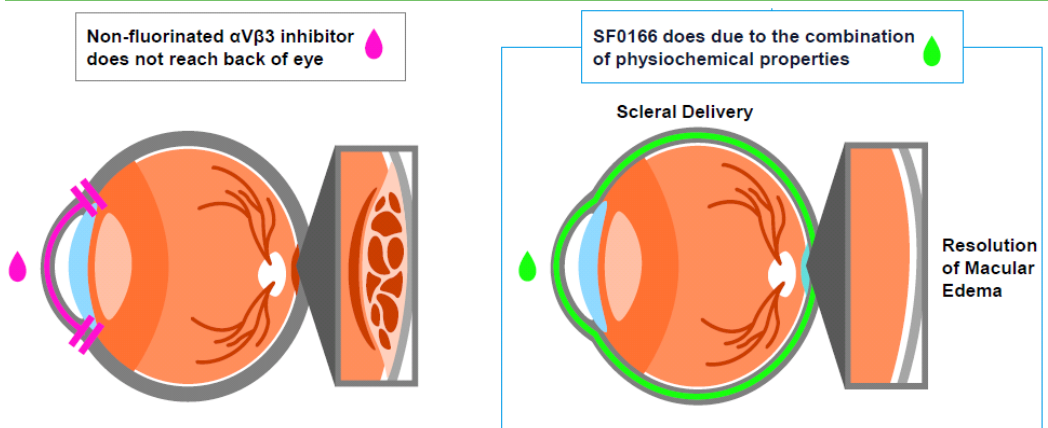
PAN-90806. Privately held PanOptica's PAN-90806 is a novel, topically applied eyedrop intended for once daily application, for NVAMD or other neovascular eye diseases (like DME). PAN-90806 is a small molecule that blocks activation of the VEGF receptor 2 through inhibition of the receptor's tyrosine kinase activity. According to the firm, unlike anti-VEGF A mABs, PAN-90806 blocks the effect of VEGF at the receptor and does not bind VEGF-A itself.

In 2016, PanOptica reported results from the first Phase I/II clinical trial of PAN-90806, which the firm indicated suggested signals of positive biological response to topical PAN-90806 in approximately 45–50% of 20 patients treated for up to eight weeks, including improvement of vascular leakage, lesion morphology and vision. Specific VA improvements were not provided in the firm's press release. However, the formulation was associated with corneal adverse events (eg edema). In May 2018, the firm announced that patient dosing began in a [Phase I/II dose-ranging clinical trial](#) of PAN-90806, investigating its new suspension formulation of PAN-90806 as monotherapy (once-daily), for up to three months, in a masked study involving 60 newly diagnosed

patients with NVAMD, randomised to one of three dose strengths at sites in the US and the EU. Results for the ongoing study are expected in or around mid-2019.

SF0166. SciFluor Life Sciences (a subsidiary of Allied Minds (ALM, LSE), a research client of Edison Investment Research) has focused on applying fluorination chemistry to design and test fluorine-containing small molecule drug candidates that can demonstrate improved potency and pharmacokinetic (PK) properties relative to existing drugs. Its lead drug, SF0166, is applied topically and has been studied in two separate multi-centre, randomised, 44-patient Phase I/II trials, in patients with **DME** and in patients with **NVAMD**. SF0166 is the result of a drug discovery effort to develop small molecule Integrin $\alpha\beta3$ antagonists with the appropriate physiochemical properties to allow distribution to the posterior segment of the eye (retina) after topical administration in an ophthalmic solution. Generally, it is extremely challenging to deliver therapeutics to the back of the eye in a non-invasive manner, given the barriers involved (anterior chamber and vitreous for topical doses, or blood-retina barrier for oral/systemic administration). SF0166 is a fluorinated descendent (that is, a fluorine side chain was incorporated into the molecular structure) of a precursor $\alpha\beta3$ antagonist originally developed by Merck to treat osteoporosis (the development was abandoned prior to completion). A non-fluorinated $\alpha\beta3$ inhibitor would not reach the back of the eye upon topical instillation, but SF0166's fluorine component enables a topically administered drop to travel through the sclera into the retina (and not through the vitreous), according to the firm.

Exhibit 4: SF0166 distributes to the retina via sclera and not through vitreous humour



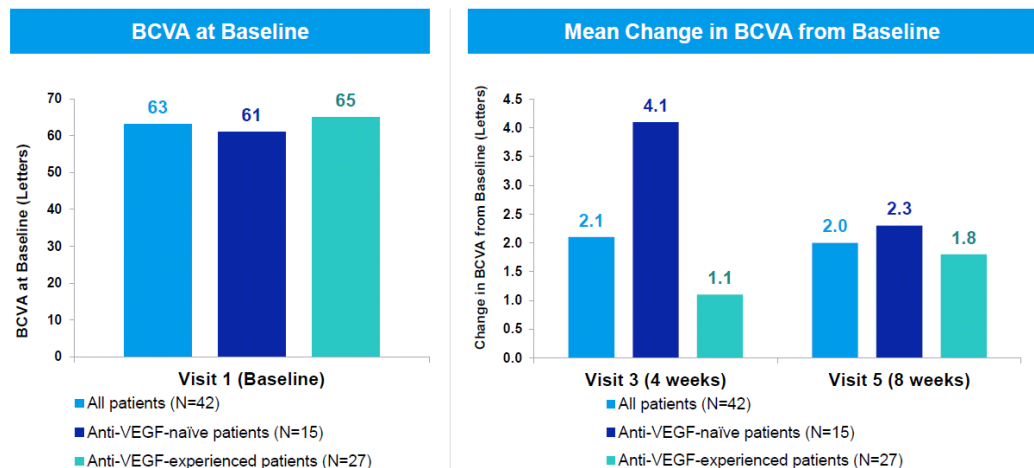
Source: SciFluor Life Sciences

SF0166 selectively inhibits Integrin $\alpha\beta3$ and in doing so is believed to inhibit multiple factors involved with DME and NVAMD disease progression, such as angiogenesis, increased vascular permeability, and endothelial cell adhesion and proliferation. Specifically, SF0166 is intended to block VEGF-A, as well as inhibit VEGF-R2 phosphorylation and VEGF-stimulated adhesion, proliferation and migration of endothelial cells.

Preclinical data (rabbits) showed that a single dose of topically applied SF0166 distributes to the sclera, retina and choroid (the eye's posterior structures) and remains a minimum of 12 hours. SciFluor conducted two 44-patient Phase I/II studies to assess safety and early signs of efficacy; each study tested SF0166 dosed twice-daily for 28 days (with a 28-day follow-up period). In September 2017 it reported data from the 40 patients who completed the Phase I/II DME study. SF0166 demonstrated biological activity in both dose ranges, with 48% (19/40) of evaluable patients showing a reduction in retinal thickness (RT) at the end of study (day 56). Improvements in visual acuity (VA) were also shown but not quantified in public data. There were no drug-related SAEs observed; ocular adverse events were all mild, and were seen in six patients with one considered to be possibly drug-related. In December 2017 SciFluor reported data from the NVAMD study. In addition to showing similar safety results to the DME study, investigators reported that SF0166 demonstrated signs of relevant biological activity in NVAMD. According to a panel of three

retinal physicians, nine of the 42 patients who completed the study had decreases in RT and/or subretinal fluid by spectral domain optical coherence tomography (SD-OCT).¹⁴ It was reported that the mean improvement in VA during the treatment period among the 15 recruited treatment-naïve patients, was approximately 4.1 letters at four weeks (end of treatment) and then 2.3 letters at eight weeks (end of study).

Exhibit 5: Effects on visual acuity of Phase I/II SF0166 study in wet-AMD



Source: SciFluor Life Sciences reports

As a means of comparison, we note that ranibizumab's Phase III efficacy study in NVAMD showed 31% to 37% experienced a clinically significant improvement in vision, defined as gaining 15 or more letters at 12 months. Ultimately, we estimate a longer study (eg at least six months of treatment) would be needed to compare SF0166 to an existing approved anti-VEGF-A drug.

SciFluor is working on designing its next clinical study for SF0166, which is a larger Phase II DME study that can potentially provide more comprehensive efficacy signals. Positive data could likely lead to subsequent studies in NVAMD. We note that parent company Allied Minds has impaired its valuation of the SciFluor division due to a prolonged inability to attract new external financing, and limited cash available to fund its future operations.

Dry AMD treatment is the next frontier

Dry-AMD represents the largest untapped eyecare market. As stated earlier, dry-AMD's prevalence is substantially higher than NVAMD, but this market captures a tiny fraction of NVAMD's revenue given the lack of broadly accepted approved pharmaceutical or medical treatments. Currently, the biopharma industry's commercial stake in dry-AMD is mostly limited to the sale of OTC dietary supplements containing formulations of antioxidants (such as lutein, vitamins C and E, beta-carotene, zinc, etc), which have been shown in some longitudinal studies (namely [AREDS](#) and [AREDS2](#)) to have very marginal effects on disease progression.

However, given the prevalence of dry-AMD market, it is foreseeable that this market could easily eclipse the >\$5.25bn size of the NVAMD market if treatments can be shown to have definitive efficacy and obtain approval in the largest markets (such as the US). The GA-AMD subsegment (c 1.1 million patients in the US alone) is the obvious low-hanging fruit within the dry-AMD segment,

¹⁴ Optical coherence tomography (OCT) is an imaging technique that uses coherent light to capture micrometre-resolution, two- and three-dimensional images from biological media. It is particularly well-suited for assessing retinal tissue and the current gold-standard for measuring the thickness of retinal structures, for the assessment of macular edema or leakage, as well as for the assessment of vascular changes associated with wet-AMD.

as many of these patients already have significant visual impairment but remain at risk for more severe losses, so they would be very keen to undergo a treatment (if one becomes available) to prevent more profound loss (such as legal blindness) that would affect their autonomy or ability to work or drive. Given that GA-AMD prevalence is comparable to NVAMD, the GA-AMD subsegment alone could approach the current size of the NVAMD market.

Most dry-AMD treatments under development are targeting the most-at-need stage (GA-AMD) but if a potential therapy could show some success at earlier diseases stages, we believe this could also capture a significant market. As stated earlier, while a large percentage of mild to moderate dry-AMD patients will not progress to the visually debilitating GA (or NVAMD) forms, if a treatment can be shown to prevent progression to advanced AMD (more effectively than current SoC, which consists mainly of lifestyle modifications and dietary supplements), we believe that a significant proportion of such patients would be interested in such a preventative therapy.

Dry-AMD requires a different therapeutic approach

To recap, VEGF-A inhibition and other anti-angiogenic drugs can provide visual recovery and stabilise NVAMD (if treatment is maintained). However, while there is some meaningful overlap between the underlying mechanisms/pathophysiologies of dry-AMD and NVAMD, the conditions remain clinically distinct in that the effective NVAMD (anti-VEGF-A) treatment does not appear to have any beneficial effect in dry-AMD or GA.

Novel approaches are being investigated to target underlying mechanisms involved with dry-AMD (which, if addressed, could potentially also be used prior to the onset of the condition's possible transition to NVAMD stage). All of the current leading candidates in later-stage development are targeting inflammatory factors (such as through complement factor targeting) and/or oxidative stress-related mechanisms of action, to decelerate disease progression.

Exhibit 6: Intermediate to late-stage pipeline in dry-AMD

Product candidate	Company	Development stage	Mechanism	Next milestones
Therapeutics administered through intravitreal injection				
APL-2	Apellis Pharmaceuticals	Phase III	Inhibit complement factor C3 activation and reduce inflammation	Complete enrolment of both Phase III studies in Q120; top-line data in 2021
Zimura (avacincaptad pegol)	Iveric Bio	Phase IIb	Inhibit complement factor C5 activation and reduce inflammasome activation and inflammation	Data expected in Q419
Risuteganib	Allegro Ophthalmics	Phase II	Target integrin receptors $\alpha v\beta 5$, $\alpha 5\beta 1$ (associated with angiogenesis and vascular leakage) and $\alpha M\beta 2$ (associated with inflammation)	Top-line positive Phase II data released in June 2019; full study results to be reported at American Society of Retina Specialists (ASRS) meeting 2019 on 27 July
Elamipretide	Stealth Biotherapeutics	Phase II	Binds to cardiolipin within inner mitochondrial membrane to increase mitochondrial respiration and reduces formation of reactive oxygen species (ROS), potentially attenuating oxidative stress	Data expected in H220
Wavelength/light-based therapy				
Photobiomodulation (PBM)	LumiThera	CE mark	Targeted light delivery may activate of mitochondrial respiratory chain components, which may promote cellular proliferation and cell protection	US IDE Study (LIGHTSITE III) to start in H219
2RT nanopulse laser	Ellex	CE mark	Targeted laser therapy to select RPE cells to promote an extracellular repair mechanism within the retina	Discussions with FDA on registration pathway or IDE study

Source: Edison Investment Research

Targeting inflammation through the complement system

As inflammation is one of the primary causes of RPE and photoreceptor damage in dry-AMD, and excessive activation (or dysregulation) of the complement system can contribute to or reinforce the inflammatory response in dry-AMD, multiple investigators and firms are assessing ways to modulate or control aspects of one or more complement pathways as a means to control the

disease. Below we discuss two clinical-stage products targeting the complement system, APL-2 and Zimura.

APL-2. One of the leading (in terms of having demonstrated human proof-of-concept) candidates for dry-AMD or GA is Apellis Pharmaceuticals' (APLS, Nasdaq) APL-2 candidate. Apellis is developing therapies that target the complement system in inflammatory processes. APL-2 is delivered through IVT to inhibit complement factor C3 activation with the aim of treating GA. APL-2 is a synthetic cyclic peptide conjugated to a polyethylene glycol (PEG) polymer that binds specifically to C3, which, according to the company, effectively blocks all three pathways of complement activation (classical, lectin and alternative). As inflammation and the local activation of the complement system may play an important role in AMD pathogenesis, targeting the complement system in this pathway is hypothesised as a method of slowing disease progression.

In the multicentre, single-masked [Phase II FILLY trial](#) (n=246) reported in 2017, APL-2 met its primary endpoint. At 12 months, APL-2, administered monthly via IVT, showed a 29% (p=0.008) reduction in the rate of GA lesion growth compared to sham. With every other month administration, a 20% (p=0.067) reduction compared to sham was shown.

Apellis received FDA fast track designation in July 2018 for the APL-2 candidate and started recruitment for two separate 600-patient Phase III pivotal studies in GA, [DERBY](#) and [OAKS](#), in H218. The primary endpoint will be the change from baseline to month 12 in total area of GA lesion(s) in the study eye (in mm²) based on Fundus Autofluorescence (FAF) diagnostics. However, recruitment was voluntarily suspended in October 2018 due to four cases of non-infectious inflammation in patients treated from a single manufacturing lot of APL-2 drug product in the Phase III program.

In March 2019, the firm announced that with the agreement of an independent safety monitoring committee, it resumed enrolment in its two Phase III APL-2 GA trials and it expects to have both trials fully enrolled by the end of Q120. The firm indicated that following an investigation, it believes the likely source of inflammation resided in an impurity in the active pharmaceutical ingredient (API) that was introduced during manufacturing scale-up to produce commercial lot sizes. Apellis has since modified its manufacturing process in order to eliminate the impurity and has manufactured sufficient supply of APL-2 utilising the modified manufacturing process to conduct the entire Phase III GA program. The APL-2 drug product produced from the modified manufacturing process had already been introduced into the firm's ongoing Phase Ib trial in low-vision patients with GA, and none of those patients had experienced inflammation to date.

Zimura (avacincaptad pegol). Iveric Bio (ISEE, Nasdaq; previously Ophthotech) is advancing Zimura (avacincaptad pegol), a C5 complement inhibitor, for GA as well as for Stargardt disease (an unrelated genetic retinal disease that leads to blindness in early adulthood). Complement factor C5 is a central component of the complement cascade believed to play a role in dry-AMD and Stargardt disease. Zimura is intended to target and inhibit the cleavage of complement protein C5 and the formation of the terminal fragments, C5a and C5b. By inhibiting the formation of complement system terminal fragments, the drug candidate may decrease the activation of inflammasomes (multiprotein complexes responsible for the activation of inflammatory responses) and potentially avoid or slow down RPE degeneration. A 286-patient, sham-controlled randomised [Phase IIb study](#) of Zimura monotherapy in GA-AMD is currently underway, with data expected in Q419 (enrolment completed in October 2018).

Targeting oxidative stress factors through integrins – Allegro's risuteganib

Privately held Allegro Ophthalmics is developing **risuteganib** (Luminate) for both dry-AMD and DME. Risuteganib is an integrin inhibitor (a comparable approach to SciFluor's SF0166, also an integrin inhibitor). Risuteganib is believed to selectively target three integrin receptors that are upregulated in response to oxidative stress, with minimal effects on 'unstressed retinas'. Integrins

are cell surface receptor proteins attached to cell membranes with structural (cell adhesion) and/or functional (eg cell signalling pathways) roles. Risuteganib is believed to target integrin receptors $\alpha v\beta 5$, $\alpha 5\beta 1$ (both associated with angiogenesis and vascular leakage) and $\alpha M\beta 2$ (associated with inflammation).

Allegro states that preclinical studies demonstrate that risuteganib localises and persists for several months in the RPE. Altogether, the firm believes that risuteganib can potentially regulate oxidative stress-related effects upstream before they can exert damaging effects in dry-AMD or DME.

[Positive results](#) for risuteganib were reported in June 2019 in a 40-patient, double-blinded, cross-over [Phase II study in intermediate-stage dry-AMD](#). We highlight that this study assessed patients in intermediate-stage dry-AMD, thus prior to the GA stages being assessed in the ongoing APL-2 and Zimura studies. In the trial, 25 patients underwent IVT risuteganib, and 15 received a sham injection. After 16 weeks, the treatment arm received a second dose and the sham arm crossed over and received a single risuteganib dose. The trial met its primary endpoint with 48% of patients in the risuteganib arm gaining at least 8 letters of vision at week 28 compared to baseline. The primary endpoint was the percentage of the population with ≥ 8 letters Early Treatment Diabetic Retinopathy Study¹⁵ BCVA gain from baseline to week 28 in the risuteganib arm versus from baseline to week 12 in the sham arm. Risuteganib was found to be safe with no reported drug-related SAEs. Secondary outcomes, including microperimetry, colour vision and low luminance visual acuity, will be released in Q319.

Overall, the oxidative stress mechanistic pathway targeted by risuteganib for dry-AMD is distinct from the VEGF-A pathways that typical NVAMD therapies approach and results from the current study provided some hints as to whether the approach may be of benefit in intermediate-stage dry-AMD (ie prior to the onset of GA).

Allegro also plans to start a Phase III DME study in H219. In 2017, it reported results from the second stage (n=80) of its [Phase II study in DME](#). This study met its primary endpoint of non-inferiority to bevacizumab in mean change in BCVA at 20 weeks when risuteganib was used in a sequential therapy algorithm, with a single bevacizumab pre-treatment (week 0), followed by three 1.0mg risuteganib injections (at weeks one, four and eight) and 12 weeks off treatment (resulting in 7.1 letter gains in BCVA), compared to five injections given every four weeks with bevacizumab (resulting in 6.7 letter gains). Stage 1 of the Phase II study (n=136) also met its primary endpoint.

Targeting ROS and oxidative stress through mitochondria

Stealth BioTherapeutics (MITO, Nasdaq) is developing **elamipretide** for GA-AMD, as well as three primary mitochondrial diseases: primary mitochondrial myopathy, Barth syndrome and Leber's hereditary optic neuropathy (LHON). The intended mechanism of action is to target oxidative stress, as elamipretide is a peptide compound that readily penetrates cell membranes, and pinpoints the inner mitochondrial membrane where it binds reversibly to cardiolipin. In preclinical or clinical studies, the firm observed that elamipretide increases mitochondrial respiration, improves the electron transport chain function in the respiratory cycle, and increase ATP (cellular energy) production and reduces formation of pathogenic reactive oxygen species (ROS) levels. The firm states that the elamipretide-cardiolipin association effectively improves mitochondrial function and potentially reverses oxidative stress, which could potentially treat GA-AMD. In April 2019, positive data from the [ReCLAIM Phase I](#) study in patients in GA-AMD were reported.

ReCLAIM was a Phase I, open-label study evaluating daily subcutaneous elamipretide for 24 weeks in patients with dry-AMD with either high-risk drusen but no GA, or with GA that did not affect

¹⁵ Early Treatment Diabetic Retinopathy Study VA chart is a specific eye chart used for measuring VA levels, and is often used in research settings, particularly in clinical studies involving ocular diseases where the VA is lower than normal. Alternative VA charts also used in clinical or research settings include Snellen and LogMAR charts.

the central macula (ie non-central GA). Patients with non-central GA (n=15) showed a mean increase in low-luminance visual acuity, or clarity of vision in low light, of 5.4 ± 7.9 letters (baseline of 43.9 ± 19.8 letters; $p=0.025$) and BCVA, of 4.6 ± 5.1 letters (baseline of 73.7 ± 9.5 letters; $p=0.003$). The FDA has granted fast track designations for elamipretide for the treatment of dry-AMD and LHON. In H119 the company started a 180-patient, placebo-controlled [ReCLAIM-2 Phase II study](#) in patients with central GA-AMD, with data expected in H220.

Wavelength/light therapy for Dry-AMD

Two companies are examining the potential use of focal light-based therapy to treat dry-AMD and/or GA-AMD. This approach is novel, non-invasive and non-pharmaceutical, and the relevant procedures can be performed in-office by ECPs. If successful and shown to be sufficiently effective, given the non-invasive nature of the proposed light-therapy based treatments, we estimate that they could potentially capture a fair percentage of the population potentially at risk for progression to late-stage AMD. We assume patients would generally be more receptive to non-invasive, light-based therapy than to IVT injections (assuming, of course, equivalent levels of efficacy, which has not yet been determined). Below we discuss the Valeda and 2RT systems, which have both obtained a CE Mark.

Valeda Light Delivery (Photobiomodulation) by LumiThera. LumiThera (privately held) has developed an office-based photobiomodulation (PBM) treatment for dry-AMD, called the Valeda Light Delivery System, which received CE mark certification in mid-2018 for use in dry-AMD patients in Europe. According to the firm, applying PBM (light-based treatments resulting in the absorption of photons at targeted retinal cells) may activate mitochondrial respiratory chain components resulting in stabilisation of metabolic function and the initiation of a signalling cascade, which promotes cellular proliferation and cytoprotection. Secondary cellular effects include increases in energy production and changes in signalling modalities such as ROS species, which can ultimately affect protein synthesis and improve cell survival.

The previous sham-controlled [LIGHTSITE I study](#) (n=30) demonstrated reductions in central drusen volume over the course of 12 months versus the sham treatment with statistical significance at 12 months ($p=0.05$). Multi-wavelength PBM treatment demonstrated clinical improvements in vision outcome measures such as BCVA and contrast sensitivity (CS). The PBM therapy (three treatments per week for three weeks) was most beneficial in dry-AMD patients immediately following the completion of the treatment sessions, and it was therefore determined that retreatments at scheduled intervals will be needed to maintain clinical benefit. Results showed that PBM therapy was most beneficial in earlier-stage dry-AMD patients.

LumiThera received a \$2.5m grant from the NIH in early 2019 to support a prospective, randomised, multi-centre US human clinical trial (LIGHTSITE III) in dry-AMD patients. The LIGHTSITE III trial, which is subject to FDA investigational device exemption (IDE) approval, will assess vision and AMD parameters following PBM treatments using the company's Valeda System. The study is planned to start in H219 and subjects will be followed for up to two years.

In April 2019, LumiThera began enrolling patients in a separate EU multi-centre post-marketing clinical study ([LIGHTSITE II](#)) in dry-AMD patients. The study will enrol approximately 100 patients suffering from dry-AMD and treat them over the course of about one year. In addition to demonstrating safety, key efficacy endpoints include visual acuity, contrast sensitivity and reduction of drusen deposits.

Altogether, there is limited data on the long-term durability of Valeda PBM treatment. The indicative data to date is promising and the CE mark approval provides an early commercial opportunity in dry-AMD, but we assume that successful completion of the subsequent trials will be needed for the product to obtain significant key opinion leader (KOL) support and optimal market potential (as well as potential US approval). In Q418, LumiThera announced a distribution agreement with Optos, a

division of Nikon, to exclusively distribute the Valeda system for the treatment of dry-AMD in 12 European countries.

2RT by Ellex Medical Lasers. Ellex (ELX, ASX), a commercial-stage firm selling ophthalmic lasers for established medical conditions (cataract, glaucoma, etc), is advancing its Ellex 2RT nanopulse laser therapy for intermediate forms of dry-AMD. The product applies a rapid nanosecond pulse, non-thermal laser intervention, also termed subthreshold nanosecond laser (SNL), targeting selected retinal pigment epithelium (RPE) cells in order to promote an extracellular repair mechanism and response within the retina by improving the retinal's transport mechanism and the hydraulic conductivity of Bruch's membrane. The non-thermal SNL laser also eliminates the thermal tissue damage inherent in conventional retinal photocoagulation procedures used at times for NVAMD or other neovascular retina diseases.

The company completed a 36-month sham-controlled randomised study in 292 patients with intermediate dry-AMD, and reported data in Q418. The primary endpoint was progression to advanced AMD in the treated eye versus sham patients. In the intent-to-treat (ITT) analysis, there was no significant difference in progression to advanced AMD in either group, although there was a non-significant trend in favour of the 2RT group. However, a post-hoc analysis was done in patients who upon presentation did not have coexistent reticular pseudodrusen (RPD) deposits, representing 76% of enrolled patients (versus 24% with RPD at baseline). RPD are fatty deposits within the retina that tend to form in the later stages of dry-AMD, and are distinct from conventional drusen found in earlier stages of the condition. RPD consist of a variety of lipid, photoreceptor debris and immune cell fragments, and are believed to be a biomarker of RPE dysfunction, and may have a high association of progression to advanced AMD. Importantly, RPD can be detected by the eye care practitioner using non-invasive imaging technologies prior to a treatment.

The post-hoc analyses showed that in the 76% of patients who did not have coexistent RPD at baseline, treatment with 2RT resulted in a clinically meaningful 77% reduction in the rate of disease progression at 36 months, and a significant treatment effect ($p=0.002$). Interestingly, in the 24% of enrolled patients with coexistent baseline RPD, the rate of progression in the 2RT-treated group was higher than in the sham group, although it was not significant ($p=0.112$).

The firm's investigators hypothesise that 2RT's mechanism of action requires the selective loss and subsequent healing of RPE cells, and that it is plausible that the SNL treatment with the 2RT laser could effectively accelerate disease progression in eyes with RPD, which already have significant RPE dysfunction and integrity loss.

The high proportion of enrolled patients without baseline RPD approximates incidence rates in prospective studies, and thus the potential target population represents a large and clinically important segment (effectively about 75% of intermediate dry-AMD patients without GA).

In July 2019, the company provided additional results on patients who attended a 48-month post-treatment follow-up visit. Of the 292 participants who were randomised into the study, 183 (63%) attended a 48-month follow-up visit. This observational study suggested that 2RT therapy has an enduring protective impact on the retina. The data showed very little change in the clinical parameters that were observed and reported at 36 months, despite no additional 2RT treatment for these patients beyond 30 months. At 48 months in patients without coexistent RPD at baseline, there was a 72% reduction in the rate of progression to late AMD versus sham, which remains clinically significant ($p=0.002$).

Ellex's 2RT is already approved for sale in the EU, Australia and New Zealand in dry-AMD and sales in H218 were A\$1.2m. The 2RT currently has 510(k) clearance for Clinically Significant Macular Edema (CSME) in the United States. Ellex is currently seeking a pathway from the FDA for registration in dry-AMD, which may involve a US-based IDE or registration-enabling study. The firm expects to announce US requirements for dry-AMD registration in H219. As with Valeda's PBM, we

believe further, confirmatory and durable clinical data will be needed for the product to obtain significant market penetration (as well as US approval), but the prospect of non-invasive light-based treatment for what has been a largely untreatable degenerative condition and leading cause of vision loss is very exciting.

Visual rehabilitation for late-stage GA patients

Unfortunately, many patients with GA or NVAMD will progress into severe central vision loss, where the large majority of central photoreceptors have been irreversibly damaged, so as to reduce the BCVA to less than 5% (20/400) of normal vision, meeting the criteria for legally blind in most countries. None of the treatments discussed above can benefit patients who have already developed such profound loss (as their intent is more to preserve vision, since there is no known proven way to regenerate damaged retinal photoreceptors or downstream ganglion cells).

Pixium Vision (PIX, Euronext Paris; a research client of Edison Investment Research) is advancing a retinal implant, the Prima bionic vision system (BVS), that aims to provide a new form of vision to restore functioning to those with profound vision loss attributable to retinal diseases such as GA-AMD. The BVS intends to replace the signal processing functions of damaged photoreceptors by electrically stimulating other healthy retinal cells. These cells would then transmit the information towards the brain via the optic nerve. Following positive results in early 2019 from a five-patient [European feasibility study](#), Pixium is planning to file applications to commence an EU pivotal study. A five-patient two-site US feasibility trial ([PRIMA FS-US](#)), is currently recruiting and screening potentially eligible patients. Management expects the first implantations to occur in H219.

Prima is a tiny wireless photovoltaic sub-retinal chip, powered by near-infrared light, that is implanted underneath the retina in a surgical procedure that may take less than 90 minutes under local anaesthesia. The current Prima iteration under human clinical development is a 2mm × 2mm wireless chip consisting of 378 electrodes (pixels) in total, with each pixel being roughly 100 microns (0.1mm) in length and width. Each photovoltaic pixel is independently controlled and self-powered by near-infrared light projected from augmented reality-like glasses worn by the patient (the glasses consist of a camera and digital mirror projector, which emit a near infrared light pattern through the patient's eye carrying the Prima implant, designed to be processed by the Prima pixels).

Located underneath the retina, the pixels embedded on the device aim to stimulate the patient's bipolar cells, which are located mid-stream in physiological visual signal processing. In normal visual function, photoreceptor cells (located on the outer portion of the retina, or closer to the choroid) send information to bipolar cells (located within the retina), which then relay information into retinal ganglion cells (RGCs, which are on the inner portion of the retina), and onto the brain through the optic nerve.

Prima is intended to deliver VA that is anticipated to be sufficient to provide meaningful quality-of-life improvements and justify implantations in patients with significant GA-AMD. For instance, Prima can potentially enable the recognition of symbols, letters and objects in patients who have lost the capacity to recognise those forms.

In early 2019, Pixium announced that Prima successfully met the endpoints of a five-patient EU feasibility study at interim six-month follow-up after implantation, in patients with dry-AMD. All five implantations resulted in successful activations and light perception in areas where no central vision remained prior to implantation. Most patients were able to identify different visual patterns, symbols or letter sequences, and safety measures to date suggest the implant is stable and well-tolerated, and that the device does not impair residual natural peripheral vision. In March 2019, at a KOL

event, it was reported that at least one patient reported VA measures of up to 20/460, which to our knowledge is among the highest level recorded with a prosthetic retinal implant device.

Pixium is working to develop advancements in the external glasses worn by the patient. The firm anticipates that future iterations of the glasses will be integrated with improved analytics and image processing functionality that can potentially improve the artificial vision and visual perception experienced by the patient.

Reaching a new wave on the AMD treatment horizon

To summarise, AMD remains the leading cause of irreversible vision loss in older adults in developed countries. As individuals increasingly seek and expect to maintain their functioning and quality of life as they age, there is an overwhelming demand for treatments to decelerate or prevent vision loss in patients diagnosed with AMD. Anti-VEGF-A therapy, which reached the market in the early-mid 2000s, definitely improved the outlook for NVAMD patients and burgeoned a recurring maintenance therapy revenue stream for industry participants. Yet despite this, data suggests that up to about a third of NVAMD patients become refractory to current anti-VEGF-A treatments and continue experiencing vision deterioration. Further, the recurring need for IVT treatments is a hassle and barrier for many patients. As shown in our report, many new candidates on the horizon (such as OPT-302, DE-122 or ICON-4) may potentially also provide options for refractory NVAMD patients in the next half-decade or so, and leading late-stage product candidates (brolocizumab, faricimab, PDS-ranibizumab) appear more likely obtain approval sooner, resulting in reduced invasive dosing frequencies for patients, and these have the backing of the industry's leading established NVAMD players (Roche and Novartis). Other next-generation NVAMD products in the pipeline (such as GB-102, KSI-301) hold the promise of even more durable treatment effects, particularly those that may employ gene therapy (namely RGX-314, OXB-201 and ADVM-022). Non-invasive NVAMD treatment candidates may also allow for patient-administered therapy (PAN-90806 or SF-0166).

Of course, a more dramatic industry shift could occur should dry-AMD or, specifically, GA-AMD products obtain approval, as c 80% of the AMD population currently has no FDA-approved treatment. We see APL-2 and risuteganib as being particularly promising in this segment with the clinical data shown to date. Light-based therapy (2RT and Valeda) could also eventually gain a meaningful foothold in the early-to-intermediate stage dry-AMD space, and the data to date is promising. This therapy could provide widespread medical device revenue as well as opportunities for non-invasive office-based treatments by ECPs, for dry-AMD patients looking for proactive measures to preserve vision. Altogether, given the pipeline, the outlook for prospective patients and industry for both dry-AMD and NVAMD appear very promising, with blockbuster-size revenue opportunities for products that can improve outcomes in the space, or in the case of NVAMD, at least deliver improved convenience or treatment durability vs current SoC.

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Frankfurt +49 (0)69 78 8076 960

Schumannstrasse 34b

60325 Frankfurt

Germany

London +44 (0)20 3077 5700

280 High Holborn

London, WC1V 7EE

United Kingdom

New York +1 646 653 7026

1,185 Avenue of the Americas

3rd Floor, New York, NY 10036

United States of America

Sydney +61 (0)2 8249 8342

Level 4, Office 1205

95 Pitt Street, Sydney

NSW 2000, Australia