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Emerging therapies in AMD

A second look at next-generation treatments

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Age-related macular degeneration (AMD) remains the leading cause of blindness in older adults in western countries. While 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 about six- to nine-fold higher), particularly those who develop geographic atrophy (GA). There also remains 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 updated overview of many of the leading candidates and technologies that will shape the AMD market in the coming decade. We expect that while not all of these products will be successful, those that are could potentially generate significant returns for investors.

A huge market opportunity

The NVAMD market size is already substantial, at over $5.75bn worldwide revenue, as ranibizumab and aflibercept combined had c 9% sales growth in 2019. All NVAMD cases are preceded by dry-AMD, and NVAMD reflects roughly only half of late-stage AMD patients. We estimate late-stage AMD (defined as those patients with GA or NVAMD) affects roughly 5.5 million people across the US and Europe, and most of these patients will become legally blind without treatment. Another c 18–22 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, effective GA or dry-AMD treatments could add billions of dollars to an already huge AMD market.

Opportunities abound in the NVAMD space

Companies are looking at ways to extend NVAMD treatment durability to reduce the frequency of IVT instillations, and Roche has two late-stage candidates (faricimab, PDS-ranibizumab) seeking to do this. Kodiak's pivotal-stage KSI-301 may reduce dosing frequency to every six months. 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 and oral (non-invasive) drug treatments could go a long way in improving treatment compliance.

Dry-AMD continues to represent an untapped frontier

Several mid- to late-stage drugs are targeting inflammation and/or oxidative stress, and promising data has been released in the past 18 months for pegcetacoplan, Zimura and risuteganib. Zimura has already shown positive 18-month GA data in a Phase II/III study and a second Phase III is underway. There are also oral drugs (Oracea and ALK-001) in Phase III trials in the untapped dry-AMD market. Proprietary light-based therapy may also potentially decelerate progression of early-to-intermediate stage patients although further clinical studies will be needed to confirm earlier data and drive adoption. Altogether, we continue to 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.

Companies mentioned in this report

Adverum Biotechnologies
AbbVie
Alkahest Inc.
Alkeus Pharmaceuticals
Apellis Pharmaceuticals
Allegro Ophthalmics
Astellas Pharma
Bayer
Chengdu Kanghong Biotech Co
Galderma
Graybug Vision
Iconic Therapeutics
Ionis Pharmaceuticals
Iveric bio
Janssen
Kodiak Sciences
LumiThera
Molecular Partners
Nova Eye Medical
Novartis
Opthea
Oxford Biomedica*
PanOptica
Pfizer
Pixium Vision*
Regenerative Patch Technologies
Roche
Regeneron
Regenxbio
Stealth BioTherapeutics

*Edison Investment Research client

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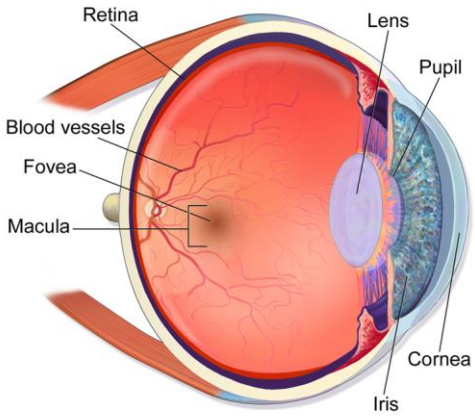
Age-related macular degeneration: Wide opportunities

Overview

AMD remains the leading cause of blindness in adults over the age of 55 in western countries, and is characterised by damage to the macular[1] 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. In early to intermediate cases, there may be a loss of up to one or two lines of central acuity on a standardised visual acuity (VA) chart as well as decreased contrast sensitivity, but often patients are not prevented from doing their day-to-day work or leisure activities.

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).

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



Eye Anatomy

Source: Wikimedia Commons; Medical gallery of Blausen Medical 2014. DOI:10.15347/wjm/2014.010

The dry form of AMD accounts for about 85–90% of cases[3] (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 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

[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

[3] Bright Focus Foundation. www.brightfocus.org/macular/article/age-related-macular-facts-figures Accessed 9 August 2020

patients with GA may have near-normal 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 10–15% of AMD cases.[4] Prior to the usage of anti-VEGF injection treatments, the current SoC for NVAMD, it accounted for over 80% of AMD patients with legal blindness.[5]

Early-stage AMD is mostly asymptomatic and characterised by drusen (deposits below the 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, and represents about 20–25% of all AMD cases. In general, RPE dysfunction and atrophy precedes the late stages of AMD (GA or CNV).

Globally, the prevalence of AMD (wet and dry, all stages) in adults above age 45 is estimated at 8.7%,[6] the prevalence in Europe has been estimated at 15.0 million people in 2013,[7] and the US prevalence of all-stage AMD was approximately 7.2 million in 2008.[8] 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 needed upon CNV diagnosis, as permanent scarring and severe vision loss often result if untreated).

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4 American Academy of Ophthalmology. www.aao.org/bcscsnippetdetail.aspx?id=9711f063-ed7b-452b-8708-c4dad0d893e8. Accessed 9 August 2020.

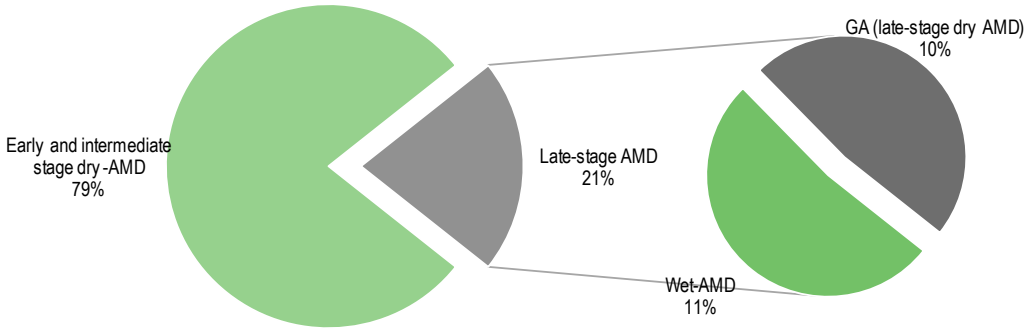
5 Legal blindness refers to patients with a central VA of 20/200 (10%) or worse in the better eye when a patient is wearing their best-corrected prescription lenses, or those with a visual field of less than 20 degrees.

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

7 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.

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

Exhibit 2: Estimated distribution of AMD in US and Europe by stage and type



Source: Rudnicka AR et al, Colijn JM et al, Klein R et al., Edison Investment Research estimates

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,[9] respectively in 2015. Based on US National Institutes of Health (NIH) data[10] that estimates that Caucasians account for 89% of all US AMD cases, we estimate that the 2015 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).[11] After extrapolating for population growth, we estimate about 5.5 million cases of late-stage AMD across the US and Europe in 2020, and between 18 and 22 million cases of early-to-intermediate stage AMD.

Current NVAMD treatments focus on VEGF-A inhibition

The current SoC for NVAMD is to reduce angiogenesis (blood vessel proliferation) by blocking 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 approved mechanism to block VEGF-A in the retina is through 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 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 VEGF-B and placental growth factor (PLGF), which itself is another growth factor involved in promoting angiogenesis. All of these products currently must be delivered through IVT.

[9] 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.

[10] US National Institutes of Health. https://nei.nih.gov/eyedata/amd Accessed 21 July 2020.

[11] 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.

In October 2019, brolucizumab (Beovu, Novartis) was approved by the FDA for NVAMD treatment. Brolucizumab is a humanised single-chain antibody fragment (scFv) designed to inhibit all VEGF-A isoforms and due its small size (26 kDa) it is intended to deliver a higher drug concentration at the targeted sites and, according to Novartis, provides more active binding agents than other approved anti-VEGF drugs. Brolucizumab approval followed positive 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 (BCVA) from baseline to week 48. Novartis also stated that significantly fewer brolucizumab-treated patients (vs aflibercept) had disease activity or (excessive) intra-retinal and/or sub-retinal fluid at week 48. Brolucizumab became the first FDA-approved anti-VEGF to provide eligible (well-controlled) NVAMD patients a maintenance dosing interval as high as three months, immediately after the three-month loading phase. However, in February 2020, instances of rare sight-threatening complications such as occlusive retinal vasculitis were reported by the American Society of Retina Specialists, prompting Novartis to evaluate the post-marketing cases and ultimately confirm the safety signal and amend the product's prescribing information worldwide to include mention of these potential complications.

Altogether, anti-VEGF-A therapy for CNV 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.

Chronic nature of therapy provides a recurring revenue stream

Under the current SoC, NVAMD patients require recurring (often every four to eight weeks, although brolucizumab may offer up to 12 weeks for maintenance therapy) IVT injections of anti-VEGF-A treatments 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 2019 global sales of $7.54bn (+12% y-o-y) and global Lucentis sales were c $3.92bn (c +5% y-o-y[12]). 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).[13] Contributions also occur from other medical retina indications associated with angiogenesis and/or hypoxia (such as macular edema following RVO). We estimate that each anti-VEGF-A treatment dose (for Eylea, Lucentis or Beovu) costs between $1,800 and $2,000 in the US per injection.[14] We

[12] H120 sales were affected by COVID-19 effects on IVT treatment accessibility, with Roche reporting that Lucentis sales in the US declined 19% yearly, and Novartis reporting that ex-US Lucentis sales declined 15% yearly (on constant-currency basis) and 17% in dollar terms; Eylea H120 global sales growth was flat year-on-year; Beovu global sales were $0.1bn in H120;

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

[14] Mukamal R. Comparison of Anti-VEGF Treatments for Wet AMD. 3 February 2020. American Academy of Ophthalmology. www.aao.org/eye-health/diseases/avastin-eylea-lucentis-difference. Accessed 7 August 2020

also highlight that biosimilar variants of ranibizumab and aflibercept could be reaching the major (US, EU, Japan) markets in the next two or three years, which may put some pricing pressure on the current branded versions (and also acts as an impetus for companies such as Roche and Novartis to develop follow-on products). A general rule of thumb is that the biosimilar drug, if approved, would likely be priced at a 20–30% discount to the original branded product.[15] Biosimilar forms of ranibizumab under development include FYB201 (from Formycon, Bioeq IP and Coherus BioSciences), SB11 (from Samsung Bioepis and Biogen), and Xlucane (Xbrane and Stada Arzneimittel). Examples of biosimilar aflibercept under development include SB15 (Samsung Bioepis and Biogen), ABP938 (Amgen) and CHS-2020 (Coherus). A more comprehensive discussion on biosimilars as they relate to the NVAMD market is beyond the scope of this report.

Room for improvement in NVAMD treatment methods

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 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%.[16] These factors provide incentives for firms to develop new therapies for NVAMD to improve convenience, efficacy and/or reduce the frequency of invasive[17] procedures.

Further, it has been estimated that 20–37%[18, 19] 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 the current NVAMD SoC.

Commercialisation considerations for AMD products

Generally, for a treatment to be approved it needs to succeed in registration-enabling randomised clinical trials powered to detect superiority (or, in some cases, non-inferiority) to existing treatments or SoC (in the case of NVAMD) or to supportive therapy (in the case of dry-AMD, as there is no approved US treatment). For pharmaceutical or biologics treatments (the vast majority of medium- to late-stage candidate products for these conditions), this involves Phase III stage clinical studies that show treatment efficacy after one year and often must also show safety up to two years (assuming ongoing periodic product dosage over this period). After successful studies, the product would need to be submitted for approval through regulatory agencies.[20] All currently US-approved NVAMD drugs are biologics products; in the US, biologics products must proceed through a Biologics License Application (BLA) whereas pharmaceuticals proceed through a New Drug Application (NDA).

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15 Sharma A, Reddy P, Kuppermann BD, et al. *Clin Ophthalmol*. 2018;12:2137-2143.

16 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.

17 Each individual procedure carrying a nonzero risk of endophthalmitis.

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

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

20 Examples include the Food & Drug Administration (FDA) in the US, and European Medicines Agency (EMA) in the European Union (or 'national competent authorities' in EU member states for applications that do not proceed through the centralised procedure for marketing authorisation applications in the EU).

For medical devices, the regulatory process differs more significantly between the US and Europe. In the US, medical devices are classified as either Class I, II or III depending on the device's risk, invasiveness, and impact on the patient's health. Low to moderate risk products, such as products emitting lasers or phototherapy, are often classified as Class II and generally go through either the:

- 510(k) notification process (when there is an existing predicate device and the goal is to establish equivalence and hence demonstrating device safety and efficacy is not required); or
- 510(k) de novo process (for low to moderate risk novel products generally seeking a new intended use that do not have a valid predicate device, and demonstrating device safety and efficacy becomes necessary).

Class III products are those that 'usually sustain or support life, are implanted, or present potential unreasonable risk of illness or injury'. Class III devices often must go through the more onerous US Premarket Approval (PMA) process, which requires a rigorous clinical trial of the medical device to demonstrate safety and effectiveness.

In the EU, all medical devices must obtain CE mark designation and generally the process to obtain CE marking requires less exhaustive pre-commercial human clinical evidence of product efficacy than for US Class III medical devices, although the product must be shown to be safe to use as indicated. Often, products obtaining CE marking are required to complete a post-market clinical follow-up study.

Reimbursement considerations

In the US, the Centers for Medicare and Medicaid Services (CMS) provides medical insurance to Americans over age 65 and since the large majority of NVAMD patients fall within this age category, CMS is the primary insurer for NVAMD treatments. All three major NVAMD-approved drugs (aflibercept, ranibizumab, brolucizumab) are covered by CMS and in fact, at a similar per-treatment price, the anti-VEGF-A products requiring the lowest dose frequency will cost the insurer less on an annual basis. Hence, we expect that if future IVT treatments are approved that would carry similar or lower annual treatment costs than these products, they would have little difficulty obtaining reimbursement.

Altogether, we do not foresee significant reimbursement challenges for new treatments, as the greatest hurdle, in our view, is obtaining regulatory approval. Once a new NVAMD product is approved, provided it can demonstrate either improvements in vision (using measures such as VA or macular thickness) compared to SoC, or have a yearly treatment cost that is not higher than the SoC in general, we would not expect any significant challenge in getting reimbursement from CMS or the major European health regimes that currently cover the existing NVAMD-approved drugs. In the event a dry-AMD or GA-AMD product is approved that can decrease the rate of vision decline associated with the condition, we would similarly not expect any major hurdles in obtaining reimbursement (up to and likely exceeding current reimbursement levels for the approved NVAMD drugs), given the significant social and pharmaco-economic benefit of preserving a person's vision (in terms of maintaining quality of life, independence, productivity, etc).

A curious case exists with bevacizumab, as that product is effective in NVAMD but is not specifically approved for the indication. To be used for NVAMD, bevacizumab must be divided into smaller doses by compounding pharmacies with the resulting US dose costing about $50 per injection (compared to $1,850–2,000 for each of the three others). However, compounding the drug has been suggested to potentially increase the risk of endophthalmitis, a point argued by Roche and Novartis to challenge its off-label use in NVAMD, although a retrospective study involving nearly 60,000 patients did not find this to be the case.[21] As co-payments may be needed to cover part of the cost of the drug, the American Academy of Ophthalmology estimates that about half of US

[21] VanderBeek BL, Bonaffini SG, Ma L. *JAMA Ophthalmol*. 2015 Oct;133(10):1159-64. PMID: 26270251

ophthalmologists prescribe bevacizumab as first-line NVAMD therapy.[22] In Europe, there is substantial variability in the use of bevacizumab in NVAMD, with the drug used in a majority of cases in Bulgaria, Finland, Ireland and the Netherlands; in a minority of cases in Belgium, Austria, Germany, Italy, Norway, Spain and the UK; and hardly used or not used at all in France, Denmark and Switzerland.[23]

COVID-19 effects on clinical development

Numerous AMD studies as detailed below remained ongoing during the peak 'lockdown' periods (March and April 2020) associated with the COVID-19 pandemic. During the lockdown period, a consortium of retinal trial investigators[24] released a set of guiding principles for ongoing retinal trials during the period. Among these, they recommended:

- For patients enrolled in studies who were able to attend study visits, time in clinic was to be minimised to reduce exposure risk.
- Study visits required for patient safety, to assess primary study outcomes, or to continue provision of study treatment, were to be prioritised.
- Study data could be collected remotely for patients unable to attend on-site study visits, with patients encouraged to self-monitor vision.
- Reasons for missed visits, assessments, treatment doses, or safety events that were due to the COVID-19 pandemic were to be documented.
- Discretion was to be applied in screening and recruitment of new patients, including consideration of disease urgency and use of non-investigational alternative treatments.

As lockdown restrictions have now eased, recruitment, treatment and follow-up visits are now generally proceeding as intended.

A closer look at the NVAMD pipeline

Below we classify different approaches under clinical investigation for ameliorating NVAMD in the market, which is already worth in excess of $5.75bn worldwide (excluding the use of VEGF-A drugs for non-NVAMD indications such as DR/DME).

Late-stage anti-VEGF NVAMD therapies

The evolutionary (lower-risk and more conventional) approach 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. Brolucizumab's development followed this pathway and the leading advanced stage drug in this category is Roche's faricimab.

Faricimab. Faricimab is a bispecific mAB that targets and inhibits both VEGF-A and angiopoietin-2 (Ang-2); Ang-2 normally binds to the Tie-2 cell surface receptor, and is 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

[22] Comparison of Anti-VEGF Treatments for Wet AMD. www.aao.org/eye-health/diseases/avastin-eylea-lucentis-difference. Accessed 13 August 2020.

[23] Bro T, Derebecka M, Jørstad ØK, et al.Graefes *Arch Clin Exp Ophthalmol.* 2020 Mar;258(3):503-511. doi: 10.1007/s00417-019-04569-8. Epub 2019 Dec 30.

[24] Including Roche, Boehringer Ingelheim, Kodiak Sciences, Apellis Pharmaceuticals, Graybug Vision, Adverum Biotechnologies, and Regenxbio. https://graybug.com/joint-statement-on-retina-clinical-trials-and-covid-19/ Accessed 13 August 2020

with recruitment completed in Q419) will compare faricimab (dosed every 16 weeks, with an option to increase frequency if needed) to aflibercept dosed every eight weeks. Results from the Phase III YOSEMITE and RHINE studies in DME are expected in late 2020.

PDS-ranibizumab. A related approach for reducing the number of patient visits or need for IVT injections is also being undertaken by Roche by developing an improved drug delivery system that is based on 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. In July 2020, the company reported positive results from the 418-patient Phase III ARCHWAY study comparing PDS-ranibizumab (dosed every 24 weeks) with IVT ranibizumab (dosed every four weeks). PDS-ranibizumab was well-tolerated and demonstrated non-inferior and equivalent VA outcomes compared to monthly IVT-ranibizumab and a favourable risk-benefit profile. The primary endpoint measured the change from baseline in BCVA averaged over weeks 36 and 40. Over 98% of PDS-ranibizumab patients were able to go six months without requiring additional treatment and obtained vision outcomes equivalent to patients receiving monthly IVT-ranibizumab. While the ongoing PORTAL long-term extension study continues to investigate the long-term safety and tolerability of PDS-ranibizumab, the company plans to submit ARCHWAY data to the FDA and European regulators, for consideration of possible approval for NVAMD treatment. Roche anticipates US market approval in 2021.

Conbercept. Conbercept is an anti-VEGF recombinant fusion protein developed by Chengdu Kanghong Biotech Co (002773, Shenzhen) that was approved in China in 2013 for NVAMD treatment. Like aflibercept, conbercept targets VEGF-A and -B and PLGF, and it also binds VEGF-C. The structure of conbercept has been hypothesized as having higher binding capacity and a longer half-life than aflibercept. In a 114-patient Phase III (PHOENIX) study based in China, the conbercept arm gained a mean of 9.20 letters of BCVA from baseline, versus 2.02 letters in the sham arm. Two global Phase III trials in NVAMD started recruiting in late 2018, PANDA-1 and PANDA-2, which if positive could result in regulatory submissions in the US and Europe. Each of these studies is evaluating 1,140 patients randomised to conbercept, 0.5mg or 1mg, or aflibercept, with mean change from baseline in BCVA at week 36 as the primary endpoint. Primary endpoint readings could occur in Q420 or H121. Conbercept could potentially be shown to be non-inferior to aflibercept and/or allow for less frequent dosing.

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 five or six months.

In Q418, the firm initiated an open-label, multiple-dose US Phase Ib study of KSI-301 in patients with anti-VEGF treatment-naive NVAMD, DME and RVO. All 121 enrolled 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. As of 10 July 2020, the firm has observed bioactivity in all three diseases tested and has only observed two instances (out of 546 doses provided to date) of minor (grade 1+) intraocular inflammation, which have resolved.

The firm observed that 82% of NVAMD eyes treated with KSI-301 were extended to four months or longer after the last loading dose, prior to receiving their first retreatment. An average of only 1.3 injections were given in the NVAMD patients in the eight months after the loading phase, suggesting a much more potent durability than current IVT approved anti-VEGF-A drugs. The company started a Phase IIb/III pivotal study (DAZZLE), which to date has recruited over 375 treatment-naive NVAMD patients in the US and Europe. Patients are randomised to receive either KSI-301 on an individualised dosing regimen (of every three, four or five months) or to receive

aflibercept every eight weeks, each after the initiating doses. The primary endpoint is change in BCVA versus baseline at 12 months, but patients will be treated and followed for 24 months. If results are positive, the company anticipates potentially filing its BLA with the FDA in 2022.

Abicipar pegol. Allergan, a subsidiary of AbbVie (ABBV, NYSE), and Molecular Partners (MOLN, SIX) have been 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) 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 these studies, the incidence of intraocular inflammation was c 15% in the abicipar pegol arms, compared to <1% in ranibizumab. In Q219 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. A BLA had been filed with the FDA but the agency declined the marketing application, citing that the rate of intraocular inflammation with the drug resulted in an unfavourable benefit-risk ratio. AbbVie indicated that it planned to meet with the FDA and then determine next steps.

Generally, the above-mentioned late-stage 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 and are not associated with particular safety concerns (eg brolucizumab), 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. 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 in the STAIRWAY trial. KSI-301's and/or Roche's PDS-ranibizumab's potential for prolonged dose intervals (up to five or six months) could be potential game-changers 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). Further, given the ongoing pandemic and potential lingering effects on human behaviour and preferences, patients and practitioners may be increasingly inclined to select treatment options that require as few in-office visits as possible, which would be a key driver for these late-stage treatments (which all promise longer dosing intervals than currently approved drugs).

Exhibit 3: Later-stage injection or invasive anti-VEGF-A product candidates for NVAMD and/or DME

Product candidate	Company	Development stage	Mechanism	Notes	Next milestones
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 and recruitment completed	Top-line DME Phase III data in Q420 and NVAMD data in H121
Port Delivery System (ranibizumab)	Roche	Phase III	Sustained delivery system of ranibizumab (implanted)	98% of patients in 418-pt ARCHWAY Phase III study went six months between device implant and first required refill; 500-pt ongoing long-term safety study (PORTAL) started in H218; Product is also being studied in the Phase III (PAGODA) trial in DME	Regulatory submission
KSI-301	Kodiak Sciences	Phase IIb/III	Targeting VEGF using proprietary antibody biopolymer conjugate (ABC) platform	82% of NVAMD eyes treated in Phase Ib with KSI-301 were extended to four months or longer after the last loading dose, prior to first retreatment. KSI-301 could potentially be a once every five- or six-month IVT treatment. 375 patients enrolled to date in Phase IIb/III	BLA filing potentially in 2022
Conbercept	Chengdu Kanghong Biotech Co	Phase III	Recombinant fusion protein that targets VEGF-A and -B and PLGF, and it also binds VEGF-C	Approved in China in 2013. Two global Phase III trials in NVAMD started recruiting in late 2018, PANDA-1 and PANDA-2, which if positive could result in regulatory submissions in the US and Europe	Primary endpoint readings could occur in Q420 or H121
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) resulting in FDA declining marketing application in June 2020	Unknown

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 data in terms 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, and 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 4: 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	Post-Phase IIb	VEGF-C/D 'trap' that blocks VEGF-C and VEGF-D	Initiate Phase III pivotal study programme
ICON-4	Iconic Therapeutics	Pre-IND	Human monoclonal antibody that binds to tissue factor (TF), targeting inflammation and CNV formation	Investigational New Drug (IND) application submission in H121
Candidates aiming to extend therapeutic doses and reduce dosing frequency				
GB-102 (sunitinib depot)	Graybug Vision	Phase IIb	Tyrosine kinase inhibitor (TKI) that blocks several receptors associated with NVAMD progression	Phase IIb results in H121
RGX-314	Regenxbio	Phase I/IIa	Gene therapy using AAV8 vector to deliver a gene encoding for a mAB/protein that neutralises VEGF activity	Start Phase III programme for sub-retinal administration in Q420; start Phase II for the suprachoroidal delivery of RGX-314 in H220
AVDM-022	Adverum	Phase I	Gene therapy using AAV capsid vector to deliver genetic cassette expressing the anti-VEGF aflibercept drug	Pivotal study planned to begin in mid-2021
OXB-203	Oxford Biomedica	Preclinical	Gene therapy using lentiviral vector derived from the Equine Infectious Anemia Virus (EIAV), designed to express aflibercept. Previous candidate OXB-201 encoded anti-angiogenic proteins endostatin and angiostatin, but the company believes that aflibercept is a better target	Firm may seek partnership opportunities before proceeding with future trials
Topical, oral or non-invasive treatment candidates				
AKST4290	Alkahest Inc.	Phase IIb	Oral small-molecule CCR3 inhibitor that blocks the action of eotaxin, an immunomodulatory protein associated with age	Results from 100-patient Phase IIb (PHTHALO) anticipated in Q321
PAN-90806	PanOptica	Phase I/II completed	Topically applied small molecule that blocks activation of VEGF receptor 2 through inhibition of the receptor's tyrosine kinase activity	Potentially start pivotal trials and/or engage in M&A and/or strategic transactions to support development

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 believed to achieve a more complete blockage of the mechanistic pathways involved in disease progression. In August 2019, the company reported positive data in a ranibizumab plus sham-controlled 366-patient Phase IIb NVAMD study. Patients administered OPT-302 2.0mg in combination with ranibizumab demonstrated a mean gain of 14.2 letters of vision vs baseline at 24 weeks, compared to 10.8 letters in the ranibizumab control group, a significant benefit of 3.4 letters (p=0.0107). Subsequent data reported in Q419 showed that in certain patient pre-specified NVAMD subgroups, such as those presenting with occult CNV lesion types (representing about 44% of recruited patients), or with polypoidal choroidal vasculopathy (PCV, reflecting c 18% of recruited patients), had even superior improvements vs the control arm, at +6.0 letters (p=0.0008) and +6.7 letters (p=0.0253). Between 23% and 60% of NVAMD patients in Asian populations are estimated to have PCV,[25] and Opthea believes that combination Anti-VEGF-A treatment with its VEGF-C/D inhibitor may provide particular additive benefit in the occult CNV and PCV NVAMD sup-populations. The next steps for OPT-302 involve finalising the design of and then starting recruitment for a Phase III pivotal programme in NVAMD.

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

[25] American Academy of Ophthalmology. www.aao.org/topic-detail/polypoidal-choroidal-vasculopathy-pcv-asia-pa Accessed 23 July 2020.

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 is expected in H220. 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. In August 2019, the company signed an agreement with Novartis providing it with an option on Iconic's ophthalmology programme, including ICON-4, in exchange for an upfront payment and an equity investment.

Therapeutic candidates aiming to deliver longer treatment effects

GB-102. Privately held Graybug Vision is advancing GB-102, a microparticle depot formulation of sunitinib intended for IVT injection. The candidate is designed to provide a standalone control for NVAMD with potentially as little as twice-yearly dosing. 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. 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 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, serious adverse events (SAEs) or inflammation, there was evidence of maintenance of VA and central retinal thickness over at least six months as measured by VA readings and optical coherence tomography[26] (OCT). 88% and 68% of evaluable patients were maintained only on a single dose of GB-102 at three and six months, respectively. Presence of medication in the anterior chamber was the most commonly reported drug-related adverse event (AE) but the firm indicated that these events were generally self-limited,

[26] 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.

reversible and without long-term adverse effects. The manufacturing process of GB-102 was subsequently optimised, and preclinical testing showed improved particle aggregation properties.

In September 2019, the company began a GB-102 Phase IIb study (ALTISSIMO), which was initially designed as a 12-month, three-arm, randomised trial evaluating two dose levels of GB-102 (1mg and 2mg) administered every six months compared to aflibercept administered every two months in NVAMD patients. The firm provided an update in March 2020 stating that 56 patients have been enrolled at 33 US sites and that an interim safety analysis supporting moving forward with the 1mg dose, potentially accelerating the final study analysis by about six months (versus the initial estimate). Emerging evidence from Graybug's current and prior GB-102 trials (in NVAMD and in macular edema) suggested that the 1mg GB-102 dose may offer improved safety and tolerability compared to the 2mg dose, including a lower incidence of presence of medication in the anterior chamber of the eye. Consequently, the ALTISSIMO protocol has been amended to allow patients originally randomised to the 2mg dose to perform their repeat dosing at six months with the 1mg dose. Graybug indicates that it is confident the ALTISSIMO trial will have a sufficiently large sample size to inform the design for a pivotal Phase III programme in NVAMD, while preserving the trial's scientific integrity since the dosing regimen will remain masked.

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-203 uses the firm's proprietary LentiVector technology (which uses the lentiviral vector derived from the equine infectious anemia virus) to deliver a gene encoding aflibercept. 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 retreatment over such a period). Below we provide details on each of them.

RGX-314. Regenxbio's RGX-314 is initially 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-rzyl (Luxturna, Spark Therapeutics). Compared to IVT 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 sub-retinal administration 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 sub-retinal 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. Patients did not receive prophylactic immune suppressive corticosteroid treatment before or after RGX-314 dosing.

The most recent study data were reported in April 2020, which stated the product was well-tolerated across all cohorts to date, with no drug-related SAEs. Patients in Cohort 5 have shown a meaningful reduction in anti-VEGF treatment burden over nine months following RGX-314 administration, with 8/11 (73%) patients remaining anti-VEGF injection-free, and a reduction across the cohort of over 80% from the mean annualised injection rate during the 12 months prior to RGX-314 administration. The company expects to report 12-month data on Cohorts 4 and 5 in Q320, which should inform the design of a Phase III pivotal programme, expected to start by YE20, for the sub-retinal delivery of RGX-314 for the treatment of NVAMD.

The data to date show a durable treatment response from Cohort 3 of the study, at 24 months. Sustained and durable RGX-314 intraocular protein expression was detected at 24 months in all six subjects in Cohort 3. There was a mean BCVA improvement of +14 letters versus baseline at 24 months. Cohort 3 subjects received a mean annualised rate of 2.8 injections following RGX-314 instillation, a reduction of over 60% from the mean annualised injection rate during the 12 months prior to RX-314 administration.

Regenxbio is also working on an alternate gene delivery approach, through the suprachoroidal space using the SCS Microinjector device in-licensed from Clearside Biomedical. Using the SCS device could potentially allow for an in-office, non-surgical procedure for product delivery into the retina without exposing the vitreous and the anterior segment of the eye. The company plans to start a Phase II study for the suprachoroidal delivery of RGX-314 using the SCS Microinjector in 2020.

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 reported that in preclinical non-human primate studies, a single IVT administration of ADVM-022 provided sustained expression of aflibercept for at least 30 months at levels comparable to those experienced three to four weeks post-injection of aflibercept protein.

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, trial in patients with NVAMD who previously demonstrated responsiveness to anti-VEGF treatment, where subjects will be administered a single IVT injection, and then monitored for two years.

Cohorts 1 (n=6) and 4 (n=9) consisted of the 'high' dose level of 6×10^{11} vg/eye, and Cohorts 2 (n=6) and 3 (n=9) consisted of a lower dose of 2×10^{11} vg/eye. Subjects in Cohorts 3 and 4 received six weeks of prophylactic steroid topical drops rather than 13 days of oral steroids (which were used in Cohorts 1 and 2). The company believes that the six-week prophylactic topical steroid regimen would likely result in fewer AEs and less inflammation. In August 2020, interim data was presented on Cohorts 1 through 3, with early indications of positive safety in Cohort 4. For Cohort 1, none of the six enrolled patients required a 'rescue' Anti-VEGF-A injection (covering between 64 and 84 weeks post ADVM-022 administration), but the mean change in BCVA was a loss of 3.2 letters vs baseline (which could pose a challenge for adoption). For Cohort 3, covering between 20 and 40 weeks post ADVM-022 administration, two (22%) required at least one anti-VEGF-A 'rescue' dose, and the mean change in BCVA was a gain of 6.4 letters among the nine patients. It appears that the inclusion of the six-week use of topical steroids (ie Cohorts 3 and 4) as part of the treatment regimen may have a beneficial effect on BCVA, but longer post-treatment data will be needed to confirm the trend. The company plans to present further data on all four cohorts in H220, and initiate a pivotal clinical study in mid-2021.

OXB-203. Under development by Oxford Biomedica (a research client of Edison), OXB-203 delivers a gene that is designed to express aflibercept. The company previously developed OXB-201, which encoded the anti-angiogenic proteins endostatin and angiostatin, but the company

believes that aflibercept is a better target. OXB-203 is in pre-clinical studies, and OXB is looking for options to advance it, which can include partnering or out-licensing.

Altogether, we believe maintaining BCVA (or preferably showing a small gain), in addition to significantly reducing the need for IVT therapy, could provide a meaningful commercial opportunity for the gene-based therapies

Topical or oral 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 and improving safety. Since a non-invasive topical or oral delivery process could be self-administered, it would be less burdensome and there could also be savings in medical procedure costs and improved patient compliance. 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 the blood-retina barrier for oral/systemic administration). If effective, and somewhat comparable to the efficacy of current leading IVT Anti-VEGF-A treatments, such a 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 or oral therapies can exceed the efficacy of current (and upcoming) IVT treatments, but it is foreseeable that if such a non-invasive treatment obtains approval, potentially up to 25–50% of NVAMD patients (who are currently well-managed by periodic IVT treatments) could switch to this form of 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. Candidates having already shown some early human data are AKST4290 and PAN-90806.

AKST4290. Privately held Alkahest Inc. is developing AKST4290, an oral small-molecule C-C chemokine receptor type 3 (CCR3) inhibitor that blocks the action of eotaxin, an immunomodulatory protein that increases with age and is associated with specific age-related diseases. By targeting eotaxin and related downstream effects, Alkahest believes AKST4290 may reduce the inflammation and neovascularisation processes involved with NVAMD (the compound is also being studied in Parkinson's disease). In 2019 the company presented results from two open-label Phase IIa monotherapy studies in NVAMD in Hungary and Poland. In study ALK4290-201, 30 patients with newly diagnosed NVAMD took ALK4290 400mg twice-daily over a six-week period and 83% (24 of 29 evaluable) of subjects' eyes had maintenance or improvement of BCVA, with a mean letter gain of +7 letters. In total, 21% of evaluable subjects gained at least 15 letters. In study ALK4290-202, 26 patients with refractory NVAMD (no longer responding to anti-VEGF-A therapy) took the same regimen (and without concomitant use of anti-VEGF-A therapy). 72% of patients (18 of 25 evaluable) showed maintenance or improvement in BCVA, the mean change across six weeks of treatment was an increase of +2.0 letters, and 8% of subjects gained 10 or more letters. While these results appear promising for a non-invasive treatment, we acknowledge that the sample sizes were relatively small, the six week duration of the studies is relatively short given the chronic nature of the condition, and the general considerations associated with the interpretation of open-label trials. In February 2020, the company started a larger 100-patient global (including three US sites) Phase IIb study (PHTHALO, also called AKST4290-205) in patients with treatment-naïve NVAMD. Patients are to receive loading doses of IVT aflibercept, and are randomised to receive twice-daily doses of either 400mg AKST4290, 800mg AKST4290, or placebo, for 36 weeks. The primary endpoint will be mean change from baseline in BCVA from screening to week 40. Given the size, randomisation and duration of this trial, we believe this study will provide a much more robust indication of whether AKST4290 can provide potent treatment effects and/or reduce IVT treatment burden compared to current standard-of-care. Results are anticipated in Q321.

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 by inhibiting 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. However, the formulation was associated with corneal AEs (eg edema). In May 2018, the firm announced that patient dosing began in a second Phase I/II dose-ranging clinical trial (PAN-01-102) of PAN-90806, investigating its new suspension formulation of PAN-90806 as monotherapy (once-daily), for up to 12 weeks, in a masked study involving 51 newly diagnosed (ie treatment-naïve) patients with NVAMD, randomised to one of three dose (2mg/mL, 6mg/mL, 10mg/mL) strengths at sites in the US and the EU. Results were reported in October 2019, which showed that 51% (26/51) of the participants completed the trial without needing any 'rescue' IVT ranibizumab treatment (at 16 weeks, reflecting one month after treatment cessation); of these, 88% (23/26) had either clinical improvement or stability of disease (based on an independent masked review by a panel of retinal experts). As would be expected, the patients who required 'rescue' IVT treatment were those with the weakest baseline VA and highest level of baseline macular thickness. There did not appear to be a dose-dependent relationship in the likelihood of requiring rescue IVT therapy (ie the mean number of IVT ranibizumab injections given per patient during the study was 0.8 in each arm). Panoptica also stated that the PAN-90806 formulation studied in the PAN–01–102 trial also exhibited improved tolerability and significantly improved safety over the previous, abandoned clinical formulation (from the first Phase I/II study).

The company believes the results suggest that topical PAN-90806 may provide clinical benefit and substantially reduce the injection burden for NVAMD patients, and it is looking into starting pivotal trials and has engaged an investment bank to examine potential M&A opportunities or other potential strategic transactions to support product development. We caution that three months of human clinical data is much less than the data set attained for other Phase III-stage AMD candidates, prior to them having started a pivotal/registration-enabling programme. Given that NVAMD is a chronic condition, there may be a risk that some longer-term safety considerations could be observed in a pivotal programme that may not necessarily have shown a signal within the three-month period covered in the PAN–01–102 study.

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 or approved pharmaceutical or medical treatments. Currently, the biopharma industry's commercial stake in dry-AMD is mostly limited to the sale of over the counter (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, it is foreseeable that this market could easily eclipse the >$5.75bn 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. Many GA-AMD 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 ie 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 5: Intermediate to late-stage pipeline in dry-AMD

Product candidate	Company	Development stage	Mechanism	Next milestones
Therapeutics administered through intravitreal injection				
pegcetacoplan	Apellis Pharmaceuticals	Phase III	Inhibit complement factor C3 activation and reduce inflammation.	Enrolment of both Phase III studies complete; top-line data in Q321.
Zimura (avacincaptad pegol)	Iveric bio	Phase III	Inhibit complement factor C5 activation and reduce inflammasome activation and inflammation.	Completion of enrolment of GATHER2 second Phase III study; 12-month analysis of GATHER2 data.
Risuteganib	Allegro Ophthalmics	Phase IIb/III	Target integrin receptors αvβ5, α5β1 (associated with angiogenesis and vascular leakage) and αMβ2 (associated with inflammation).	Start a Phase IIb/III pivotal study in intermediate dry-AMD in Q420.
Oracea (doxycycline)	Galderma and Medarva Foundation	Phase III	Doxycycline is a tetracycline-class antibiotic with anti-inflammatory properties a lower dose levels which may slow down AMD progression.	In or around late 2020.
ALK-001	Alkeus Pharmaceuticals	Phase III	Once-daily orally administered modified form of vitamin A designed to prevent its aggregation into dimers within the retina and potentially slow AMD progression.	Top line data expected near in Q123.
IONIS-FB-LRx	Ionis Pharmaceuticals and Roche	Phase II	Generation 2+ ligand-conjugated antisense (LICA) drug designed to reduce the production of complement factor B (FB).	Results from Phase IIb study (GOLDEN); completion date is estimated in H222.
RO7171009 (RG6147)	Roche	Phase II	Antibody that inhibits HTRA1, a serine protease gene associated with GA.	Study completion date of Phase II (GALLEGO) anticipated in Q122.
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.	Enrolment expected to be completed 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 Investigational Device Exemption (IDE) study (LIGHTSITE III) results in H221.
2RT nanopulse laser	Nova Eye Medical	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[27] 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. We note that Genentech/Roche's lampalizumab, a mAB against complement factor D (a rate-limiting enzyme involved in the activation and amplification of the alternative complement pathway), did not perform any better than a sham treatment at slowing GA-AMD in a 975-patient Phase III trial reported in September 2017. Novartis's LFG316 (tesidolumab), a mAB against complement pathway protein C5, was also discontinued as a standalone candidate in a Phase II study after an interim efficacy analysis. LFG316 was also assessed in combination with CLG561, a human Fab (antigen-binding fragment) that neutralises properdin, a positive regulator of alternative pathway activity. A Phase II study (n=114) evaluated CLG561 as a monotherapy and also in combination with LFG316 compared with sham in subjects with GA. Results showed that neither treatment arm met statistical significance in terms of a change in GA lesion size as measured by fundus autofluorescence (FAF). Hence, while there is some justification for targeting the Complement system for treating dry-AMD, it is certainly not without development risks and no complement system-targeting dry-AMD treatment has yet succeeded through pivotal stage studies.

APL-2 (pegcetacoplan). 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 (pegcetacoplan) candidate. Apellis is developing therapies that target the complement system in inflammatory processes. Pegcetacoplan is delivered through IVT to inhibit complement factor C3 activation with the aim of treating GA. pegcetacoplan 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, pegcetacoplan met its primary endpoint. At 12 months, pegcetacoplan, 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 of administration, a 20% (p=0.067) reduction compared to sham was shown. When the study eye was compared to the fellow eye (post-hoc analysis), there was a 23% difference (p=0.083) in GA lesion growth in the once monthly pegcetacoplan treatment arm (n=69).

Apellis received FDA fast track designation in July 2018 for the pegcetacoplan candidate and started recruitment for two separate 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 mm^2) based on 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 pegcetacoplan drug product in the Phase III programme.

In March 2019, the firm announced that with the agreement of an independent safety monitoring committee, it resumed enrolment in its two Phase III pegcetacoplan GA trials. The firm indicated that following an investigation, it believes the likely source of inflammation resided in an impurity in the active pharmaceutical ingredient 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 pegcetacoplan utilising the modified

[27] The complement system is a component of the immune system consisting of more than 30 proteins that work to improve ('complement') the ability of phagocytic immune cells and of antibodies to eliminate infectious microbes.

manufacturing process to conduct the entire Phase III GA programme. The pegcetacoplan drug product produced from the modified manufacturing process had already been introduced into the firm's Phase Ib APL2-103 trial (n=12) in low-vision patients with GA, and none of those patients had experienced inflammation after 12 months (as reported in April 2020) and the formulation was well tolerated. In that study, the nine study patients who had bilateral GA, and for whom data were available for at least 12 months, had a growth rate of GA lesions in the treated eye that was on average 31.1% slower than the fellow untreated eye. The patient population enrolled in the Phase Ib study is similar to DERBY and OAKS but allowed for more advanced disease.

Apellis announced in July 2020 that it completed enrolment in both the DERBY and OAKS Phase III trials, with the total recruitment of 1,259 patients. The company plans to report top-line results in Q321.

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.[28] 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. Positive top-line 12-month efficacy data from a 286-patient, sham-controlled randomised Phase II/III study (GATHER1) of Zimura monotherapy in GA-AMD was reported in October 2019. Zimura met the prespecified primary endpoint in reducing the rate of GA growth in dry-AMD patients, as the reduction in the mean rate of GA growth over 12 months vs sham was 0.110mm (p-value = 0.0072) for the Zimura 2mg group and 0.124mm (p-value = 0.0051) for the Zimura 4mg group. The company reported an approximate 27% relative reduction in the mean rate of GA growth over 12 months when compared with sham for both dose groups. 18-month follow-up data was reported in June 2020, showing the product was safe and well tolerated over this period (there was no Zimura-related inflammation, trial discontinuations or AEs, and no cases of endophthalmitis). More importantly, the efficacy signals of the 12-month data were confirmed. The reduction in the mean GA growth rate over 18 months was 28.11% for the Zimura 2mg group vs sham (p=0.0014) and 29.97% for the Zimura 4mg group vs sham (p=0.0021), although the firm notes that the p-values for the 18-month statistical analyses are descriptive in nature. Altogether, the results appear impressive in demonstrating a meaningful potential improvement in GA and we believe the GATHER1 study is the first late-stage GA study data point showing GA suppression for as long as 18 months. Iveric bio in June 2020 announced the first patient has been dosed in GATHER2, the second Phase III trial for Zimura in GA-AMD.

The GATHER2 trial will randomise approximately 400 patients to receive either monthly administration of Zimura 2mg or sham during the first 12 months of the trial, at which time the primary efficacy analysis (of the mean rate of change of GA growth) will be assessed. If the 12-month results are positive, Iveric bio plans to file an application with the FDA and European authorities for marketing approval in GA-AMD, supported by the data from both GATHER1 and GATHER2.

IONIS-FB-LRx. IONIS-FB-LRx is a Generation 2+ ligand-conjugated antisense (LICA) drug developed by Ionis (IONS, Nasdaq) and designed to reduce the production of complement factor B (FB), which the company believes may play a role in dry-AMD progression (by modulating complement in posterior eye segment regions such as the RPE, Bruch's membrane and

[28] Also called Stargardt macular dystrophy or Stargardt macular degeneration; refers to a genetic retinal disease that damages the macula and leads to blindness in early adulthood. Mutations in gene ABCA4 are the most common cause of Stargardt disease, as this gene makes a protein that normally controls the transport of Vitamin A by-products in the retina. Retinal cells lacking the ABCA4 protein accumulate clumps of lipofuscin, leading to vision impairment and cellular damage.

choriocapillaris). In October 2018, a collaboration agreement was signed with Roche where Ionis received a $75m upfront payment (with up to $684m in milestones and fees, and tiered royalties up to 20%). Ionis became responsible for conducting a Phase II study in dry-AMD and in a rare renal indication, with Roche having the option to license IONIS-FB-LRx after the studies are completed. Ionis began a randomised Phase IIb study (GOLDEN) on IONIS-FB-LRx in H119 to assess the rate of change of the area of GA secondary to dry-AMD by measuring FAF in up to 330 participants with GA-AMD.

Other approaches targeting inflammation

Doxycycline (Oracea). Doxycycline, a tetracycline-class antibiotic with anti-inflammatory properties at lower dose levels, is being assessed in a 286-patient Phase II/III study (TOGA) in GA-AMD supported by the Medarva Foundation. Patients are being randomised at to take either Oracea (40mg doxycycline, a formulation by Galderma (privately held) initially designed to treat rosacea) or placebo capsule once-daily for 24 months. Results are expected in or around late 2020. The primary endpoint is the rate of enlargement in area of GA during the treatment period, and secondary endpoints including change in BCVA. Some studies have previously found that doxycycline may reduce the frequency of IVT anti-VEGF-A doses needed to control the condition.[29]

RO7171009 (RG6147). Roche, through its Genentech division, has another Phase II stage candidate being studied for GA-AMD. The company in Q219 started a 285-patient Phase II study (GALLEGO) for RO7171009 (also called RG6147 or FHTR2163) for GA. The trial will evaluate the safety, tolerability and efficacy of IVT injections of RO7171009 administered every four weeks or every eight weeks for approximately 76 weeks, compared with sham control. The candidate is an antibody that inhibits HTRA1 (trimeric serine hydrolase high-temperature requirement 1), a serine protease gene associated with GA.[30] Roche/Genentech believe that the HTRA1 enzyme breaks down extracellular matrix protein, resulting in retinal atrophy, thus explaining the rationale for targeting it.

Targeting the visual cycle through vitamin A modification

Privately held Alkeus Pharmaceuticals is developing ALK-001, a once-daily oral drug candidate that is a chemically modified form of Vitamin A designed to prevent its aggregation into dimers. ALK-001 is in various clinical trials for the treatment of GA-AMD as well as for Stargardt disease. Vitamin A is essential for vision as it is the precursor to 11-cis retinal, a molecule that forms light-absorbing pigments in the retina. Vitamin A must be 'recycled' by RPE cells to maintain ongoing visual perception in a process called the visual cycle.

In normal aging, or due to rare genetic defects, improper recycling of vitamin A leads to accelerated formation of vitamin A dimers in the RPE. Some researchers hypothesise that these vitamin A dimers could be responsible for AMD progression by triggering a detrimental biological cascade in the retina, which includes the dysregulation of complement. Dimers form through the cleavage of specific chemical bonds of the vitamin A molecule. ALK-001 is a deuterated form of natural vitamin A, whereby the specific placement of deuterium (a hydrogen isotope containing one extra neutron, also called 'heavy hydrogen') on the molecule results in a c five-fold slowing of dimer formation, which could potentially slow the progression of GA.[31] [32]

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[29] Mirshahi A, et al. *Med Hypothesis Discov Innov Ophthalmol*. 2017. PMID: 29367931

[30] Tom I, et al. *Proc Natl Acad Sci* U S A. 2020. PMID: 32345717.

[31] Kaufman Y, Ma L, Washington I. *J Biol Chem*. 2011 Mar 11;286(10):7958-65. doi: 10.1074/jbc.M110.178640. Epub 2010 Nov 12. https://pubmed.ncbi.nlm.nih.gov/21075840/

[32] Charbel Issa P, et al. *Proc Natl Acad Sci U S A*. 2015. PMID: 26106163. https://www.pnas.org/content/pnas/112/27/8415.full.pdf

Aside from slowing the formation of dimers, ALK-001 behaves like natural vitamin A. In clinical studies, the drug rapidly reaches bioactive levels in the retina and enables vision in the same way as natural vitamin A without any indication of compromising the visual cycle in studies to date.

Alkeus completed a four-week Phase I study in c 40 volunteers, which showed a significant replacement of plasma vitamin A with deuterated vitamin A after four weeks of daily administration without dietary changes. No adverse effects, particularly ones that would be typical of vitamin A deficiency, were recorded.

Interim 12-month safety data on 50 patients in a separate two-year Phase II study in Stargardt disease, partly funded by the FDA, was presented in Q219 at the annual Association for Research in Vision and Ophthalmology (ARVO) meeting. ALK-001 was well tolerated with no unexpected AEs, no reports of night blindness or impaired dark adaptation and no meaningful increases in liver function tests or in total circulating vitamin A. The study has been expanded to 140 subjects, and some clinical efficacy data from this trial are expected in Q420.

We are not aware if any data on potential clinical efficacy for ALK-001 in dry-AMD or GA-AMD has been shown in any human trials to date. Alkeus in H119 started a 200- to 300-patient randomised Phase III study studying ALK-001 versus placebo for 24 months in patients with GA-AMD. The study is partly funded by the NIH and the primary endpoint is the growth rate of GA lesions, as assessed by FAF at 24 months. Top-line data are expected in Q123.

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 regulating synthetic peptide and its mechanism of action through this integrin regulation is based on mitochondrial stabilisation and the suspension of apoptosis (programmed cell death). 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 αvβ5, α5β1 (both associated with angiogenesis and vascular leakage) and αMβ2 (associated with inflammation). The company states that based on the drug candidate's ability to lower oxidative stress (occurring primarily in the mitochondria and driven by its destabilisation) and prevent further cell death, it believes the drug may be able to restore vision in patients with intermediate levels of Dry-AMD, namely patients whose macular cells have incurred damage but have not fully atrophied, and thus can be potentially salvageable. Allegro has thus been using an endpoint of restoration of vision (unlike the Dry-AMD studies discussed above focusing on later-stage Dry-AMD, where GA lesion size change was the primary endpoint).

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 (through mitochondrial stabilisation) before they can exert damaging effects in dry-AMD or DME.

Positive results for risuteganib were reported in June 2019 in a 45-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 pegcetacoplan and Zimura studies. In the trial, 25 patients underwent IVT risuteganib, and 14 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 primary endpoint was the percentage

of the population with ≥ eight letters of Early Treatment Diabetic Retinopathy Study (ETDRS) [33] scale BCVA gain from baseline to week 28 in the risuteganib arm versus from baseline to week 12 in the sham arm. The trial met its primary endpoint with 48% of patients in the risuteganib arm gaining at least eight letters of vision (at week 28) compared to baseline, versus 7% in the sham arm (at week 12, p=0.013). 20% of risuteganib-arm patients gained at least 20 letters versus none in the sham arm. Altogether, Allegro believes this study shows the first reversal of vision loss seen in any double-masked, placebo controlled Dry AMD trial.

Risuteganib was found to be safe with no reported drug-related SAEs. In reviewing the data, Allegro also identified some baseline anatomic predictors on OCT imaging that can be used to better predict which patients may better respond to treatment; the key consideration is that the macular tissue must be 'salvageable' (so cells must be diseased, but not dead), so the level of macular damage must not be so severe (or atrophic) to be 'past the point of no return' for some vision restoration to be possible.

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 plans to start a Phase IIb/III pivotal study in intermediate dry-AMD in Q420.

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 (although the primary endpoint of a Phase III study was not met in Q419), 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, increases adenosine triphosphate (ATP; cellular energy) production and reduces formation of pathogenic 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 the central macula (ie non-central GA). Patients with non-central GA (n=15) showed a mean increase in low-luminance VA, 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 enrolment expected to be completed in H220.

Cell-based therapies

The relatively immune-privileged[34] environment of the sub-retinal space has brought interest to cell-based therapies, which aim to either deliver cells that provide protective factors in the region or

[33] The ETDRS 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.

[34] Certain parts of the body (such as the eyes and central nervous system) have immune privilege, which refers to their ability to tolerate the introduction of foreign antigens without eliciting an immune response.

deliver new RPE cells (to support the health of the remaining photoreceptors). Several groups have attempted delivering cells into the retinal space through subretinal implantation. Some of these results suggest the potential for meaningful improvement, but considerations on the surgical implantation technique safety and long-term safety (including risk of neoplastic change) will likely need to be addressed before large-scale use in broad dry-AMD populations can be considered.

- Palucorcel (CNTO-2476) by Janssen (a subsidiary of Johnson & Johnson (JNJ, NYSE)) uses human umbilical cord tissue-derived cells (hUTC) and underwent a Phase I/IIa study (n=35) in patients with GA-AMD. While 34.5% of patients had VA gains of over 10 letters at a 12 months, the surgical procedure involved with placing cells in the sub-retinal space resulted in retinal perforations in 37.1% (13/35) subjects, including a 17.1% (6/35) rate of retinal detachments. While palucorcel was well tolerated, the study was suspended due to the significant risk of AEs. A subsequent Phase IIb study (n=21) was performed with the treatment delivered using a proprietary suprachoroidal surgical approach for subretinal delivery (designed to reduce the risk of AEs). While no retinal detachments, perforations or serious AEs occurred, no apparent treatment effect was observed at 12 months in this trial.
- Ocata Therapeutics, acquired by Astellas Pharma (4503, Tokyo) in 2016, had developed a human embryonic stem cell (hESC) based product, hESC MA09-hRPE, that had been tested in dose escalation Phase I/II studies (both via sub-retinal injection method, and n=13 each) in GA-AMD and Stargardt's macular dystrophy. There was no evidence of graft failure or rejection, and patients had a mean ~12 letter gain after treatment in the GA-AMD study but these gains gradually decreased (to 3.5, after excluding two patients with cataracts) by 36 months. Across both studies, there were two serious infectious treatment emergent AEs (appendicitis, urinary tract infection), a case of syncope, two events of squamous cell cancer and one event of basal cancer. Since the acquisition, a new cell line and enhanced formulation were developed resulting in a new drug product, ASP7317, which is compliant with regulations/guidance on cell therapies in each region (including the US FDA). ASP7317 is now being studied in a 150-patient Phase Ib/II trial assessing three cohorts for up to 26 weeks (primary study period), and for up to 60 months for safety.
- Privately held Regenerative Patch Technologies has developed a composite subretinal implant, called the California Project to Cure Blindness-Retinal Pigment Epithelium 1 (CPCB-RPE1), consisting of a polarised monolayer of hESC-derived RPE on an ultra-thin, synthetic substrate designed to mimic Bruch's membrane. The product was assessed in a 16-patient Phase I/II study and interim results report[35] that the implant was found to be safe for at least 120 days and that one patient had a VA gain of 17 letters in follow-up.
- The London Project to Cure Blindness (a collaboration involving the University College London Institute of Ophthalmology, Moorfields Eye Hospital and the National Institute for Health Research) reported that the implantation of an RPE patch, comprising a fully differentiated hESC-derived RPE monolayer on a synthetic basement membrane, resulted in significant VA gains of 29 and 21 letters in two NVAMD patients at 12 months.[36] Study investigators are planning to also assess the platform on dry-AMD.

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

Tissue grafts, for instance, can survive for longer periods of time in immune privileged sites by avoiding or delaying immune rejection.

[35] Kashani AH, Uang J, Mert M, eg al. *Ophthalmol Retina*. 2020 Mar;4(3):264-273.

[36] da Cruz L, et al. *Nat Biotechnol*. 2018. PMID: 29553577. http://rdcu.be/Js1a/ Accessed 3 August 2020.

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). We believe further clinical data will be needed to confirm previously reported trends in order to build confidence among physicians and stakeholders in the therapies and drive adoption. 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), at specific wavelengths and at controlled durations and locations, 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 company has stated that 670nm and 850nm energies, each acting in different ways, serve to 'stimulate metabolic activity (ATP), [and] inhibit inflammation and cell death'.

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. 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 also showed that PBM therapy was most beneficial in earlier-stage dry-AMD patients, as the majority of patients who had at least five letters BCVA improvement vs baseline did not have disease involvement at the foveola (the most central zone of the fovea, which itself is the central region of the macula).

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 will assess vision and AMD parameters in about 100 patients randomised to receive either PBM treatments using the company's Valeda System, or sham treatments (with the same device). The first patient was enrolled in October 2019, and subjects will be followed for up to two years. The primary endpoint will be mean change from baseline in BCVA at 21 months and other efficacy endpoints include contrast sensitivity and reduction of drusen deposits. Results are expected in H221.

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.

Currently, 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, but there is limited information on how much sales have been achieved to date or on the rigor of marketing efforts to generate sales at the current stage, particularly as LumiThera's current focus appears to be on building supportive data in the ongoing clinical studies.

The company raised $14m in a Series C round of funding in July 2020, in addition to having raised $10m in another round in January 2020 (Nikon was one of the investors in this round).

2RT by Nova Eye Medical. Nova Eye Medical (EYE, ASX), previously named Ellex Medical Lasers, completed the sale of most of its ophthalmic lasers business (treatments for cataract, glaucoma, etc) to Lumibird in June 2020. Nova Eye is now focussed on its iTrack minimally invasive glaucoma surgical product and its 2RT nanopulse laser therapy for intermediate forms of dry-AMD. 2RT applies a rapid nanosecond pulse, non-thermal laser intervention, also termed subthreshold nanosecond laser (SNL), targeting selected 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 (LEAD) 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 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 ECP 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).

The 2RT is already approved for sale in the EU, Australia and New Zealand in dry-AMD and sales in the second half of CY19 were A$0.8m (in European markets), down from A$1.3m in H218. In February 2020, the firm attributed the sales decline to 'negative sentiment, induced by competitive pharmaceutical company interests on the effectiveness of the therapy.' Hence, the current LEAD

post-hoc data, while promising, does not appear to have captured significant KOL attention to drive adoption in the currently approved regions. The 2RT currently also has 510(k) clearance for clinically significant macular edema in the US. Nova Eye submitted in H219 a clinical registration-enabling trial protocol for dry-AMD and held a meeting with the FDA in early 2020. The company is awaiting finalisation and acceptance by FDA of its IDE application and/or further clarity on the way forward for 2RT in the US market, which the company believes can also support overall product sentiment. 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 or clearance), but the prospect of non-invasive light-based treatment for what has been a largely untreatable degenerative condition and leading cause of vision loss appears promising.

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 (ALPIX, Euronext Growth; a research client of Edison Investment Research) is advancing a photovoltaic retinal implant-based platform, the Prima 2 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.

The Prima 2 platform is an integrated prosthetic visual system comprising an implant chip, augmented reality (AR) glasses, and an external pocket computer that processes the image data captured by the glasses before it is transferred wirelessly (by the AR glasses) to the implanted chip. The core element is a miniaturised photovoltaic wireless sub-retinal implant that is implanted underneath the retina in a surgical procedure that may take less than 90 minutes under local anaesthesia. The current Prima chip iteration under human clinical development is a 2mm × 2mm wireless chip (with 30 micron thickness) consisting of 378 electrodes (pixels) in total. Each photovoltaic pixel is independently controlled and self-powered by near-infrared light projected from the AR 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 RGCs (which are on the inner portion of the retina), and onto the brain through the optic nerve. The Prima 2 system is designed to restore the function of individuals whose retinal photoreceptors have been damaged by retinal disease such as severe GA associated with dry-AMD.

Initial human Prima chip implantations as part of a five-patient European feasibility study (PRIMA-FS) occurred in H217. These patients underwent visual rehabilitation and were initially adapted to use a first-generation of AR glasses and pocket computer to resolve prosthetic vision. Pixium had since worked on refining the system to improve functionality and enable it to allow patients to combine both prosthetic and natural residual (ie peripheral) vision, as the initial-generation glasses were opaque. The Prima 2 system employs the same (current-generation) 378-electrode implant

chip, but utilises an enhanced second-generation and transparent version of the AR glasses, and a new pocket computer employing improved algorithms, designed to incorporate more advanced image processing, magnification and artificial intelligence features to enhance the functional visual experience of patients. In mid-2019 Pixium amended the PRIMA-FS study to enable the patients (already enrolled and implanted with the 378-electrode chip) to transition towards use of the second-generation Prima 2 glasses and pocket computer instead of the initial-generation components.

Positive 18-month results were reported in late March 2020, and were based on the second-generation AR glasses and pocket computer, and showed improvements of between three and seven lines on the Landolt C VA scale versus baseline, as well as a continued favourable safety profile. Effective device-assisted prosthetic VA for the four remaining subjects (one of the five patients implanted has passed away due to health reasons completely unrelated to Prima implantation or usage) was between LogMAR 0.5 (approximately 20/60, or c 33% of normal VA expected in healthy subjects) and LogMAR 0.69 (approximately 20/100, or c 20% of normal VA). Altogether, these measures are markedly superior to the baseline results, representing significant improvements in the ability of the patients to resolve visual details, even given that they were assisted to a degree by the device's magnification features. Further, we are reassured that there is no degradation in Prima prosthetic visual performance between months 12 and 18 (and management indicates that this remains the case in some early 24-month data).

Altogether, this level could be sufficient to provide meaningful improvements and justify implantations in patients in late stages of dry-AMD, such as those with retinal scarring or GA reducing best-corrected VA in each eye to below 20/400 (5% of normal vision). For instance, the Prima 2 system can enable the recognition of symbols, letters and objects in patients who have lost the capacity to recognise those forms due to the severity of their disease; this could provide quality-of-life improvements for such patients.

Pixium intends to file a regulatory submission in H220 with, at minimum, the European regulators for approval to start the PRIMAvera pivotal study. We expect this registration-enabling study will start in H121 and could lead to EU commercialisation in H223. Our most recent sales forecasts are discussed in our 22 June 2020 Outlook report. Pixium remains in discussions to explore the possibility of conducting this study in parallel in Europe and the US, which if accepted by the FDA could lead to a US launch earlier than our baseline estimate of H225. A five-patient two-site US feasibility trial (PRIMA FS-US) is currently also underway, with two US patients having been implanted to date, although further US implantations are currently on hold due to the COVID-19 pandemic.

On the cusp of breakthroughs in AMD treatment

Altogether, AMD remains the leading cause of irreversible vision loss in older adults in developed countries. As people 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 discussed in our report, many new candidates on the horizon (such as OPT-302, ICON-4 or AKST4290) may potentially provide new treatment options for refractory NVAMD patients in the next half-decade or so. Further, current leading late-stage product candidates (faricimab, PDS-ranibizumab, KSI-301) appear more likely obtain approval sooner,

resulting in the potential for reduced invasive dosing frequencies for patients (as high as six months between treatments versus the current standard of two to three months for currently approved NVAMD drugs). Other next-generation NVAMD products in the pipeline (such as GB-102) hold the promise of even more durable treatment effects, particularly those that may employ gene therapy (namely RGX-314 and ADVM-022). Non-invasive NVAMD drug candidates may also allow for patient-administered therapy (namely AKST4290 or PAN-90806), greatly improving treatment compliance and overall safety by reducing the need for IVT or invasive treatments, but we believe longer studies will be needed to confirm the durability of these non-invasive drug treatments.

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 pegcetacoplan, Zimura and risuteganib as being particularly promising in this segment with the clinical data shown to date, although we are mindful of the failures of high-profile complement factor inhibitors like lampalizumab and LFG316. 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 appears promising but confirmation in subsequent trials appears to be needed for these products to obtain commercial traction in currently approved territories (and to gain commercial access to the US market). 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 the industry for both dry-AMD and NVAMD appears 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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