Corporate M&A pace gathers momentum

BY ROD MCNEIL

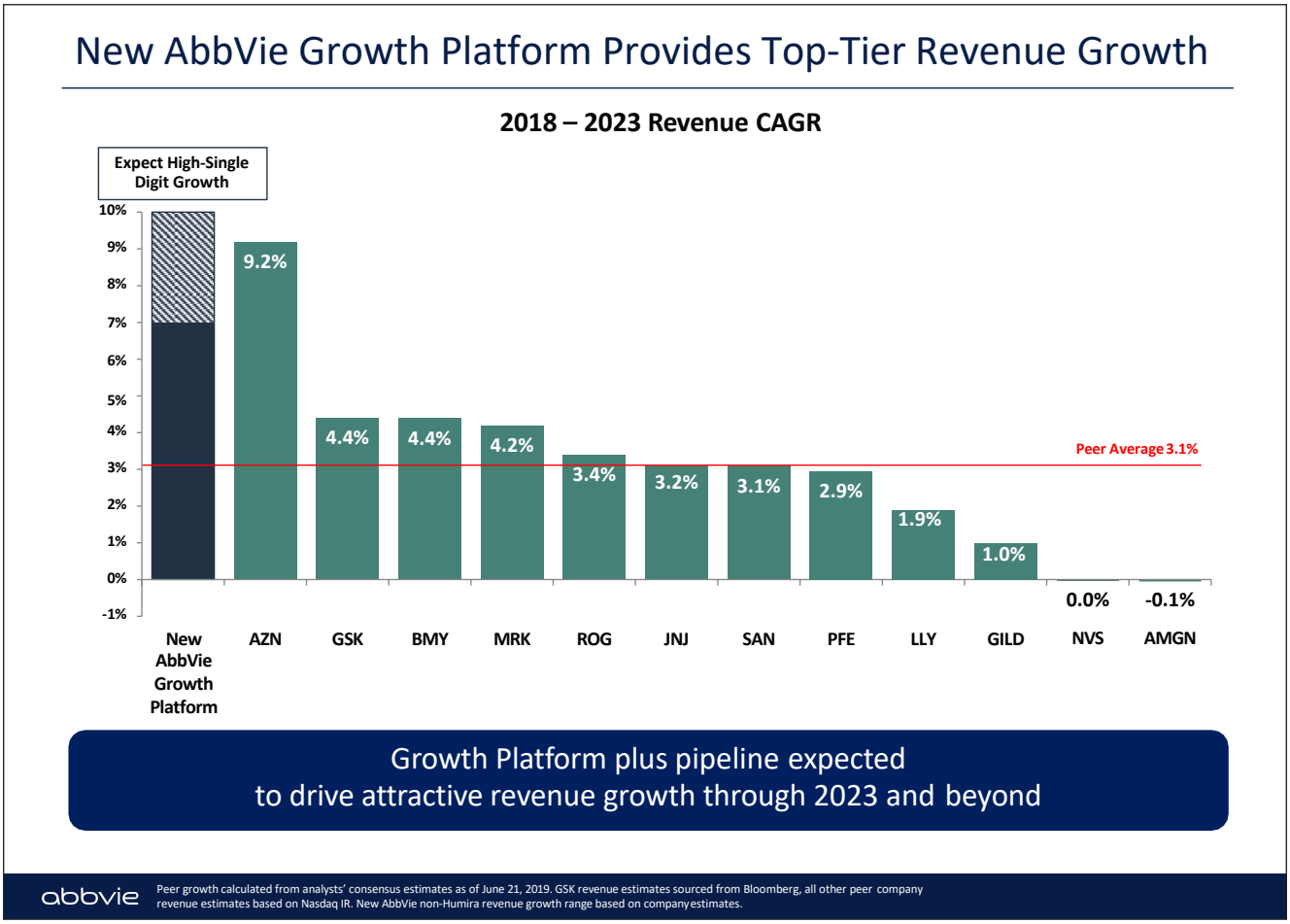
Intensifying franchise competition, maturing product development pipelines and looming loss of exclusivity spur renewed merger and acquisition (M&A) activity in the ophthalmics sector. **Rod McNeil** reviews recent deals and related strategic developments.

AbbVie to acquire Allergan in $63 billion mega-combination, creating an innovative, diversified biopharmaceutical leader

Chicago-based AbbVie, a spin-off from Abbott Laboratories, announced in June 2019 an agreement to acquire Allergan for a transaction equity value of approximately $63 billion, with the aim of establishing an innovative and diversified biopharmaceutical leader and described as transformational for both companies. The transaction significantly expands and diversifies AbbVie's revenue base ahead of the Humira US patent expirations in 2023, the arthritis drug currently accounting for around 60% of total revenue.

In a press statement, AbbVie said the combined company will comprise a number of attractive franchises with leadership positions across immunology, haematologic oncology, medical aesthetics, neuroscience, women's health, eye care and virology. The transaction is anticipated to close by early 2020, subject to regulatory and Allergan's shareholder approvals. AbbVie Board of Directors will include two Allergan board members, including current CEO Brent Saunders.

For AbbVie, Allergan represents a collection of highly attractive, durable growth assets, with revenues of $15.8 billion in 2018, including $4.3 billion from medical aesthetics and $2.3 billion (excluding Restasis revenue of $1.262 billion) from eye care. The eye care franchise provides multiple late-stage pipeline opportunities, offering potential to expand presence by targeting unmet needs in retinal disease and innovation in glaucoma toward drop-less therapy. Overall, the new AbbVie



Figures 1 and 2: 2018 – 2023 revenue CAGR and AbbVie Track Record.
Source: Abbvie. Creating a new diversified biopharmaceutical company. The combination of AbbVie and Allergan. Investor Presentation June 25, 2019.

growth platform is forecast to provide top-tier revenue growth, significantly mitigating 2023 US Humira loss of exclusivity (Figures 1 and 2). Synergies and cost reductions of more than $2 billion in year three are expected. Key franchise funding levels "will remain untouched allowing them to maximise performance."

Allergan posted revenues of $7.68 billion for the six months ended June 2019, down 1.4% compared with the same period last year. Sales of intravitreal dexamethasone implant (Ozurdex) were $204.3 million in the first half of 2019 (US, $60.2m; International, $144.1m), an increase of 10.2% over the first half of 2018. Significant launches expected over the next 12 months include glaucoma treatment bimatoprost sustained-release (SR) (first half 2020) and abicipar for neovascular age-related macular degeneration (nAMD) (mid-2020 in the US) (Table 1). In July Allergan announced that the US Food & Drug Administration (FDA) accepted its new drug application (NDA) for bimatoprost SR in patients with primary open-angle glaucoma or ocular hypertension. Bimatoprost SR if approved would be the first-in-class sustained-release, biodegradable implant for the reduction of intraocular pressure in patients with glaucoma or ocular hypertension.

The NDA is based on the positive results from the ARTEMIS phase 3 studies. Bimatoprost SR reduced IOP by 30% over the 12-week primary efficacy period, meeting the predefined criteria for noninferiority to the study comparator, timolol. After three treatments with bimatoprost SR, greater than 80% of patients remained treatment free and did not need additional treatment to maintain IOP control for at least 12 months. Bimatoprost SR was well

Table 1: Allergan eye care franchise: key pipeline catalysts over the next 12-18 months.

Product	2H'19	2020
Abicipar (nAMD, DMO)	Filing of Biologics License Application with US FDA and validation of EMA Marketing Authorisation Application for abicipar pegol in nAMD	LAUNCH in nAMD; Phase 3 initiation in DMO
Brimonidine DDS, intravitreal implant (Geography Atrophy)	Initiation of Phase 3 studies	
Brimonidine SR (Glaucoma)	NDA filed with FDA. PDUFA in 1H'20	LAUNCH
Presbysol (Presbyopia)		Phase 3 topline results

Abbreviations: nAMD, neovascular age-related macular degeneration; DDS, drug delivery system; DMO, diabetic macular oedema; SR, sustained release.
Source: Allergan.

tolerated in the majority of patients.

Abicipar-pegol (abicipar), a designed ankyrin repeat protein (DARPin), is a selective, high-affinity, long-acting vascular endothelial growth factor (VEGF) inhibitor under evaluation as a treatment for retinal diseases. In two phase 3 clinical trials (SEQUOIA, n=949; CEDAR, n=939) in treatment-naïve patients with nAMD, each abicipar 2mg regimen (every eight weeks and every 12 weeks, after loading doses) met the primary endpoint of noninferiority to ranibizumab (Lucentis, Novartis) administered every four weeks for stable vision (<15-letter loss in best corrected visual acuity (BCVA) from baseline) at week 52 [1]. Reductions in central retinal thickness at week 52 were similar between abicipar (after six to eight injections) and ranibizumab (after 13 injections) in both studies. As a result of improvements in the manufacturing process, the incidence of intraocular inflammation was 8.9% in the MAPLE study, lower than the rate observed with abicipar in prior phase 3 studies (>15%).

Efficacy and safety results from both phase 2a and 2b studies support continued development of brimonidine drug delivery system (DDS) intravitreal implant for geographic atrophy. In the BEACON phase 2b study, brimonidine significantly reduced mean geographic atrophy area growth at 24 months (10% reduction) and 30 months (12% reduction) [2]. The effects seen in phase 2a and 2b studies were driven primarily by patients with lesions above baseline median. Quarterly administration of brimonidine DDS had an acceptable safety profile over 30 months.

New Alcon, independent eye care devices company

Novartis completed the spin-off of the Alcon eye care devices business as a separate public company on 9 April 2019, with Geneva-based Alcon reaching a market capitalisation of 28 billion swiss francs on its debut on the SIX Swiss Exchange. This now positions Alcon as an independent leader in ophthalmology while strengthening the position of Novartis as a diversified medicines company.

Earlier in 2019 Alcon acquired PowerVision, Inc., a privately-held, US-based medical device development company focused on creating fluid-based accommodating intraocular lenses (IOLs) for cataract surgery patients. Under the terms of the agreement, Alcon paid $85 million to PowerVision at closing with additional payments based on specified regulatory and commercial milestones starting in 2023. The acquisition demonstrates Alcon's commitment to driving growth and innovation in advanced technology IOLs (AT-IOLS) to meet the needs of cataract surgery patients who desire spectacle independence. In December 2018 Alcon acquired Tear Film Innovations, Inc. ("Tear Film"), a privately-held company and manufacturer of the iLux Device, an innovative therapeutic device used to treat meibomian gland dysfunction. The iLux device is currently available in the US and Canada.

Alcon aims to consolidate and expand its position as a growing eye care device leader, leveraging its top or leading position in all product categories within the ophthalmic surgical and vision care markets. For the second quarter to end June 2019, surgical net sales of $1.1 billion, which include implantables, consumables and equipment / other, increased 2%, or 5% on a constant currency basis, compared with the second quarter of 2018. Strong international demand for PanOptix and monofocal IOLs, pull-through of dedicated consumables, strong cataract equipment and service revenue were the primary drivers of growth. Vision Care net sales of $0.8 billion, which include contact lenses and ocular health, increased 3%, or 6% on a constant currency basis, compared with the second quarter of 2018. For the first six months of 2019, Alcon's worldwide sales were $3.6 billion, up 1%, or 5% on a constant currency basis, compared with the first six months ended June 30, 2018. Figure 3 shows Alcon's mix of vision care and surgical products, based on Q2 2019 financial results.

Novartis boasts 'catalyst-rich pipeline'

Novartis said it has a 'catalyst-rich pipeline' with 10 potential blockbuster launches expected in the next two years and an additional 20 potential blockbusters (individual assets with peak annual sales >$1 billion across all indications) on the horizon. Of these potential blockbuster launches, four are planned in 2019, including brolucizumab (RTH258, brandname Beovu) for nAMD, filed in the European Union (EU) and US and

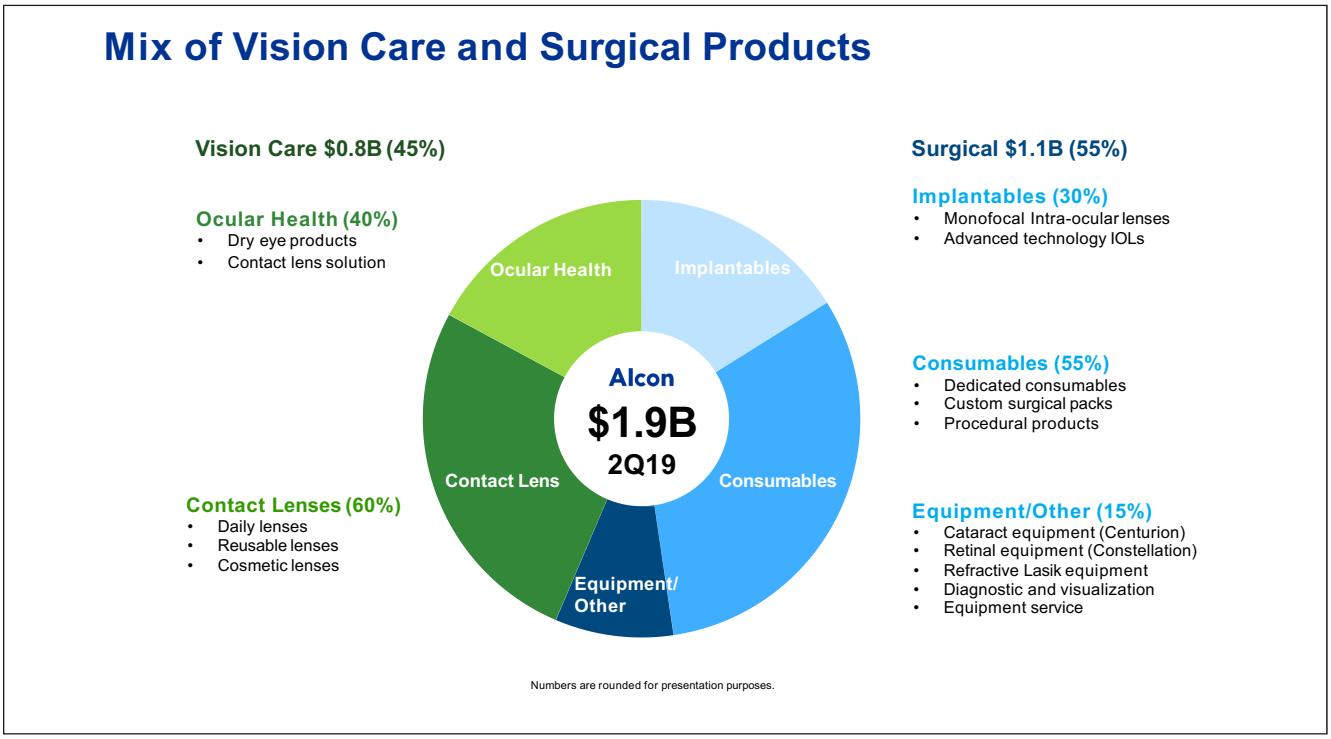


Figure 3: Alcon mix of vision care and surgical products.
Source: Alcon. 2Q19 Earnings Conference. August 21, 2019.

launch in the US anticipated in Q4 2019. Launch is anticipated in Australia / Canada in Q1 2020 and in Europe / Japan in Q2 2020. The Novartis ophthalmology pharmaceuticals business generated sales of $4.6 billion in 2018 and the pipeline, in addition to brolucizumab, includes potential novel treatments for presbyopia, dry eye, chronic ocular pain and genetic diseases.

Novartis completed the acquisition of Xiidra (lifitegrast ophthalmic solution) 5% from Takeda Pharmaceutical Company on 1 July 2019. Xiidra, a lymphocyte function-associated antigen-1 (LFA-1) antagonist, is the first and only prescription treatment approved to treat both signs and symptoms of dry eye with a mechanism of action that targets inflammation [3]. It is approved in multiple markets including the US, Canada and Australia and is under regulatory review in a number of additional markets. Xiidra achieved $0.4 billion of revenue in 2018. Deal terms include a $3.4 billion upfront payment with potential milestone payments of up to $1.9 billion. Novartis believes the product has clear blockbuster potential, given high unmet medical need with strong product profile. It has a fast onset of action, two weeks to three months, with a tolerable safety profile. US prescriptions are expected to climb with increasing incidence of dry eye and use of more effective therapies.

The safety and efficacy of lifitegrast for the treatment of dry eye disease were assessed in a total of 1181 patients with dry eye disease (1067 of which received lifitegrast 5%) in four 12-week, placebo-controlled studies [3]. The mean age was 59 years and the majority of patients were female (76%). In all four studies, a larger reduction in the Eye Dryness Scale (EDS) score was observed with Xiidra at six and 12 weeks. In two of the four studies, an improvement in EDS was seen with Xiidra at two weeks. At week 12, a larger reduction in inferior corneal staining score (ICSS) favouring Xiidra was observed in three of the four studies. The most common adverse reactions reported in 5-25% of patients were instillation site irritation, dysgeusia (an unusual taste sensation) and reduced visual acuity.

Roche to acquire Spark Therapeutics

Roche announced its planned $4.3 billion acquisition of Spark Therapeutics, Inc. in February 2019, following a definitive merger agreement between both companies. Spark Therapeutics, founded in 2013 and headquartered in Philadelphia, US, is a fully integrated, commercial company committed to discovering, developing and delivering gene therapies for genetic diseases, including blindness, haemophilia, lysosomal storage disorders and neurodegenerative diseases.

Spark Therapeutics was the first company to receive FDA approval for a gene therapy for a genetic disease in 2017. Luxturna (voretigene neparvovec-rzyl), a one-time gene therapy product indicated for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy is currently marketed in the US by Spark Therapeutics. The company shipped 75 vials of luxturna in the US in 2018, posting total revenue of $64.7 million, of which $27.0 million was net product sales of luxturna and $37.8 million was contract revenue associated with agreements with Pfizer and Novartis. The European Commission granted marketing authorisation for luxturna in 2018, representing the only gene therapy approved in EU for patients with an inherited retinal disease. Spark Therapeutics will manufacture and supply luxturna for Novartis, while Novartis has exclusive rights to pursue development, registration and commercialisation in all other countries outside the US.

The acquisition provides Roche with an expanded haemophilia portfolio that includes multiple investigational gene therapies, with three programmes now in clinical trials, including lead clinical asset SPK-8011, a novel gene therapy for the treatment of haemophilia A.

Roche also announced in July 2019 it had secured global rights to the ranibizumab port delivery system (PDS) intravitreal implant, designed to release ranibizumab over a period of months. Phase 3 clinical trial (Archway) results – evaluating the PDS with ranibizumab implanted at baseline and refilled at fixed 24-week intervals compared to monthly ranibizumab injections in participants with nAMD – are expected mid-2020. Roche acquired the PDS technology through its acquisition of biotechnology company ForSight VISION4 in January 2017, and Novartis had an option to commercialise it with ranibizumab outside the US. Table 2 provides an outline of Roche's ophthalmology product development portfolio.

Nightstar matures

Biogen acquired gene therapy company Nightstar for $800 million in June 2019. Nightstar has two mid- to late-stage clinical product candidates, including preclinical programmes, in ophthalmology. Nightstar's lead product candidate is NSR-REP1, currently in phase 3 development for the treatment of choroideremia (CHM), a rare, degenerative, X-linked inherited retinal disorder. Nightstar's second product candidate, NSR-RPGR, is currently being evaluated in a phase 1/2 clinical trial for the treatment of patients with X-linked retinitis pigmentosa.

Syncona founded Nightstar in 2013 with Professor Robert MacLaren of Oxford University. In its annual results statement for the year ended 31 March 2019, Syncona commented: "It is a strong example of our differentiated approach of founding, building and funding innovative companies and we look forward to seeing Nightstar work to deliver transformational treatments to patients during the next phase of its development with Biogen."

DORC to expand geographically with support from new owner Eurazeo

Global investment company Eurazeo Capital acquired DORC in April 2019 from Montagu Private Equity. Eurazeo said the acquisition "fits perfectly with our investment strategy to support growing businesses with a strong international development potential as they scale up."

Headquartered in the Netherlands, DORC designs, manufactures and distributes ophthalmic surgery equipment, instruments and consumables worldwide. DORC generated revenues of €125 million in 2018, with an average annual growth rate of 9% over the past three years and significant market share gains achieved in Europe and the US. The company is valued at c. €430 million (enterprise value), of which approximately €300 million equity was funded by Eurazeo and its affiliates. Eurazeo Capital expects to leverage its international network to accelerate DORC's growth.

In January 2019 DORC introduced an upgrade to its high-performance EVA phaco-vitrectomy system, including an integrated footswitch to maximise surgeon control and a new LED module for enhanced illumination during small-gauge vitrectomy. DORC recently launched a 27G ultra-short vitrectomy kit for surgical challenges of smaller eyes, an enhanced soft tip backflush design, and a new 25G illuminated curved laser probe, enabling bimanual vitreoretinal surgery during laser photocoagulation.

Thierry Leclercq, CEO of DORC, explained: "With support from Eurazeo, we fully expect to invest – organically and through M&A – and expand geographically as a priority. Moreover, we also want to deliver innovation through our ophthalmic portfolio in posterior surgery and also adjacent anterior surgical segments. We are confident of the significant growth potential in both segments building on our existing strong or market leadership positions."

Glaukos acquisition of Avedro establishes cornerstone of its new corneal health franchise

Glaukos Corporation and Avedro announced in August 2019 a merger agreement under which Glaukos will acquire Avedro in an all-share transaction. Avedro is a hybrid ophthalmic pharmaceutical and medical

Table 2: Roche ophthalmology product development portfolio, July 2019.

Compound / generic name	Indication	Clinical trial phase	Expected filing
RG6179	Diabetic macular oedema	1	
RG7921	Neovascular age-related macular degeneration	1	
IONIS ASO factor B, an antisense oligonucleotide that inhibits complement factor B gene expression by binding with factor B mRNA	Geographic atrophy	2	
RG6147	Geographic atrophy	2	
RG6321 ranibizumab delivered via port delivery system, sustained delivery implant	Age-related macular degeneration port delivery system with ranibizumab	3	2021
RG7716 faricimab, bispecific antibody developed with CrossMab technology to tightly bind VEGF-A on one arm and angiopoietin (Ang)-2 on the other arm	Neovascular age-related macular degeneration	3	2022+
RG7716 faricimab	Diabetic macular oedema	3	2022+

Source: Roche.

technology company focused on treating corneal disease and disorders. Glaukos aims to build a comprehensive and proprietary portfolio of micro-scale surgical and pharmaceutical therapies in glaucoma, corneal health and retinal disease, creating a "hybrid pharma and device ophthalmic leader."

Glaukos said in a press statement the acquisition establishes the cornerstone for its new corneal health franchise. Avedro launched Photrexa in the US in 2016, a bio-activated topical pharmaceutical therapy for corneal cross-linking treatment of keratoconus disease. Avedro has also developed a pipeline of novel single application bio-activated topical ophthalmic pharmaceuticals for common refractive conditions, including presbyopia, low myopia and post-cataract refractive error.

Glaukos launched its next-generation iStent inject device in the US in September 2018. Glaukos will be the exclusive distributor of Santen's MicroShunt in the US, responsible for sales and distribution of the product, upon potential US regulatory approval. In the US, the MicroShunt (DE-128) is an investigational ab-externo, minimally-invasive surgical implant being studied for the treatment of primary open angle glaucoma in patients where IOP is uncontrolled under maximum tolerated medical therapy or where the progression of disease warrants surgery. Marketed under a CE mark in Europe as InnFocus MicroShunt, the minimally invasive glaucoma surgery (MIGS) device has been rebranded under the new global commercial name of PreserFlo MicroShunt.

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