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Novartis Sees The Light And Plumps For Alcon Spin-Off

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Hot on the heels of divesting its stake in the **GlaxoSmithKline PLC** consumer joint venture, **Novartis AG** is to spin off its eye care unit Alcon and focus on becoming "a leading medicines company," in the words of CEO Vas Narasimhan.

The Swiss major has completed a strategic review that examined all options for Alcon ranging from retention, sale or spin-off and has now plumped for the latter. The board intends to seek shareholder approval for the spin-off at Novartis' annual general meeting in February next year.

Since splashing out $52bn to buy Alcon from **Nestle SA** back in 2011, the group's fit within Novartis has been problematic. Its two main sub-divisions of surgical and vision care (such as contact lenses) have struggled to grow and it was only from the second half of last year, following heavy investment by its parent, that the Alcon business began its turnaround.

Narasimhan said in a statement that "Alcon has returned to a position of strength and it is time to give the business more flexibility to pursue its own growth strategy as the world's leading eye care devices company." When the spin-off is completed, it will create a new Switzerland-based company with more than 20,000 employees and around $7bn in sales (2017 figures).

Alcon is going to be listed on both the Swiss and the New York stock exchanges and Novartis stressed that Fort Worth in Texas would continue to be a key location for the group. It is too early to put a specific valuation on Alcon but the figure being bandied around is $20-25bn, way below what Novartis originally paid, though it should be noted that the Basel-headquartered giant will retain Alcon's ophthalmology pharmaceuticals business.

The latter unit had 2017 sales of $4.6bn and currently has in the pipeline the potential blockbuster brolucizumab. The drug is in development for neovascular age-related macular degeneration and diabetic macular edema.

Analysts have responded positively to the spin-off plan, which Novartis expects to be tax neutral. Deutsche Bank issued a note saying that "the split makes sense to a combination that made little sense," adding that "the decoupling puts an end to what was an uncomfortable marriage of two good businesses that, in our view, had limited reason in being together except in a quest for diversification and earnings bridging through patent expiries."

The broker added that stockholders would essentially receive shares in both companies "and the deal should allow them to better realise the sum of Novartis' parts while allowing greater strategic flexibility for both management teams." The analysts went on to say that "given there was little overlap between the business functions and the carve-out of shared admin services is largely done, we see only modest additional earnings disruption."

PharmaVitae analyst Oliver Spray told *Scrip* the decision to spin off Alcon followed the strategic pathway set out by Narasimhan when he became CEO earlier this year "which seeks to focus on cutting-edge therapies for oncology and rare diseases." It will allow Novartis "to focus on the increasingly

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Dermira and Array celebrate market debuts (p12-13)

Private Equity Digs In
PE interest apparent in Recordati and Sanofi sales (p4-5)

End Of The Road?
FDA panel throws doubt on abuse-deterrent opioids (p10-11)

from the editor

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With Novartis having decided finally to sell Alcon, questions arise again about the future of Sandoz. CEO Vas Narasimhan acknowledges that the generics business faces price erosion in the US and his team is working out how to keep it competitive (see cover story). As our story on the 2017 rankings of the world's top generics firms on p9 shows, it is not the only one struggling in the US.

Meanwhile, Novartis' branded pharma business is an enthusiastic innovator in value negotiation. It and partner Amgen recently presented a migraine study at the American Headache Society's annual meeting which provides a concrete example of how pharma companies could gain a better reception for their value proposition. In short, Novartis backed a patient study that shed light on the burden of migraine in workplaces by putting numbers of the productivity cost of the disease.

Still, this kind of data doesn't get the best reception in traditional health technology assessments. If pharma is frequently frustrated in getting healthcare payers to acknowledge the broader value to society of their medicine, then it makes sense to take the message where the costs of not treating the disease are felt more acutely. In Novartis/Amgen's migraine case, this means engaging with employers by offering workplace programs that help cut the number of days people take off work.

It's not stated explicitly, but getting employers on side may well help Novartis and Amgen sell more of their new migraine drug *Aimovig*. Which should help offset its competitive price.

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Aquinox, Astellas Mull Options As Rosiptor Fails
https://bit.ly/2KIt5fv
Astellas' late-stage bet on Aquinox's urology drug now looks highly unlikely to pay off following the molecule's "definitive" failure in a Phase III trial, which is also forcing the originator to consider its business and R&D options.

Roche's IMpassion130 Is First Positive Phase III Immunotherapy Study In Triple Negative Breast Cancer
https://bit.ly/2zgNUh5
Phase III IMpassion130 study showed Tecentriq plus Abraxane significantly reduced the risk of disease worsening or death in people with metastatic triple negative breast cancer.

Lilly's Taltz Gets Closer To A Level Playing Field With Novartis' Cosentyx
https://bit.ly/2tUkMGY
Lilly reported positive results for Taltz in a second Phase III study in ankylosing spondylitis and plans to file for FDA approval this year, which would give the IL-17A inhibitor a label similar to its rival Cosentyx, for which Novartis is working hard to build, maintain and grow market share.

Celgene Notches A Needed Win As Acceleron-Partnered Luspatercept Succeeds In MDS
https://bit.ly/2tVsEY6
Celgene delivers positive top-line Phase III results for a key pipeline drug as luspatercept reduces the need for blood transfusions in patients with myelodysplastic syndromes. Partner Acceleron's stock soars ahead of a detailed data presentation later this year.

Deal Watch: Amazon Moves Into Rx Services With Acquisition Of PillPack
https://bit.ly/2IPHHIb
Celgene makes play into RNA-expression correction via neuroscience partnership and equity investment with Skyhawk. Novartis' Sandoz agreed to commercialize Adamis' Symjepi, a competitor to EpiPen, in the US.

Finance Watch: Is The IPO Boom Making Anyone Nervous Yet?
https://bit.ly/2KIJmkN
Public Company Edition: Is the IPO bubble getting ready to burst? It's anybody's guess, but biopharma companies are forging ahead, having launched 11 first-time offerings during the past week and a half. Also, Heron leads recent follow-on offerings with a $200m stock sale to fund what may soon be its third commercial product.

inside:

Recordati Founding Family Sells €3bn Stake

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The Recordati family has sold the holding company that owns the majority stake in the Italian pharma firm that bears its name to a consortium of private equity funds led by CVC.

The latter is paying €3.03bn for FIMEI SpA, which owns 51.8% of the company. The value of the deal is almost 18% below the closing price of **Recordati Industria Chimica & Farmaceutica SPA**'s shares on the Milan stock market prior to the announcement. However, the share price had been pushed up in recent weeks by rumors of a pending buyout valued at up to €9bn, and general stock market turbulence in Italy.

CEO Andrea Recordati has invested alongside the private equity partners, and will retain his position at the firm, as will incumbent managing director and chief financial officer Fritz Squindo.

CVC said it would be looking to expanding Recordati's rare disease business, helped by its own "expertise and global healthcare network" to "build a global leader in the industry."

Recordati reported first-quarter revenue growth of 7.2% to €366.5m on May 8, and net income growth of 10.3% to €86.6m. It reiterated a forecast of 2018 sales of €1.35-1.37bn and net income of €310-315m, up from €1.29bn and €289m respectively in 2017. EBITDA was €455m in 2017. In recent years the company has looked to diversify away from a focus on primary care into the potentially more lucrative orphan drug and specialty care space.

However, it suffered a setback recently when partner **Erytech Pharma SA** announced it was pulling its European marketing authorization application for *Graspa* (eryaspase) for acute lymphoblastic leukemia because of the rapid pace of improvements in treatment options for the disease, which was already a small market opportunity. The product, which Credit Suisse described in a May 9 note as Recordati's "most significant late-stage R&D asset," had been expected to win approval in Europe in the fourth quarter.

STOCK EXCHANGE LISTING EXPECTED TO STAY

Once the FIMEI acquisition has closed, the CVC Fund VII-led consortium will make a tender offer to the remaining minority shareholders, as required by Italian law, at €28.00 per share in cash. This is the implied value of the shares under the holding company buy-out, which would give Recordati a 100% equity value of €5.86bn.

The investors however expect Recordati to remain listed on the Italian stock exchange. Its shares only briefly fell below €28.00 in late March and otherwise have traded higher than that since February 2017, peaking at €40.60 in November 2017 and closing at €34.06 on June 29, 2018, the last trading day before the deal was announced. The shares opened down 17.4% at €28.12 after the deal was announced on July 2.

The €3.03bn will include a €2.3bn cash payment and €750m in subordinated long-term debt securities to the Recordati family. Other investors in the consortium include PSP Investments (the Canadian public sector pension investment manager) and StepStone.

Andrea Recordati took over as CEO of the firm, which was founded in 1926, following the death of his step-brother Giovanni Recordati in 2016. Giovanni's brother Alberto Recordati is current chairman but it is likely CVC will nominate a successor once the transaction closes.

CVC invests across a range of sectors, and is already active in healthcare with investments in medical providers. It also completed the purchase of the women's health business of **Teva Pharmaceutical Industries Ltd.** in Feb. 2018, forming London-based **Theramex**.

Private equity (PE) firms are showing increasing interest in the life sciences space, with several investments in outsourced clinical services businesses and less frequently pharma businesses themselves. Martin Gouldstone, partner at corporate advisory firm Results Healthcare, flagged up at a recent event focused on private equity activity in the healthcare/biotech/medtech space the factors that are driving deals, including the large amounts of capital PE has built up. He noted that the scarcity value of suitable investment opportunities in the space, new market entrants in PE and competition from "strategics" (ie, other companies in the sector looking to consolidate) were driving a boom in PE investment in life sciences.

Gouldstone's fellow partner Kevin Bottomley underscored that for his clients, PE can prove to be the "best buyers, who will invest in the business going forward." Gouldstone noted that these days, "PE can enable management to retain some control and grow the business."

He doesn't see PE activity in the health space declining for some time because firms have raised "significant funds" and are "expanding geographically, trying to capture opportunity."

Another private equity source said that their firm was investing in the healthcare space with an interest in "commercial risk rather than development risk." They highlighted as attractive targets for PE old drugs with potential for future commercial growth to be optimized, and companies with two or three products in a specialty pharma niche looking to expand their portfolio.

Sanofi only last week finalized the sale of its generics business **Zentiva BV** to PE group Advent, for €1.9bn.

Last year, German pharma **Stada Arzneimittel AG** was sold to PE buyers Bain Capital and Cinven for about €5.4bn.

And contract research organization **Parexel International Corp.** was bought by Pamplona Capital Management in 2017's other biggest PE healthcare buyout, worth $5bn including debt.

The Recordati/CVC deal was valued at 13.3 X EBITDA, giving it the highest multiple of the recent specialty pharma PE buy-outs. Zentiva and Stada were around 12.5-13 X EBITDA.

According to Tommy Erdei, joint global head of pharma and life sciences at Jefferies, which acted as financial adviser to the Recordati family on the agreement, the increasing participation of PE in pharma deal-making reflects the changing dynamics in the specialty pharma subsector: where once there were strategic firms like **Valeant Pharmaceuticals International Inc.**, Teva, **Mylan NV** and Meda very actively pursuing significant M&A tactics, "those strategics are currently more internally focused, after a spree of deals allowing these PE opportunities," and PE is now less likely to be "trumped" by such companies.

He said that as funds got bigger and found it challenging to find large enough opportunities to put their equity to work, the "very natural buy and build strategy" that works better in pharma than in many other sectors made it attractive.

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CONTINUED FROM COVER

competitive area of digital technologies which companies like **Roche** are already using to augment their cancer therapies," he said, adding that the group was also increasing its exposure to gene and cell therapies "in an attempt to stake a leadership position in this growing market."

In January, Novartis gained European rights to **Spark Therapeutics Inc.**'s gene therapy *Luxturna* (voretigene neparvovec) in Europe, and then in April spent $8.7bn on the gene therapy biotech **AveXis Inc.**. At the beginning of this year, it also completed the $3.9bn acquisition of French oncology specialist Advanced Accelerator Applications.

$5BN SHARE BUYBACK, SANDOZ SAFE FOR NOW

The focus on innovative pharma drove Novartis' decision in March to sell its stake in a consumer healthcare joint venture with GSK. That deal brought in $13bn and proceeds from that transaction will be used to fund a share repurchase program of up to $5bn to be executed by the end of 2019.

Narasimhan said the share buyback "is fully aligned with our strategic capital allocation priorities, reflects our strict financial discipline and our confidence in future top-line growth and margin expansion."

The Alcon spin-off plans and the exit from consumer health have again led some observers to wonder whether the next divestment by Novartis could be the generics business Sandoz, which has struggled in US markets in recent months. Spray told *Scrip* that the PharmaVitae team very much doubted such a move would take place, saying "we believe that Novartis will opt instead to follow the industry-wide trend of focusing on products that are insulated from pricing pressure and towards more complex and expensive alternatives." He added that the success of Sandoz would also hinge on strong launches of drugs in its biosimilar program, which currently consists of eight products.

On a conference call, Narasimhan said that Sandoz was a core business, noting that it was the number two generics company in the world, and arguably number one in biosimilars. However, he acknowledged the price erosion problems the unit was facing in the US and said Novartis was evaluating how to optimize Sandoz and ensure that it stayed competitive.

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Sanofi Finalizes Zentiva Sale

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Almost a decade after the purchase of **Zentiva BV**, **Sanofi** has now finished negotiations with the private equity firm Advent International for the €1.9bn sale of its European generics business, as the French drugmaker continues to reshape its operations and focus on its newer purchases **Bioverativ Inc.** and **Ablynx NV**.

Sanofi and Advent have now signed a share purchase agreement for the sale of Zentiva, having announced April 17 that they had entered into exclusive talks. In a statement, the companies said that the signing marked "a critical step on the way to the closing of the deal," and the transfer was anticipated during the fourth quarter of 2018.

Sanofi bought Zentiva for €1.8bn in 2009, a year that also saw the firm acquire Medley, Brazil's largest generics manufacturers and Laboratorios Kendrick, one of Mexico's leading generics companies. Although only getting a bit more than it paid for Zentiva, the Czech-headquartered business has made solid contributions to Sanofi's coffers, with sales last year coming in at around €760m.

Advent is getting its hands on a company which claims on its website to reach over 40 million patients in 25 European countries, "operating throughout a large marketplace with attractive levels of both short- and mid-term growth outlook." Zentiva says that it "stands apart with the expertise and agility to tailor customer-centric solutions in the three European generics market archetypes (pharmacy, physician and tender/wholesaler)" and its "flexible manufacturing facilities in Prague and Bucharest work with partners to produce and distribute more than 350 million packs each year."

Announcing plans to sell in April, Sanofi CEO Olivier Brandicourt described Zentiva as "a robust business with a highly talented workforce and we believe it has demonstrated its potential for growth." However, a comprehensive review of strategic options has revealed that a European generics business is not part of the turnaround Brandicourt has been directing since taking over the helm in February 2015.

Charged with tackling the challenge of dealing with the decline of its diabetes franchise, the CEO has not been shy in embracing M&A. Sanofi sees consumer healthcare as core, with the Paris-headquartered big pharma exchanging its animal health business for **Boehringer Ingelheim GMBH**'s consumer health portfolio last year while 2018 has already seen the company splash out €16bn on the hemophilia specialist Bioverativ and the nanobody platform Belgian firm Ablynx.

Selling Zentiva adds €1.9bn to Sanofi's warchest but observers will probably have to wait until July 31 when the company reveals its second-quarter financials for clues as to what the money will be spent on. As to what those figures will look like, analysts at Deutsche Bank recently issued an investor note saying that "we expect 2Q to be another tough quarter in a turnaround year," and claiming that the second quarter "is a risk event that needs to pass before investors could become increasingly comfortable with Sanofi's then-likely positive earnings momentum."

The broker is forecasting sales of €8.3bn. Currency "will be a clear negative" but a full quarter of Bioverativ sales, from *Eloctate* (recombinant Factor VIII) for hemophilia A and *Alprolix* (recombinant Factor IX) for hemophilia B, "will be a tailwind."

Next week will also see the official arrival of John Reed, former global head of pharma Research & Early Development (pRED) at **Roche.** who will join Sanofi as the head of global R&D effective July 1, succeeding the company's long-time research chief Elias Zerhouni. Reed actually joined Sanofi on April 30 to help ensure a smooth transition and it will be interesting to see which areas he focuses on. Some observers believe that Sanofi may look to strengthen in oncology, a field it has fallen behind in of late, although it has high hopes for cemiplimab, its **Regeneron Pharmaceuticals Inc.**-partnered anti-PD-1 candidate which has been filed on both sides of the Atlantic for cutaneous squamous cell carcinoma (CSCC).

It seems that Sanofi's fondness for generics will continue to dwindle but private equity groups like Advent see value in the sector. The Zentiva deal comes a year after the German generics and OTC company, Stada Arzneimittel AG, was sold to two such companies, Bain and Cinven, for €5.4bn.

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Roivant Cuts Jobs, Reallocates Staff

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Roivant Sciences GMBH's big star **Axovant Sciences Ltd.** failed the first big test of the parent company's risk-reducing strategy, but a reorganization announced on June 26 is meant to strengthen and launch other Roivant subsidiaries, with different programs pushed into the spotlight.

The organizational changes were announced just two weeks before the first-ever Roivant Pipeline Day scheduled for July 10 where the parent company will showcase its clinical programs and subsidiaries. The reorganization will split Roivant into two business units focused separately on company creation and emerging markets, spin out a new subsidiary – or Vant – called **Altavant Sciences**, shift certain Roivant employees to its various Vants, and cut overall headcount by less than 10%.

Roivant was designed to centralize administrative and other costs for subsidiaries created to rapidly advance specific drug development programs. If an asset succeeded, rewards would flow back to the parent, but if it failed the subsidiary would take most of the hit. But job cuts after the Phase III failure of intepirdine in Alzheimer's disease last year apparently weren't limited to Axovant, since Roivant's reorganization will put 67 people out of work.

TWO NEW BUSINESS UNITS

Roivant Chief Business Officer Myukh Sukhatme is now president of the new business unit Roivant Pharma, which will focus on biopharmaceutical company creation in new therapeutic areas. Sukhatme already oversees Roivant's in-licensing activities, but also will lead company formation around assets that don't fit into existing subsidiaries.

Vants to date include neurology-focused Axovant, women's health firm **Myovant Sciences Ltd.**, dermatology specialist **Dermavant Sciences Ltd.**, the rare disease firm **Enzyvant Sciences Ltd.**, urology drug developer **Urovant Sciences Ltd.**, RNA-based therapeutics joint venture **Genevant Sciences Ltd.**, and **Metavant Sciences Ltd.** with an interest in cardiometabolic diseases.

Two other existing Vants appear to belong under Roivant's other newly created business unit, Roivant Health. Roivant's Head of Special Projects Benjamin Zimmer will be president of Roivant Health. The unit will focus on new biopharma companies targeting emerging markets, such as the previously launched **Sinovant Sciences Ltd.**, and subsidiaries with technology aimed at improving drug development and commercialization, such as the Zimmer-created company **Datavant Sciences**.

Newly created Altavant, which is focused on "next-generation drug development," will advance RVT-1201 for pulmonary arterial hypertension (PAH) and other indications. Roivant declined to say where the drug was licensed from, how it works and what stage of development it's in, but said that it plans to share more information during its Pipeline Day next month.

Altavant is led by CEO William Symonds, who has been with Roivant since 2014, serving most recently as chief development officer. Symonds previously oversaw development of hepatitis C blockbusters *Sovaldi* (sofosbuvir) and *Harvoni* (ledipasvir/sofosbuvir) at **Pharmasset Inc.** and **Gilead Sciences Inc.**

IN-LICENSING FOCUS NOW

Roivant founder and CEO Vivek Ramaswamy said in the announcement about the company's reorganization that he is "excited to elevate several of Roivant's talented leaders" and noted that going forward the company will not focus exclusively on in-licensing drug candidates already in the clinic.

"Going forward, we will expand the scope of our focus to include the advancement of potentially transformative assets into clinical development, even if they are at earlier stages of development than much of our pipeline to date," Ramaswamy said.

Roivant framed its reorganization as one that allows the company to accelerate new company formation and pursue earlier-stage science. However, the changes also will move some of the parent company's employees into existing subsidiaries "to further the advancement of their pipelines and ensure greater organizational autonomy." Roivant said this led to a reduction in headcount of less than 10%; a spokesman confirmed that 67 employees lost their jobs.

The company's decision to now consider preclinical assets is notable, since Roivant has focused since its launch in 2014 on acquiring clinical drug candidates that have been deprioritized by big pharma and other established firms. The strategy change gives Roivant an opportunity to license more assets at lower costs, since the owners of preclinical development programs and technology platforms won't have invested as much of their own capital as big pharma partners put into discontinued clinical-stage assets.

Roivant's investors may appreciate such frugal spending, since the company so far has made big bets without generating sizeable returns. Barely a month and a half after Roivant raised $1.1bn in private equity to fund new company formation in August, Axovant announced the Phase III failure of intepirdine in Alzheimer's, which cut the neurology-focused subsidiary's value by 74% in September.

Axovant discontinued development of intepirdine following the failed Phase IIb HEADWAY study in dementia with Lewy bodies in January. Then Axovant lost its recently hired, high-profile CEO – **Medivation Inc.** founder and former CEO David Hung – and hinted at additional job cuts in February.

NEXT PHASE III MILESTONES

With intepirdine's failure, the most advanced drug candidates in Roivant's portfolio are being developed by Myovant, Enzyvant and Urovant – and possibly Altavant if RVT-1201 is in Phase III.

Enzyvant licensed global rights to RVT-802, a Phase III tissue-based therapy for the rare congenital immunodeficiency disease complete DiGeorge syndrome (cDGS) from **Duke University** early last year. Enzyvant intends to submit a biologic license application (BLA) based on the Duke-generated Phase III data to the US FDA during the first half of 2018 – a milestone that may be announced at Roivant's Pipeline Day on July 10.

Also in Phase III, Myovant is Roivant's only other company besides Axovant that is publicly traded. However, Ramaswamy has said that Roivant does not intend to pursue any other initial public offerings for its subsidiaries, because it wants the firms to focus on drug development, not the responsibilities that come with being a public company. Even so, with a closing price of $24.05

per share on June 26, Myovant's stock is trading near its one-year high of $25.54.

The company's stock is rising due to optimism for its lead drug candidate relugolix, which was bolstered by Phase III data from **Takeda Pharmaceutical Co. Ltd.** in Japanese women with uterine fibroids in October. Myovant is expected to report results from its international Phase III studies for relugolix in uterine fibroids and endometriosis in 2019.

Roivant founded Myovant in 2016 when it licensed rights to relugolix from Takeda outside of Japan and certain Asian countries. Now, Myovant is in a race with **AbbVie Inc.** to win the first FDA approval for an oral gonadotropin-releasing hormone (GnRH) receptor antagonist for women with uterine fibroids or endometriosis.

AbbVie's elagolix may get there first, since it is under FDA review for endometriosis and in Phase III for uterine fibroids. However, both products may have competition from Allergan PLC's selective estrogen receptor modulator (SERM) *Esmya* (ulipristal), which the FDA is reviewing for the treatment of uterine fibroids, though safety concerns pushed back an approval decision.

Further behind Myovant within Roivant's portfolio, Urovant launched a year ago when Roivant licensed the oral beta-3-adenergic agonist vibegron for overactive bladder (OAB) from **Merck & Co. Inc.** The company initiated a Phase III OAB study in March based on positive Phase IIb results generated by Merck. Those data give vibegron a 66% likelihood of FDA approval – 4% above average – according to Biomedtracker.

Also, Sinovant acquired rights in China and a few other Asian territories at the end of March for **Nabriva Therapeutics PLC**'s anti-infective lefamulin after the successful completion of Nabriva's first Phase III international study for the drug. There were safety concerns in a second Phase III trial that also was deemed a success, but Nabriva intends to seek FDA approval based on both studies. Roivant may update Sinovant's plans for lefamulin in China on July 10.

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Mylan Pursues 'Market First' Playbook, Partners Lupin

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Mylan NV is leap-frogging plans for biosimilar etanercept in certain key markets via an alliance with **Lupin**, along the lines of similar efforts for biosimilar adalimumab earlier this year.

The US firm has inked a deal to commercialize Lupin Ltd.'s biosimilar version to **Amgen Inc./Pfizer Inc.**'s *Enbrel* (etanercept) in Europe, Australia, New Zealand, Latin America, Africa and most markets throughout Asia.

Lupin will receive an upfront payment of $15m and is entitled to potential commercial milestones together with an equal share in net profits of the product.

Lupin's CEO, Vinita Gupta, said that Mylan was "well-positioned" to commercialize the firm's etanercept biosimilar given its significant expertise and global infrastructure.

The deal with Mylan marks Lupin's second alliance on the trot for the biosimilar etanercept, developed under a JV with **Yoshindo**. Lupin recently firmed up a deal with **Nichi-Iko Pharmaceutical Co. Ltd.** for its distribution, promotion and sale in Japan.

Lupin's etanercept filing in Japan follows a successful Phase III study that included more than 500 patients with RA in 11 countries; the partners will launch the product there following approval from the Pharmaceuticals and Medical Devices Agency (PMDA).

Mylan's latest alliance suggests that getting the market timing right is a priority for the US firm's overall biosimilar play and it won't shy away from deal-making for products alongside existing alliances. Mylan president Rajiv Malik said the deal with Lupin was yet another positive step to bring key biosimilars like etanercept to patients around the world "as quickly as possible". **Biocon Ltd.**'s etanercept is in the preclinical stage, a May 2018 company presentation indicated.

In April this year, Mylan acquired commercial rights in Europe to **Fujifilm Kyowa Kirin Biologics Co. Ltd.**'s biosimilar adalimumab, with an eye on early market entry; it also has an ongoing program for biosimilar adalimumab with partner Biocon.

Mylan president Rajiv Malik at the time maintained that "nothing is wrong with the Biocon partnership" but the market comes first.

"And when we realize that we will not be in time for Europe for market formation with our biosimilar to Humira, we had to make the call in favour of the FKB product. We are very happy and that we could find an opportunity to be in the market at the time of the market formation," Malik said at the investor meet April 11.

In the case of biosimilar etanercept, *Benepali* (**Biogen/Merck & Co/Samsung Bioepis**) has already been launched in certain EU markets; **Sandoz International GMBH**'s biosimilar etanercept *Erelzi* was approved by the EMA in June 2017. Enbrel reported global sales of about $11.6bn for the 12 months ended December 2017. In Europe, Informa's Datamonitor Healthcare expects rheumatologists' initial caution with biosimilars to translate into relatively slow uptake of biosimilar etanercept, with use limited primarily to new patients.

"In the long term, growing confidence in biosimilars driven by increasing familiarity and post-marketing data, in conjunction with further expected decreases in the cost of biosimilar etanercept, will lead to greater erosion of Enbrel's patient share to biosimilar etanercept," Datamonitor Healthcare said in a recent report. The report forecasts Enbrel will lose up to 55% of its patient share to biosimilar etanercept in Europe.

Meanwhile, Biocon said that it would "benefit" from the opportunity to "accelerate commercialization" of etanercept under Mylan's latest deal with Lupin.

"Biocon clarifies that it retains its economic interest in this arrangement vis-à-vis Mylan in accordance with its existing collaboration agreement," the company informed the Bombay Stock Exchange June 28. It had maintained a similar position at the time of Mylan's deal with FKB for adalimumab.

Biocon, however, also has entered into an alliance with Sandoz for developing and commercializing the next-generation of biosimilars.

It's not immediately clear if Mylan could be Lupin's logical partner for the US too for entanercept.

Lupin anticipates a US filing for etanercept in Q4 FY20.

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Biogen Ups Samsung Bioepis Stake In $700m Bet On Biosimilars

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Biogen Inc. has exercised an option to purchase additional shares in **Samsung Bioepis Co. Ltd.**, a joint venture established in 2012 by **Samsung BioLogics** and the US firm, in a move that will raise its stake to nearly 50% and allow Biogen to jointly run the biosimilars venture.

Under the terms of the original joint venture agreement, Biogen will pay Samsung BioLogics about $700m for the option shares, increasing Biogen's ownership in Samsung Bioepis from about 5.4% to about 49.9%. The completion of the share purchase remains subject to certain regulatory conditions but is expected to close in the second half of 2018.

The exact share purchase price will depend on the timing of the closing and foreign currency exchange rates at that time, Biogen said in a statement. The US company has been responsible for commercializing Samsung Bioepis's anti-TNF biosimilar product candidates in Europe.

"We are very pleased with the progress made to date at Samsung Bioepis and believe exercising this option is an opportunity to create meaningful value for our shareholders," said Biogen CEO Michel Vounatsos. "This option allows us to increase our ownership share in a leading biosimilar company at what we believe are attractive terms. We look forward to building an important relationship with Samsung BioLogics."

The move wasn't a complete surprise given that during its first quarter 2018 earnings call, Biogen said it planned to exercise an option to increase its equity stake in the JV in the belief this would be an attractive value creation opportunity.

"Biogen's option to increase its stake in the Samsung Bioepis joint venture was set to expire in mid-2018, so I'm not surprised Biogen made a decision about the investment," said Datamonitor Healthcare analyst Amanda Miklus.

But what is surprising is that only a month ago, Vounatsos made comments at a Bernstein Strategic Decisions Conference indicating his company might not even continue with the joint venture, saying "Biogen's agenda is not to remain in a JV for the long run and would instead focus on its neuroscience assets," the analyst noted.

However, the $700m investment Biogen is making to significantly up its stake in Samsung Bioepis says quite the opposite. "I think this has been a successful collaboration for both Biogen and Samsung BioLogics, with Bioepis launching several biosimilars and some in the pipeline. Now Biogen will be more heavily involved than before in decision-making and development I imagine," Miklus said.

IMPACT ON ACCOUNTING PROBE?

Biogen's stronger commitment to the joint venture is poised to help further beef up Samsung Bioepis's presence and leadership in the global biosimilars market. However, in South Korea, the focus is more on how the option could affect ongoing accounting issues at Samsung BioLogics. Biogen's call option exercise has been at the center of an accounting controversy involving Samsung BioLogics – a leading biopharma contract development and manufacturing organization in South Korea – and the country's financial authorities.

It is unclear how or how much Biogen's increased stake may affect the authorities' probe. Some local media have speculated it is likely to work in favor of Samsung BioLogics, while others say that the investigation will focus more on whether Samsung has appropriately reflected the JV in its accounting rather than whether Biogen will exercise its option or not.

Samsung BioLogics shares gained 2.1% on the main Kospi market on June 29 on the expected hefty cash inflow from Biogen, a transaction set to lower Samsung BioLogics's debt-to-equity ratio to 35.2% from 88.6%, the Korean company said.

ACCOUNTING PRACTICES UNDER SCRUTINY

South Korea's Securities and Futures Commission, which is under the Financial Services Commission, has repeatedly held meetings to determine if Samsung BioLogics has violated accounting standards related to the reflection of Samsung Bioepis in its books. The FSC is expected to unveil the results of its review in July.

In May, financial authorities reportedly concluded that Samsung BioLogics violated accounting standards when it changed in 2015 its accounting related to Samsung Bioepis. Samsung BioLogics had been reflecting Samsung Bioepis as a subsidiary in its consolidated financial statements, but changed it to affiliated company status in 2015.

As a result, Samsung BioLogics reflected the value of its stake in Samsung Bioepis to market value from book value, which resulted in hefty one-off investment income. Samsung BioLogics said it had made the change in accordance with IFRS requirements, and that this had been confirmed as adequate by external auditors.

Local media have recently reported that the commission is now checking Samsung BioLogics' books from 2012, when it first established Samsung Bioepis as a joint venture with Biogen.

STRONGER BIOGEN REPRESENTATION

With the exercise of the option, Biogen will jointly run Samsung Bioepis with Samsung BioLogics and have an equal number of seats on the JV's board. Samsung BioLogics expects the transaction to be completed within three months.

Since the joint venture was established, Biogen has been providing its biologics development technology and know-how, helping to turn Samsung Bioepis into a leading biosimilars player globally, generating the highest number of products in its pipeline referencing global top 10 drugs within just six years, Samsung BioLogics noted.

Samsung BioLogics CEO Tae Han Kim vowed to cooperate with Biogen to further boost Samsung's biosimilar business in global markets.

Samsung BioLogics announced in May that the company had received approval from the US FDA for the manufacture of three commercial biologic drug substances at its second plant within 26 months of the facility becoming GMP-ready in 2016.

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Teva Retains Top Slot As Industry Faces US Pushback

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Despite increasing desire by payers to curb drug costs by switching to less expensive generics and biosimilars, most of the world's leading companies in the space struggled during fiscal 2017. According to the latest rankings by *Generics Bulletin*, a sister publication of *Scrip*, companies operating in the US generics and biosimilars market have struggled to maintain sales and operating margins owing to an increase in competitive products and consolidation among customers.

Indeed, the US headwinds are a major driver for **Teva Pharmaceutical Industries Ltd.**'s renewed focus on profitability which has seen the Israeli giant cutting headcount and announce the closure of 10 production plants. Teva retained pole position after incorporating Actavis's Anda distribution business from the end of 2016. In the US, specifically, Teva has announced plans to drop about 80% of its portfolio, moving them to other suppliers, while looking to push price increases on its remaining 20%. In the first quarter, Teva's North American generics sales plummeted 23%.

Year on year, there was little change in the positions of the top ten companies, only **Lupin Ltd.** slipped out of the top tier, down one place in 11th. With the top seven companies retaining the same positions between 2016 and 2017, **Valeant**, up eight places on the 2016 ranking, was the top climber in at eighth place. Privately held **Stada Arzneimittel AG**, like seventh-ranked **Fresenius Kabi AG**, benefited from doing as much business in Europe as it does in the US and saw it rise one place to ninth in the table. With its intention to make more acquisitions in Europe and the MENA region, as well as plans to invest $100m in biosimilars in the next three years, it is likely the company might continue its rise in the charts. Endo was the biggest faller in the top 10 slipping three places to tenth.

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2017 Rankings For Generics Firms by Revenues ($m)

COMPANY	2017 RANK	2017 GENERICS/ OTC/ BIOSIMILARS REVENUES ($M)	2016 GENERICS/ OTC/ BIOSIMILARS REVENUES ($M)	YOY CHANGE ($M)
Teva	1 - No change	11,504	11,214	290
Mylan	2 - No change	11,060	10,967	93
Sandoz	3 - No change	9,544	9,625	-81
Pfizer Essential Health	4 - No change	6,204	6,337	-133
Perrigo	5 - No change	4,891	5,201	-310
Sun	6 - No change	3,726	4,336	-610
Fresenius Kabi	7 - No change	3,175	2,751	424
Valeant	8 - Up 8 places	2,686	1,544	1,142
Stada	9 - Up 1 place	2,642	2,253	389
Endo	10 - Down 3 places	2,281	2,565	-284

Akebia And Keryx To Merge

In a transaction that "makes so much sense" according to CEO John Butler, two Boston-area biotechs focused on kidney disease – Butler's clinical-stage **Akebia Therapeutics Inc.** and **Keryx Biopharmaceuticals Inc.** with struggling *Auryxia* already on the market – will merge in a deal they say will establish a leader in their market segment.

Complementary Franchise

The two companies announced the planned all-stock merger June 28, a transaction expected to close by the end of 2018 that will leave Keryx shareholders owning 50.6% of the combined entity and Akebia shareholders 49.4%. Operating under the Akebia name, the new firm will be led by Akebia's existing CEO Butler, with Keryx getting the right to appoint the chairman of the board. The other eight seats on the board will be split evenly between the two companies.

While the deal requires shareholder approval to be finalized, it has good momentum. Both boards of directors gave unanimous approval, Akebia Chairman Muneer Satter agreed to contribute his 5.3% ownership stake in that company to the merger, and Baupost Group LLC, which owns roughly 21.4% of Keryx, has agreed to convert its outstanding convertible notes into Keryx common stock before closing and entered into a voting agreement to back the merger.

In an interview, Butler said the company's strategy would revolve around optimizing the revenue potential of Auryxia (ferric citrate), a phosphate binder approved by the US FDA in 2014 to treat hyperphosphatemia in chronic kidney disease (CKD) patients on dialysis. Last November, the drug added a second indication for treating iron-deficiency anemia in CKD patients not on dialysis. This drug and Akebia's Phase III vadadustat would create a complementary franchise, CEO Butler asserted.

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PTI's Remoxy: Negative FDA Panel Review May Be The End Of Abuse-Deterrent Opioid's Road

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Pain Therapeutics Inc. is standing on the verge of a regulatory dead-end for *Remoxy* (oxycodone extended-release) following a US FDA advisory committee's negative review June 26, and the company's CEO warns that the "changing goalposts" might deter future development in the abuse-deterrent opioid space.

The committee's 14-3 vote against approval suggests the long-acting opioid formulated with abuse-deterrent properties is headed for its fourth complete response letter in a 10-year regulatory saga.

Most members of the agency's anesthetic/analgesic drug products and risk management/drug safety panels concluded that Pain Therapeutics (PTI) had established Remoxy's ability to deter intranasal abuse.

However, they were troubled by the safety and public health implications of the product's intravenous abuse potential – concerns that the FDA reviewers and the panel equated to those that led to the withdrawal of **Endo Pharmaceuticals Inc.**'s *Opana ER* (oxymorphone extended-release).

Panelists were also worried about the ability to partially defeat the Remoxy capsule's extended-release properties by chewing it.

> 'A sponsor would have to be pretty naive, if not stupid, to develop an abuse-deterrent opioid from scratch today because the goalposts keep changing'

'IT'S OVER'

When asked by *Scrip* about prospects for Remoxy's continued development if PTI receives a complete response letter by the Aug. 7 user fee goal date, Chairman and CEO Remi Barbier said "it's over," not because the company is giving up on the data, but "because the goalposts keep changing."

In an interview, Barbier said the shifting preapproval regulatory requirements that PTI has experienced in trying to bring an abuse-deterrent opioid formulation to market will dissuade other sponsors from entering this space.

"A sponsor would have to be pretty naive, if not stupid, to develop an abuse-deterrent opioid from scratch today because the goalposts keep changing," he said.

He asserted the company did not receive the "fair and neutral" advisory committee hearing to which it was entitled. The panel meeting "was all over" as soon as the FDA pronounced Remoxy and Opana in the same sentence, Barbier said.

The CEO declined to comment on what recourse the company might seek if it receives another complete response letter. However, an appeal through the agency's dispute resolution process seems unlikely to provide much relief.

The FDA is not likely to exercise its regulatory flexibility for a drug targeting a common condition (pain) and for which numerous other long-acting opioids are available, including some that the agency already has determined satisfy its preapproval requirements for demonstrating abuse deterrence.

In addition, PTI would be hard-pressed to overcome the comparisons made by FDA reviewers and advisory committee members of Remoxy's intravenous abuse potential to that of Opana, given the latter's safety issues and regulatory history.

Endo removed Opana from the market after the FDA concluded the product's reformulation led to a shift in the route of abuse from intranasal to intravenous, which in turn led to needle-sharing, transmission of bloodborn infections such as HIV and hepatitis C, and other serious adverse events. *(Also see "Opana ER Withdrawal Adds Weight To Endo's Ongoing Revenue Decline" - Scrip, 7 Jul, 2017.)*

In the FDA's June 2017 announcement that it had asked Endo to withdraw the product, then-newly installed Commissioner Scott Gottlieb highlighted the regulatory action as part of the tough approach the agency would take under his leadership to addressing the opioid crisis.

Even if the FDA were to relent and approve Remoxy – a decision that no doubt would unleash a fury of criticism from lawmakers and public health advocates – the drug likely would be saddled with negative labeling on oral abuse-deterrence studies, further dimming its commercial prospects in the eyes of any potential marketing partner.

10-YEAR PURSUIT OF APPROVAL

Remoxy has had a long, difficult regulatory journey in the US that has coincided with the growing opioid epidemic and an evolution in preapproval requirements as the FDA has focused increased attention on the potential unintended consequences and adverse public health impacts from the approval of new opioid products, even those with properties aimed at deterring abuse.

The drug has been the subject of three complete response letters since its initial submission in June 2008. The most recent letter in September 2016 cited the need for a human intranasal abuse liability study and additional laboratory-based in vitro manipulation and extraction studies.

The current NDA seeks abuse-deterrent labeling by the intravenous, intranasal and smoking routes of abuse. However, as other sponsors in this space have learned, gaining such labeling is no guarantee for commercial success. *(Also see "Abuse-Deterrent Opioids: Where Are They Now?" - Scrip, 20 Mar, 2018.)*

A total of nine long-acting opioids and one immediate-release product have been approved with abuse-deterrent labeling as described in the FDA's April 2015 final guidance. This list includes two single-ingredient, extended-release oxycodone products: **Purdue Pharma LP**'s *OxyContin* and **Collegium Pharmaceutical Inc.**'s *Xtampza ER*.

OxyContin holds the lion's share of the abuse-deterrent formulation (ADF) opioid market, accounting for nearly 88% (or 3.4m) of the 3.8m ADF prescriptions dispensed in 2017. Yet even OxyContin's market-leading share represents only about 20% of the 17.5m total prescriptions for extended-release/long-acting opioids dispensed in 2017, according to outpatient retail pharmacy data cited by the FDA in its briefing document for the Remoxy advisory committee meeting.

Several formulations approved with ADF labeling have never launched. On May 2, the new drug application (NDA) for one of those, **Pfizer Inc.**'s *Troxyca ER* (oxycodone/naltrexone extended-release), was withdrawn at the sponsor's request. "We made the decision not to introduce another oxycodone medicine as there are several abuse-deterrent oxycodone treatment options available to patients," Pfizer told *Scrip*, though it said it remains committed to innovation in treating chronic pain.

Pfizer, which markets an ADF formulation in *Embeda* (morphine/naltrexone extended-release), once owned the rights to Remoxy through the big pharma's acquisition of **King Pharmaceuticals Inc.** However, it returned those rights to Pain Therapeutics in 2014.

Remoxy is PTI's lead pipeline product, and the negative advisory committee review had an outsized impact on the company's valuation. Trading in the company's stock was halted on the day of the advisory committee meeting, but the stock lost 71% of its value the following day, closing at $2.44 on June 27, down from the June 25 close of $8.53.

Remoxy incorporates **Durect Corp.**'s *Oradur* technology, and the company would be owed milestone payments upon approval. Durect stock closed at $1.70 on June 27, down 11% from its June 25 close.

THUMBS UP FOR NASAL DETERRENCE, BUT CONCERNS ABOUT CHEWING

At the advisory committee meeting, Division of Anesthesia, Analgesia and Addiction Products (DAAAP) Medical Officer Lisa Wiltrout said that PTI's intranasal human abuse liability study data provided in the most recent submission met the current standards for abuse-deterrent labeling.

Pharmacokinetic results demonstrated that intranasal administration of Remoxy may result in significantly lower plasma oxycodone concentrations compared to intranasal administration of crushed immediate-release oxycodone. Remoxy was associated with statistically significantly lower scores than immediate-release oxycodone on visual analog scales that measured drug effect liking, drug high, desire to take the drug again, and overall drug liking, and it was shown to be more difficult to administer intranasally than immediate-release oxycodone powder, the FDA said.

However, Wiltrout appeared to foreclose the path to a smoking abuse-deterrence claim. "Based on our analysis of available epidemiological and in vitro data, we do not consider smoking a relevant route of abuse for oxycodone," she said.

In the current application, PTI did not request deterrence labeling language by the oral route of abuse, even though the formulation – consisting of a sticky gel – is intended to deter such abuse.

Some panelists suggested that if approved, the FDA should include in Remoxy labeling negative results of studies aimed at demonstrating the formulation's oral abuse-deterrent effects. In a human oral abuse liability study, chewing Remoxy resulted in much higher peak serum concentrations, and greater drug liking effects, than swallowing the drug intact as intended, the agency said.

EXTRACTION DATA DEAL A FATAL BLOW

What might have been the fatal blow for the Remoxy NDA were data from in vitro extraction studies conducted by the FDA and presented at the meeting.

These study results were not included in the publicly released briefing document because the agency received them only a few days before the meeting, the FDA told *Scrip*. "We did not share the actual data with the company before the meeting, but did let them know that we would be presenting data from our lab that was different than their data," the agency said.

PTI's in vitro studies suggested that oxycodone is more difficult to extract from Remoxy than from OxyContin and Xtampza ER, and that the product's thick, sticky viscosity makes it difficult to draw up into a syringe for injection purposes.

However, studies performed by the FDA showed that 72% of the oxycodone content could be extracted from Remoxy using a particular method, solvent, volume and time, and a "slightly more involved process" involving pretreatment resulted in extraction of up to 83% of oxycodone, Wiltrout said.

"The take-home message is that fairly basic manipulation and extraction methods generated a high yield of oxycodone suitable for injection," Wiltrout said. "Moreover, these manipulation and extraction methods are presumed to be readily available in the community."

"Implications of the FDA lab findings are clear," Wiltrout said. "Oxycodone suitable for I.V. use can be extracted from Remoxy ER. The amount of extracted oxycodone and the extraction volume may lead to sharing among I.V. drug users. Given what happened with Opana ER, other important public health consequences are to be expected."

Wiltrout also said that PTI had not sufficiently studied the safety of Remoxy's excipients when the product is manipulated for purposes of extracting oxycodone for intravenous use. She noted that Opana I.V. drug users experienced thrombotic microangiopathy, which investigations showed was due to injection of an excipient in Endo's formulation.

The regulator's drawing of parallels between Remoxy and Opana resonated for several advisory committee members.

"I do have concerns this this will be manipulated and is able to be extracted, and you could see similar HIV and HCV transmissions, because we know that if it can be extracted people are going to do that," said Jon Zibbell, senior public health scientist at RTI International.

The panel's consumer representative, Suzanne Robotti, executive director of DES Action USA, noted she sat on the March 2017 advisory committee review of the postmarketing experience with Opana. "That's a terrible unforeseen outcome" that should be prevented from happening again, she said.

FDA STATEMENT 'BORDERS ON SLANDEROUS'

For PTI, the FDA's comparison of Remoxy to Opana was both surprising and unjustified. "We had not seen their extraction data," Barbier said of the FDA's studies. "Remoxy is very difficult to extract." He noted also that the FDA showed no data on extraction rates of comparator drugs using the same methods.

Opana "was a dangerous drug," Barbier told *Scrip*. "For the FDA to compare Remoxy and Opana in the same breath in the same sentence during a public hearing, in my opinion, borders on slanderous."

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Array Raring To Go With First Approval: Mektovi/Braftovi

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The US FDA approved **Array Biopharma Inc.**'s MEK inhibitor *Mektovi* (binimetinib) and BRAF inhibitor *Braftovi* (encorafenib) for combination treatment of metastatic melanoma on June 27. This marks Array Biopharma's transition into a commercial enterprise, and the company has been preparing to launch immediately.

Prior to approval, it had already put 60 customer facing team members in place, including representatives working with prescribers and payers and medical science liaisons working with thought leaders. This is about the same size as a large pharma would have in place, CEO Ron Squarer told *Scrip* in an interview.

"We are matching what is common," the exec said.

The combo, cleared just before the June 30 user fee date, is indicated to treat patients with unresectable or metastatic melanoma with either a BRAFV600E or BRAFV600K mutation, as determined by an FDA-approved diagnostic test. Braftovi is not indicated for wild-type BRAF melanoma. Array said Mektovi/Braftovi is now available through select US specialty pharmacies.

Array negotiated rights to both drugs in 2015 from **Novartis AG**, which at the time was gaining the BRAF and MEK inhibitors *Tafinlar* (dabrafenib) and *Mekinist* (trametinib), respectively, from **GlaxoSmithKline PLC**.

The combination is partnered with **Pierre Fabre Group** in Europe and emerging markets. Filings in Europe, Australia and Switzerland are under review.

Array also is in talks with the FDA regarding accelerated approval of the combination – for use with Lilly's anti-EGFR *Erbitux* (cetuximab) – in a subset of colorectal cancer based on interim PFS and response rate data from the Phase III BEACON study, which is due to report at the end of the year. Jefferies analyst Eun Yang has estimated a sales opportunity of $1bn, as colorectal cancer is a much larger patient population.

Between Novartis' Tafinlar/Mekinist duo and **Roche**'s *Zelboraf* (vemurafenib) and *Cotellic* (cobimetinib), breaking into the BRAK/MEK segment of the metastatic melanoma marker will be tough, especially as the melanoma market is now dominated by immuno-oncology.

Array is hoping to gain share by offering eligible commercial patients a zero copay deal for the drug and supporting patients and physicians, to make getting therapy as easy as possible.

HOW TO COMPETE

Array likely will find that the melanoma market is a bit daunting, as the other targeted BRAF/MEK inhibitors have a long lead. Roche's Zelboraf was approved in 2011 followed by Cotellic in 2015, while Novartis' combination was approved in 2013.

Novartis has reported strong sales for its combo, up by 29% to $873m in 2017.

Roche didn't break out sales of Zelboraf and Cotellic in its 2017 report. Although Zelboraf was the first approved BRAF inhibitor, Novartis was first to market with a BRAF/MEK combination and adding a MEK inhibitor substantially improves the BRAF agents' adverse event profile.

TAKING COMPETITION IN STRIDE

Array acknowledges the competition but believes it has a few things on its side aside from the patient assistance plan, including the data supporting the filing. Backing the NDA was the Phase III COLUMBUS study in 577 patients with BRAF-mutant melanoma.

The first part of the trial was designed to evaluate what binimetinib was contributing: 577 patients were randomized to encorafenib at 450 mg with binimetinib at 45 mg, encorafenib monotherapy (300 mg) or vemurafenib at 960 mg. In Part 2, the company compared progression-free survival in patients treated with binimetinib at 45 mg twice daily with encorafenib 300 mg daily to an arm treated with encorafenib at 300 mg daily.

The study met its primary endpoint, with encorafenib/binimetinib demonstrating superior PFS over vemurafenib (14.9 months vs. 7.3 months, p<0.0001). But a secondary endpoint evaluating the encorafenib/binimetinib combination compared to encorafenib alone was missed, as the combination was numerically but not statistically superior to encorafenib alone (median PFS of 14.9 month versus 9.6 months (p=0.051)), raising questions about what binimetinib was contributing. Labeling does not report the encorafenib alone comparison, and states that overall survival data were not mature at the time of analysis.

The company noted that in the study median overall survival was 33.6 months for the combination versus 16.9 months for those taking Zelboraf monotherapy.

Array reported that the combination was generally well tolerated in COLUMBUS, with side effects including rash, pyrexia and serous retinopathy. Labeling notes that adverse events caused dose interruptions in 30% of patients on the combo, dose reductions in 14% and permanent discontinuation in 5%.

This is the first oral combination in the indication to offer median overall survival greater than 30 months, Squarer said.

HEAVY COMPETITION

Array says it is not concerned about the entry of Novartis' BRAF/MEK combo into adjuvant melanoma. Many patients are not diagnosed until they are metastatic and retreatment with BRAF/MEK combination would still be possible. Furthermore, Squarer believes that a PD-1 inhibitor is going to be preferred in the adjuvant setting over a BRAF/MEK combination due to a better safety profile.

"That is our assumption and that is what we have consistently what we have heard from thought leaders," Squarer said.

There are still only two modalities in melanoma – IO and BRAF/MEK – and the vast majority of patients will get both, he said.

Meanwhile, the company is developing the BRAF/MEK combination in combination with checkpoint inhibitors in the larger indication of colorectal cancer.

The Phase III BEACON study is evaluating binimetinib/encorafenib and **Eli Lilly & Co.**'s *Erbitux* (erlotinib) in BRAF mutant metastatic CRC (BEACON CRC). Data for 30 patients in a lead-in part of BEACON were presented at the European Society of Medical Oncology gastrointestinal cancer meeting in Barcelona on June 23. Median progresion-free survival was eight months for the triplet and the confirmed objective response rate was 48% overall and 62% in those who had only one prior line of therapy, the company reported. Median overall survival had not yet been reached.

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Dermira Wins First FDA Approval, For Qbrexza

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Dermira Inc. claimed an important victory when it won US FDA approval for *Qbrexza* (glycopyrronium) – a topical anticholinergic delivered by a cloth wipe – on June 29 for the treatment of primary axillary hyperhidrosis (excessive underarm sweating) in patients aged 9 and older.

The agency's decision marks the company's first-ever drug approval and it provided the Menlo Park, Calif., company with a needed win after highly anticipated Phase III clinical trials for its now-discontinued drug candidate DRM01 failed in March. Dermira intends to make once-daily Qbrexza available for prescription in October with high hopes for growing an underserved market and winning reimbursement for the novel product.

Hyperhidrosis is a 15m patient market in the US, including 10m people with axillary, or underarm, hyperhidrosis. Aluminum salts, i.e. the prescription antiperspirant *Drysol*, and **Allergan PLC**'s *Botox* (onabotulinumtoxinA) are the two main prescription therapies, but Dermira estimates that only 800,000 patients are receiving those or other treatments for the condition.

Qbrexza inhibits the interaction between acetylcholine and the cholinergic receptors that activate sweat glands. Dermira may also purse development of the drug in palmar hyperhidrosis or excessive sweating of the hands.

Patients have been seeking new therapies for hyperhidrosis and not just for excessive sweating on the hands and underarms. Available therapies can be expensive, since many payers won't cover the costs of Botox or microwave thermolysis, and those treatments can be burdensome; Botox requires up to 100 injections per treatment.

Dermira CEO Tom Wiggans said in the company's statement about the approval that "our goal was to develop an approach that went beyond masking a person's excessive underarm sweating and instead focused on treating the condition in a clinically meaningful way."

The FDA considered the company's two successful Phase III clinical trials, known as ATMOS-1 and ATMOS-2, in deciding whether to approve Qbrexza. The primary endpoints in both studies were the absolute change from baseline in sweat production and the proportion of patients with at least a four-point improvement from baseline in sweating severity as measured by the Axillary Sweating Daily Diary (ASDD), Dermira's proprietary patient-reported outcome (PRO) instrument.

Dry mouth, dry skin, dry eyes, dry throat, dry nose, urinary hesitancy and constipation were among the drug's most common side effects, which wasn't surprising based on the known side effects for systemic anticholinergic agents. Labeling recommends that Qbrexza is not prescribed to patients taking other anticholinergic drugs.

MODEST SALES EXPECTED INITIALLY

Since the drug isn't launching until October, Evercore ISI analyst Umer Raffat estimated in a June 29 note that Qbrexza will generate $30m in 2019 sales, rising to $68m in 2020 and $118m in 2021. Raffat forecast $200m in peak annual sales. That would make Dermira's product the market leader in hyperhidrosis, since annual Botox sales in this indication have plateaued at about $70m as Allergan has de-emphasized its marketing efforts in hyperhidrosis.

Dermira Chief Financial Officer Andrew Guggenhime said during a May 24 investor day presentation that "we expect it will be about five years to six years for us to achieve peak sales with glycopyrronium tosylate. The market opportunity is significant, but the investment required to build awareness and activate the patients is not trivial, so we do expect a slow initial build, though a significant opportunity in the long-term."

The company already has made significant investments in direct-to-consumer advertising to create patient awareness of this new treatment option, since only about 15% of individuals with excessive underarm sweating are seeking treatment, even though it's estimated that about 50% have talked to their doctor about their condition.

Dermira brought in a patient and doctors to speak with investors during its presentation in May to illustrate the severity of hyperhidrosis and the need for new treatment options.

Patient Timothy Lawrence, for instance, talked about changing clothes multiple times per day and sweating through three layers of clothing – an undershirt, dress shirt and suit coat – during the course of a single business meeting. Yet, he said the psychological and emotional impacts of excessive sweating were more severe than the physical symptoms of hyperhidrosis.

Dermira Chief Commercial Officer Lori Lyons-Williams worked on the hyperhidrosis launch for Botox and said during the company's investor day presentation that she drew three lessons from that experience that apply to her thinking about Qbrexza: 1) the disease has a meaningful impact on patients' lives, 2) there were not – and 15 years later, still are not – great treatments options for this disease, and 3) a treatment that does work is life-changing for these patients.

Lyons-Williams noted that the Dermira product has a good chance of becoming a significant product, because "the fact that it's novel and topically delivered and can cut sweat in half … I think is really something that, at least according to our testing with patients, is something that's going to resonate quite well."

GOOD PRESCRIBER, PAYER RESPONSE ANTICIPATED

She noted low patient and prescriber satisfaction with available therapies, and said 50% of doctors surveyed by the company would prescribe Qbrexza as a first-line therapy after over-the-counter antiperspirants. The other 50% said they'd try prescription-strength aluminum chloride-based antiperspirants first.

Fortunately, Lyons-Williams said, payers are interested in novel therapies for hyperhidrosis and have indicated a willingness to pay for the product. They already cover Botox and have said that Dermira's data in patients as young as nine years old is differentiating. That's good news for Dermira, which has no imminent competition in this space, since there are no late-stage drugs, devices or procedures in development for this disease.

Compounded versions of topical creams or ointments containing glycopyrronium sometimes are prescribed, but those products have not been consistent, according to dermatologist Dee Anna Glaser, professor and interim Chair of Dermatology at Saint Louis University School of Medicine, during Dermira's investor presentation.

"I think the issue is that each time I write a prescription, I get something different."

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GW's Epidiolex Approval Encouraging For Pharma-Grade Cannabinoid Pipeline

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US FDA approval of **GW Pharmaceuticals PLC**' marijuana plant-derived product *Epidiolex* in rare epilepsy disorders sets a regulatory precedent and is encouraging for the large pipeline of cannabinoid candidates in development for various disorders.

The agency cleared Epidiolex (cannabidiol, or CBD) oral solution on June 25 for the treatment of Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS), noting that this is "the first FDA-approved drug that contains a purified drug substance derived from marijuana." In addition to setting a precedent in that the drug is the first plant-derived cannabinoid to win approval, the decision is also ground-breaking because Epidiolex is the first approved for Dravet syndrome.

Importantly, Epidiolex does not include tetrahydrocannabinol (THC), which is associated with the psychoactive effects of marijuana. Synthetic versions of THC that have been approved by FDA include **AbbVie Inc.**'s *Marinol* (dronabinol) and **Mylan NV**'s *Cesamet* (nabilone). GW Pharma markets *Sativex* (nabiximols) buccal spray, which includes CBD and THC and is derived from cannabis plants, outside the US for spasticity associated with multiple sclerosis.

FDA Commissioner Scott Gottlieb stressed in a statement about the Epidiolex news that this is not a broad approval for marijuana. "This is the approval of one specific CBD medication for a specific use. And it was based on well-controlled clinical trials evaluating the use of this compound in the treatment of a specific condition," Gottlieb said.

Epidiolex currently has Schedule I status with the US Drug Enforcement Agency, which would severely limit access, but the company believes that it will likely be rescheduled to a very unrestricted level – Schedule IV or V.

The rescheduling of Epidiolex, ensuring wide access, would be an encouraging development for GW in terms of its own further development and the cannabinoid pipeline generally, noted Datamonitor Healthcare analyst Stephanie Yip.

GW Pharma also has Epidiolex in Phase III for tuberous sclerosis complex and Phase II/III for infantile spasms.

COMMERCIAL TEAM READY, PRICING STILL IN THE WORKS

The company already has a commercial team in place to market the drug for its initial indications in the US, with 70 reps geared up to reach 4,000 to 5,000 specialist epilepsy prescribers. The patient populations are small – 8,000 people have Dravet Syndrome and 35,000 have Lennox-Gastaut syndrome.

GW has not set a price yet for Epidiolex, but Yip notes that there is no other FDA-approved option for Dravet syndrome so there is high unmet need in a niche space and this is a first-in-class drug, so it could be priced at a premium. Yip points out that **Eisai Co. Ltd.**'s *Banzel* (rufinamide), which is FDA-approved for Lennox-Gastaut Syndrome, commands an annual price of about $20,000, whereas the average annual price across other key branded anticonvulsants is approximately $6,500. *(Also see "Eisai's Banzel gets US approval and complete response letter for epilepsy" - Scrip, 18 Nov, 2008.)*

The market factors will allow GW to maximize the commercial opportunity, Yip told *Scrip*, and noted that Datamonitor is projecting sales of $822m in 2025.

Although there is nothing else approved for Dravet Syndrome, Epidiolex does have a competitor on the near horizon. **Zogenix Inc.**'s oral serotonin reuptake inhibitor ZX008 (low-dose fenfluramine) has shown impressive effects in reducing the number of monthly seizures for patients with this condition. *(Also see "Stellar Zogenix Phase III Epilepsy Data Lift ZX008's Competitive Position" - Scrip, 29 Sep, 2017.)* A filing is expected in the second half.

A TURNING POINT FOR CANNABINOIDS

The development space for cannabinoids has been challenging. Initially, they were developed for obesity. **Sanofi** withdrew an NDA for *Zimulti* (rimonabant) in 2007 and took the drug off the market in 2008 in Europe due to the risk of psychiatric side effects. Since then, the field has shifted to development in what is considered more serious conditions, like severe forms of epilepsy.

GW sees its plant-based approach as offering advantages over other drugs in the pipeline, which largely consists of synthetic candidates. The company aims to provide a standardized, entirely pure formulation, with no other parts of marijuana aside from CBD, or impurities.

Stephen Schultz, GW's vice president of investor relations, said in an interview that the company has refined the science over 20 years of working in the space and is able to grow plants with a specific cannabinoid profile. Generation after generation, the plants are exactly the same, which is what patients and physicians expect from a medicine, he said. The cannabinoid pipeline includes at least 27 drugs in clinical development, according to Informa's Pharma Intelligence Biomedtracker database.

In addition to Epidiolex in tuberculosis sclerosis complex, the late-stage compounds include **Insys Therapeutics Inc.**'s synthetic formulation of cannabidiol, which is in Phase III for seizure disorders and infantile spasms. Other drugs are in clinical development for a range of conditions, including acute pain, graft-versus-host disease, scleroderma, schizophrenia and substance use disorder.

There also are 49 pipeline products in preclinical development that target the cannabinoid type 1 receptor and these are being tested in 47 different indications spanning neurology, psychiatry, oncology, metabolic diseases, respiratory disease, endocrine and infectious disease, according to Biomedtracker.

"This reflects the excitement surrounding the potential for medical marijuana as companies are willing to invest in testing these products for a wide array of diseases, as they perceive the commercial opportunity for this new drug class," Datamonitor's Yip said.

Over time as clinical data roll in, the field may become more targeted at particular conditions.

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Cablivi CHMP Backing Helps Validate Sanofi's €3.9bn Ablynx Purchase

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The logic behind **Sanofi**'s purchase of **Ablynx NV** this year has had an important validation from the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) which has recommended approval of *Cablivi* (caplacizumab) in Europe for treating adults experiencing an episode of acquired thrombotic thrombocytopenic purpura (aTTP), a rare blood-clotting disorder.

Cablivi was developed by Ablynx, now a Sanofi company. It is a first-in-class anti-von Willebrand factor (vWF) Nanobody for the treatment of aTTP.

Marketing approval by the European Commission for Cablivi is now expected around the end of August or early September. It has orphan drug status in both the EU and US. Sanofi expects to launch the drug in the US next year as a treatment for aTTP.

Analysts at Berenberg said Cablivi "for acquired TTP, has proven efficacy and should be widely adopted. Depending on price, this should easily become a €500m-plus product. We forecast sales approaching €600m by 2025."

Sanofi's internal projections are more optimistic. A presentation made by Ablynx at JP Morgan in January estimated annual market potential for Cablivi being €1.2bn, aided by patent protection up to 2035.

Acquired thrombotic thrombocytopenic purpura is a life-threatening disorder with a sudden onset caused by impaired activity of the ADAMTS13 enzyme, resulting in a severe low platelet count (thrombocytopenia) and micro-clot formation in small blood vessels throughout the body that cause thrombotic complications and widespread organ damage.

Cablivi's EU marketing authorization application includes data from the Phase II TITAN study in patients with aTTP which demonstrated a statistically significant and clinically meaningful benefit of Cablivi treatment in reducing the time to platelet count normalization and reducing recurrences while on drug treatment. Results of post-hoc analyses of the Phase II TITAN study further demonstrated that Cablivi dramatically reduced the number of patients experiencing major thromboembolic events, as compared to placebo.

> 'Cablivi significantly curtails costly plasma exchange, a risky procedure, reduces the risk of exacerbations, and protects organ damage'

Cablivi will be made available to patients by **Sanofi Genzyme**, Sanofi's specialty care business, and will be part of the unit's new rare blood disorders franchise that will launch in 2019 and which will also include Bioverativ's treatments for hemophilia A and B.

The CHMP said Cablivi will be available as a 10 mg powder and solvent for solution for injection. It is proposed that Cablivi be prescribed and supervised by physicians experienced in the treatment of management of patients with thrombotic microangiopathies.

Detailed recommendations for the use of the product will be described in the summary of product characteristics, which will be published in the European public assessment report (EPAR) and made available in all official European Union languages after the marketing authorization has been granted by the European Commission.

Analysts at Jefferies in a note said Cablivi "significantly curtails costly plasma exchange, a risky procedure, reduces the risk of exacerbations, and protects organ damage, providing a window for physicians to resolve the underlying disease acquired TTP."

ABLYNX REWARDED LOYAL SHAREHOLDERS

Ablynx's investors have already been hugely rewarded, although they needed patience after its initial IPO on Euronext Brussels in 2007 as Cablivi was developed.

But in September 2017, positive Phase III results for aTTP catalyzed a rerating for Ablynx stock from around €12 per share, and in January 2018, **Novo Nordisk AS** bid €28/share (plus €0.50 in CVRs) for the company, which the board rejected. *(Also see "Novo Outbid As Sanofi Agrees €3.9bn Ablynx Acquisition" - Scrip, 29 Jan, 2018.)* Just weeks later, Sanofi announced that it would acquire Ablynx at €45/share, a staggering 112% premium to its undisturbed price. Sanofi on June 19 completed its acquisition of Ablynx for a total consideration of around €3.9bn.

The acquired Belgium-based division of Sanofi develops Nanobodies, proprietary therapeutic proteins based on single-domain antibody fragments, which combine conventional antibody drugs with some of the features of small-molecule drugs. Ablynx has more than 45 proprietary and partnered programs in development in various therapeutic areas including inflammation, haematology, immuno-oncology, oncology and respiratory disease.

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AbbVie To Take Flight From Galapagos As PELICAN Flounders?

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The first Phase II data for **Galapagos NV**'s novel C2 corrector for cystic fibrosis, GLPG2737, may have hit the primary endpoint in the PELICAN study but its efficacy can't hold a candle to rival **Vertex Pharmaceuticals Inc.**'s investigational products, raising the likelihood of partner AbbVie taking off.

The trial tested GLPG273, a corrector molecule that helps the cystic fibrosis transmembrane conductance regulator (CFTR) protein to move to the cell surface, added to *Orkambi*(lumacaftor + ivacaftor), Vertex's combination of a corrector and a potentiator (ivacaftor, a molecule that helps chloride flow through the CFTR protein channel), but the top-line results were mixed.

Compared with placebo, the product significantly reduced sweat chloride from baseline by a mean 19.6 mmol/L (p=0.02) in 22 adult CF patients who were homozygous for the Class II F508del mutation and on stable treatment with Orkambi.

But there was only a positive trend in ppFEV1 change, a secondary endpoint. The mean absolute change from baseline in ppFEV1 for the GLPG2737 treatment arm versus placebo through day 28 was 3.4% (p=0.08). Further details are still to be presented.

This 3.4% increase in ppFEV1 falls short of the +5% threshold that is generally deemed the minimum needed for an effective drug. It falls still further short of the 7.8% to 13.8% improvements seen for Vertex's own candidates (VX-659 and VX-445) when added to its newer dual combination of tezacaftor/izacaftor (*Symdeko*) in similarly homozygous patients or the difficult-to-treat F508del/minimal function mutations. Corresponding changes in sweat chloride for these drugs were -31mmol/L to -54.3mmol/L.

On the back of the data, AbbVie has decided not to proceed with a second triple combination consisting of the same corrector components combined with potentiator GLPG3067 and Galapagos said it was reviewing the future of the CF collaboration with AbbVie.

The two firms have long been playing catch-up to Vertex in this field. They signed a potential $405m deal back in 2013 with the explicit aim of developing a superior treatment to Vertex's CFTR potentiator ivacaftor (*Kalydeco*), the first disease modifying therapy for CF.

> 'Clearly this is another Galapagos/AbbVie partnership that is now frayed, and we believe it will likely need to be terminated in the near future'

But they have since found themselves left well in Vertex's wake as it sped ahead with development of a range of new therapies. Vertex launched Orkambi in 2015, for the treatment of CF in patients aged 12 years and older with two copies of the F508del mutation. And earlier this year in the US, Vertex launched its third disease-modifying therapy *Symdeko*, containing its next-generation CFTR corrector-potentiator combination, tezacaftor/ivacaftor, for people aged 12 and older who have two copies of the F508del mutation in the CFTR gene or who have at least one mutation that is responsive to tezacaftor/ivacaftor.

Vertex is now pressing ahead with potential triple therapy combinations of its investigational CFTR corrector therapies added to the tezacaftor/ivacaftor backbone. It recently chose two – VX-659 and VX-445 – to take into Phase III trials. Triple therapies are expected to bring treatment options to more patients expanding what is predicted to become a multibillion-dollar market.

SALVAGE OPERATION

In the meantime, Galapagos is left to salvage what it can from its CF program. The company has already begun dosing in the FALCON trial, looking at higher doses of GLPG2737 in CF patients which it hopes will reveal a potential synergistic effect of GLPG2737 on top of its own dual combination compounds. This triple combination comprises potentiator GLPG2451, C1 corrector GLPG2222, and C2 corrector GLPG2737, and initial data for the lower doses being tested are expected in the third quarter.

Credit Suisse analysts said the PELICAN data raised significant concerns about FALCON and the competitiveness of the entire CF franchise.

Moreover, a second collaboration with AbbVie now lies under a cloud following its previous decision to drop the JAK inhibitor filgotinib in 2015 (it was soon picked up by **Gilead Sciences Inc.**). "Clearly this is another Galapagos/AbbVie partnership that is now frayed, and we believe it will likely need to be terminated in the near future," Credit Suisse analysts said in a June 29 research note.

The analysts do note a glimmer of hope for the CF franchise based on the fact that Galapagos has another triple combination ('3067 + 2222 + 3221) that does not involve 2737. But then again, they added, "Without the CF franchise and AbbVie collaboration one could argue Galapagos is now a cleaner story for a potential takeout, especially for a company like Gilead that is already partnered with Galapagos on filgotinib."

Analysts at Jefferies said AbbVie's decision on the second triple combination came "as a surprise, as this has been viewed as the preferred triple since potentiator '2451 has a long metabolite half-life." But they feel that the news could help reset expectation on the program that they feel may have been overdone. "We highlight the '1972 osteoarthritis (OA) and '1690 idiopathic pulmonary fibrosis programmes, which we believe are under-recognized despite better economics for Galapagos."

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Click here to read "AbbVie Calico Extend Their Collaboration On Aging": **https://bit.ly/2ITXCMG**

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Novo Nordisk Touts First-Line Potential For Oral Semaglutide

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Novo Nordisk AS believes the dataset for its oral GLP-1 receptor agonist semaglutide support the investigational drug's potential to one day unseat the generic mainstay metformin as a first-line pill for type 2 diabetes.

The American Diabetes Association (ADA) annual meeting, held June 22-26 in Orlando, was like a coming out party for Novo's oral semaglutide.

Just days before the meeting, the company announced topline results from the pivotal PIONEER 4 study showing that the drug outperformed its successful once-daily GLP-1 injectable *Victoza* (liraglutide) – a major coup.

During a June 24 investor briefing, the company said that it thinks oral semaglutide is well-placed to become a first-line oral GLP-1 agonist based on data from the first pivotal trial PIONEER 1, which was detailed at the ADA meeting, and celebrated the early commercial success of the subcutaneous weekly injectable formulation *Ozempic*.

Ozempic (semaglutide) was approved by the US FDA at the end of 2017, having bested **Eli Lilly & Co.**'s once-weekly GLP-1 *Trulicity* (dulaglutide) in terms of blood sugar lowering and weight loss in the SUSTAIN-7 study.

Mads Krogsgaard Thomsen, executive VP and chief science officer at Novo Nordisk, told the investor briefing there is much for the company to be excited about, but he is most excited about the PIONEER data rolling in for oral semaglutide.

Novo notes that its PIONEER program covers the entire treatment cascade, with studies in a variety of settings, including as monotherapy and as an add-on to insulin and in patients with renal impairment (*see graphic*). All of the studies will read out this year, with the final release in the fourth quarter.

Thomsen noted that PIONEER 1, which tested oral semaglutide as a monotherapy in treatment-naïve patients, supports this "cradle to grave" approach.

Novo had reported positive top-line data from PIONEER 1 in February, but the way it released the data left a lot of questions.

For approval and labeling purposes, the FDA generally prefers clinical trial data from an intent-to-treat (ITT) population of all comers in a trial, not the number who adhered to treatment. But Novo Nordisk reported only minimal data for the intent-to-treat population while offering more details for those who adhered to therapy and did not need rescue medication. The on-treatment population data is what clinicians and payers traditionally used to compare products.

Oral semaglutide met the statistical definition for blood sugar lowering (hemoglobin A1c, or HbA1c) at three doses using the FDA's preferred ITT method, and met the weight loss goal at the highest dose tested (14 mg). And with the on-treatment approach, all three doses achieved significant blood sugar lowering vs. placebo, but only patients on the highest dose achieved significant weight loss.

At the ADA meeting, the company reported the detailed results for both methods in the 703-patient study. Biomedtracker analysts note that in general for the high dose, there was not much difference in the magnitude of the A1C results for both methods in the PIONEER data reported so far, except for PIONEER 1, due to the placebo comparator. Looking at weight loss, there was generally a lesser effect in PIONEER 1 and other trials for the ITT method vs. the on-treatment analysis, Biomedtracker said.

In PIONEER 1, the placebo group did surprisingly well in terms of weight loss, but those on oral semaglutide continued to lose weight, which is a unique feature of the molecule, Thomsen said during the ADA investor briefing.

"These data really just tell us the story that we have an extremely efficacious first-line agent," Thomsen said.

As to whether the drug could displace metformin for first-line use, Thomsen noted that there has been debate on this topic and pointed out the limitations of metformin. Metformin cannot be used in renally impaired patients, for example, and there is a need for more substantiation of cardiovascular/mortality benefits in the company's view.

Oral semaglutide clearly would cost more than generic metformin. However, the exec said he can work with the "price versus the volume elements of the franchise," and so it is "not unrealistic in the future oral semaglutide could be considered a highly realistic first-line treatment option in big parts of the world." That is why the company did studies from cradle to grave with PIONEER 1 to 10, he explained.

Stephen Gough, chief medical officer, acknowledged that "there's a massive comfort factor with metformin because it's been around a long time," but added that the company has to think ahead about the advantages of the newer drugs that could exceed metformin.

"It's not going to change overnight, but I think there will be a move to displace [metformin]. And I think at some point, it will happen. I hope it will happen," Gough said.

However, current ADA guidelines indicate that metformin monotherapy is the first treatment for type 2 diabetes unless there are contraindications, and that metformin is "effective, safe and inexpensive and may reduce risk of cardiovascular events and death."

PIONEER 4 MAKES A SPLASH

A key goal for Novo Nordisk has been to develop a tablet with the same efficacy as its injectable GLP-1 Victoza, to expand the class' reach into a broader patient population. Primary care doctors are reluctant to prescribe injectables, Ted Hobbs, Novo's North American chief medical officer for diabetes, explained to *Scrip* in an interview.

That goal was achieved in the PIONEER 4 study, which compared oral semaglutide to Victoza. Results were announced in a topline release on June 20, along with positive data from PIONEER 7, which tested oral semaglutide against **Merck & Co. Inc.**'s DPP-4 inhibitor *Januvia* (sitagliptin).

The results from PIONEER 4 looked strong in both the intent-to-treat and the on-treatment analyses.

"This data is important, as it positions oral [semaglutide] as at least as good as the market leading injectable GLP-1. The result should

PIONEER 1 Analysis: Oral Semaglutide vs. Placebo

ANALYSIS	SEMAGLUTIDE 3 MG VS. PLACEBO	SEMAGLUTIDE 7 MG VS. PLACEBO	SEMAGLUTIDE 14 MG VS. PLACEBO
Difference in HbA1c at week 26, ITT	0.6%, p<0.001	0.9%, p<0.001	1.1%, p<0.001
Difference in HbA1c, on-treatment	0.7%, p<0.001	1.2% p<0.001	1.4%, p<0.001
Difference in weight loss at week 26, ITT	0.1 kg	0.9 kg	2.3 kg, p<0.001
Difference in weight loss at week 26, on-treatment	0.2kg	1 kg, p<0.05	2.6 kg, p<0.001

Source: Biomedtracker, Novo Nordisk

grace Novo with pricing flexibility above that of current orals and up to that of injectables, depending on Novo's chosen price vs volume approach," Deutsche Bank analyst Tim Race said in a June 20 note.

"We continue to believe oral-[semaglutide] has the potential to become a >$5bn blockbuster product and should allow Novo to grow in the higher margin GLP-1 diabetes segment for the coming years," Race added.

Evercore ISI analyst Umer Raffat said in a June 20 note that PIONEER 4 is "critical for commercial positioning" and that the outcome is likely as good as the company could have hoped for.

After proving to be as good if not better than Victoza on blood sugar lowering and weight loss, oral semaglutide is a very compelling offering, Raffat said.

WANTED: CV OUTCOMES DATA

When it comes to competing with other oral drugs, semaglutide needs to be tolerable and also demonstrate a cardiovascular benefit, as SGLT2 inhibitors have proven an outcomes benefit.

Nausea has been the main side effect of concern with semaglutide relative to oral classes. Novo noted during its call that the rates of nausea in pivotal trials reported so far ranged from 16% to 21%, which is on par or lower than other GLP-1 agonists on the market.

Outcomes data are coming soon. The PIONEER 6 cardiovascular outcomes study comparing oral semaglutide against placebo in 3,176 patients is due to report this year, along with the rest of the PIONEER program.

Ozempic demonstrated a 26% reduction in major adverse cardiovascular events in the SUSTAIN-6 study, but the company said at the time the data were released that it would need a larger, longer outcomes study post-approval in order to get a claim for a cardiovascular benefit.

The company now says that if PIONEER 6 is positive, the data along with SUSTAIN-6 may be enough to support a cardiovascular claim for both products. Novo also said that following discussions with the FDA, it no longer plans to run a large outcomes study of Ozempic. Instead it will run a large outcomes study of oral semaglutide and the results could support a claim for both products. This study will start enrolling in 2019.

IMPACT ON LILLY'S TRULICITY

If oral semaglutide was the only key launch for Novo, the pivotal data reports would matter a lot to Lilly's competing Trulicity – but that's not the case, Evercore ISI's Raffat said.

Instead, Novo is very focused on the weekly Ozempic, and that works in Lilly's favor because it forces Novo into segmenting the market into daily use with oral semaglutide vs. weekly with Ozempic and Lilly has a market position in that weekly GLP-1 segment, the analyst said.

At the ADA meeting, Novo Nordisk presented a post hoc analysis from the SUSTAIN-7 study, showing that Ozempic provided greater weight reductions compared to Trulicity across levels of body mass index. Since launching in the US a few months ago, the company is in the "fortunate position" of having more than 50% coverage in commercial and Medicare plans, Thomsen said. Globally, the company still expects sales of at least DKK1bn ($157m) or more this year and says that the GLP-1 market growth is healthy in the US – above 20%. Ozempic now has over 10% of new-to-brand scripts.

In a June 21 note, Societe Generale analyst Florent Cespedes warned of the risk of oral semaglutide cannibalizing Victoza, which accounts for 20% of company sales. However, Hobbs told *Scrip* that he doesn't see oral semaglutide competing with either Victoza or Ozempic, rather a new market will open up for people who need the robust A1c lowering and weight loss possible with a GLP-1 agonist and haven't had access to it.

"We really believe that there are a lot of type 2 patients out there that could benefit from GLP-1 and are not getting it. We want to expand that number of patients who can achieve the benefits," Hobbs said.

Meanwhile, Lilly is moving forward with higher dosing of Trulicity in a bid to boost blood sugar and weight loss. The drug is currently approved at doses of .75 mg and 1.5 mg.

The company presented Phase II data at the ADA meeting for two higher doses: 3 mg and 4.5 mg. In the trial, three doses – 1.5 mg, 3 mg and 4.5mg – were tested against placebo over 18 weeks.

"We believe that investigation of additional doses for Trulicity can provide an important choice for patients," Brad Woodward, senior medical director at Lilly Diabetes, said in an interview.

Commenting on the Phase II data, Biomedtracker analysts said that while higher doses of Trulicity were associated with numerically greater reductions in A1c and body weight compared with the 1.5 mg dose, it is not quite clear yet whether their profile will match Ozempic.

"On tolerability, the 3 mg dose had nausea and vomiting that were close to 1.5 mg, the 4.5 mg dose had rates of nausea that were appreciably higher (30.3% compared to 22.2%), with only a slight numerical increase in vomiting," Biomedtracker analysts commented.

Lilly's Phase III AWARD-11 study is evaluating the higher doses on a much larger scale, and the company aims to share results with regulatory authorities next year.

"Overall, it is probably worthwhile for the company to have started a Phase III trial with higher doses to narrow the gap with semaglutide somewhat, but injectable semaglutide may retain a moderate advantage," Biomedtracker analysts said.

There will also be increased competition from oral semaglutide, they added.

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AstraZeneca Looks To Deliver On Its Promises In Oncology

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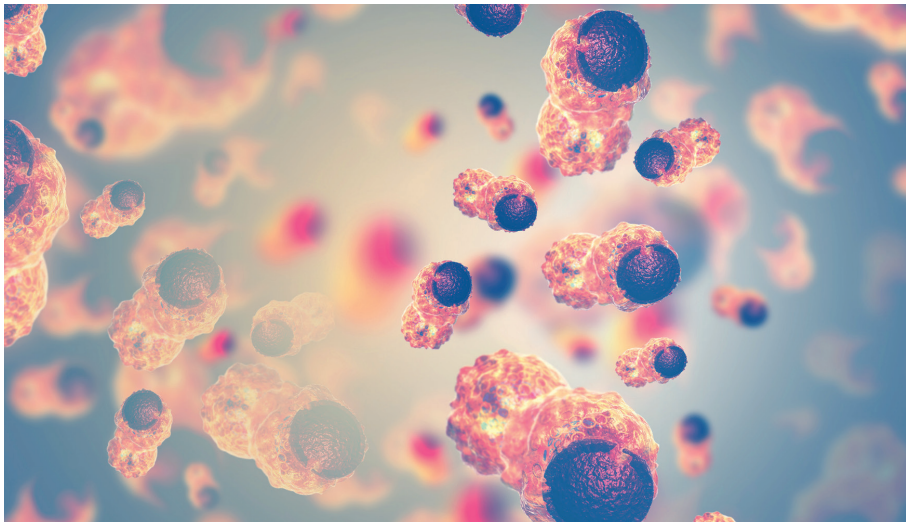
AstraZeneca PLC has a budding oncology portfolio that includes four new medicines launched since 2015 and more on the way. The company is focused on competing against market-leading PD-1/L1s in lung cancer, expanding the PARP inhibitor *Lynparza* (olaparib) beyond women's cancer, building out a new hematology franchise and figuring out what combinations of drugs will provide the most durable benefits in the future.

The UK drug maker has a heritage in oncology and was ahead of its time with the launch of the targeted cancer drug *Iressa* (gefitinib) in 2003 – though it took time to clarify the drug's role. But AstraZeneca has been better known for selling primary care blockbusters like *Crestor* and *Nexium*, both now generic, and *Symbicort* for asthma. Increased investment in oncology has been a priority under the leadership of CEO Pascal Soriot, and that is starting to deliver a changing portfolio mix. *(Also see "AstraZeneca Under Soriot: Progress Report" - Scrip, 14 Jul, 2017.)*

Oncology remains the company's smallest business unit behind cardiovascular/metabolic and respiratory disease, but it is the fastest growing. Oncology generated sales of $4.02bn in 2017, representing growth of 19% and accounting for 20% of the company's consolidated revenues. Sales of respiratory drugs declined 1% and CV/metabolic, the largest business, declined 10%.

The approval of AstraZeneca's first-in-class PARP inhibitor Lynparza (olaparib) in January 2015 was the firm's first oncology approval in 15 years, but it is close to delivering on its promise to have five novel oncology approvals by 2020, with the subsequent approvals of its PD-L1 inhibitor *Imfinizi* (durvalumab) and BTK inhibitor *Calquence* (acalabrutinib). Another drug, a first-in-class anti-CD22 immunotoxin moxetumomab could soon be on the market for hairy cell leukemia.

In addition to the three newer drugs, the oncology portfolio also includes the top-seller, the third-generation EGFR inhibitor *Tagrisso* (osimertinib), the first-generation EGFR inhibitor Iressa, and a portfolio of older legacy products, mainly hormone therapies like *Faslodex*, *Zoladex* and *Casodex*.



Tagrisso still has plenty of room to grow, having received FDA approval for frontline non-small cell lung cancer (NSCLC) in patients with an EGFR mutation in April. *(Also see "Keeping Track: A Fresh Wave Of Approvals" - Pink Sheet, 22 Apr, 2018.)* The legacy products help to buffer the cancer portfolio, accounting for more than half of sales, but the pressure is on AstraZeneca to build new big-ticket brands. None of the company's cancer drugs crossed the blockbuster revenue threshold in 2017.

BLOCKBUSTERS IN THE MAKING

Exec VP and Global Head-Oncology Business Unit Dave Fredrickson has an ambition to change that, however. "The commercial engine is really starting to deliver in an important way across our four marketed brands. I believe that with Lynparza, Tagrisso, Imfinizi and Calquence, each of those has an opportunity to be a blockbuster brand, if not a multi-blockbuster," he said during an interview at the American Society of Clinical Oncology meeting in early June.

Fredrickson was tapped to lead the commercial oncology group in October 2017, moving over from president of AstraZeneca K.K. in Japan and having previously served as VP for specialty care for AstraZeneca in the US, which included oncology at the time. He joined AstraZeneca from Soriot's alma mater. **Roche** in 2014, where Fredrickson managed oncology in Spain. In his current role, he is accountable for AstraZeneca's commercial performance in the top eight markets: the US, Japan, China and top five European countries.

Fredrickson sees the four marketed growth drivers as the foundation to build AstraZeneca into an oncology powerhouse. "We have the life cycle programs, [and] we can now begin to build around them to turn them into significant, important franchises," he said. "I can see line of sight into being a top three oncology player based on those assets."

The expansion in oncology is a big initiative and Fredrickson said his top priority is delivering commercial success. "The way that we are building out our field force, our market access, our medical affairs, all of that is focused with an eye towards what is needed to maximize for oncology," he said.

But the company's ambition to become a top oncology player will face real commercial challenges. For starters, AstraZeneca shares profits on one of the most promising growth drivers in its portfolio, Lynparza, with **Merck & Co. Inc.** under a 2017 collaboration. AstraZeneca accepted a $1bn upfront payment in exchange while also granting Merck shared rights to the MEK in-

hibitor selumetinib. *(Also see "A Whopper Of A Deal: AZ Hands Half Of Lynparza To Merck" - Scrip, 27 Jul, 2017.)*

When it comes to Imfinizi, the company was fifth to market and is facing fierce competition from the other PD-1/L1 inhibitors, especially in the biggest commercial market, NSCLC: Merck's *Keytruda* (pembrolizumab), **Bristol-Myers Squibb Co.**'s *Opdivo* (nivolumab) and Roche's *Tecentriq* (atezolizumab), as well as **Pfizer Inc./Merck KGAA**'s *Bavencio* (avelumab).

AstraZeneca has embraced a come-from-behind strategy, forgoing the lead indications for the class to prioritize development in untapped indications. *(Also see "AstraZeneca's Imfinzi Scores First Early Lung Cancer Approval" - , 16 Feb, 2018.)*

But the immuno-oncology (IO) playing field is rough, and as AZ and BMS have seen some clinical setbacks, Merck is solidifying its lead. *(Also see "Merck's Keytruda Enjoys Clean Sweep In Lung Cancer, At Bristol's Expense" - Scrip, 17 Apr, 2018.)* It was the big headliner at ASCO with the release of new data on Keytruda in lung cancer showing the drug resulted in benefits in patients as monotherapy and in combination with chemotherapy, regardless of PD-L1 mutation burden. *(Also see "Merck's Keytruda Monotherapy May Get Stuck With Small Role In First-line Lung Cancer" - Scrip, 4 Jun, 2018.)*

IMFINZI: WINNING IN STAGE III AND FUTURE EXPANSION

Imfinizi scored an FDA approval for Stage III NSCLC in patients whose disease has not progressed on concurrent chemotherapy in February based on positive progression-free survival data, and updated data from the PACIFIC trial released in May also showed an improvement in overall survival. *(Also see "PACIFIC Pays Off Again For AZ With Imfinzi Lung Cancer OS Success" - Scrip, 25 May, 2018.)*

The approval is a win for AstraZeneca, as the company is the only PD-1/L1 inhibitor approved for Stage III NSCLC. The challenge is that three other checkpoint inhibitors have been approved for Stage IV NSCLC that has spread, which encompasses a broader patient population, since patients with lung cancer are typically diagnosed late.

Fredrickson is bullish on the opportunity in Stage III lung cancer because it is a potentially curative setting, compared to metastatic lung cancer.

"We are the only PD-1/L1 in the Stage III setting, so today what we compete against is active surveillance, which is nothing," he said. "That's not to make it sound easy, because we have a big educational gap in front of us … but in Stage III we have at least a two-year head start over any of the competitors."

AstraZeneca also hopes to add an indication for advanced NSCLC as well, though it has faced setbacks with an IO/IO combination it hoped would give it a leg up versus the competition. Earlier this year, the initial results of the ARCTIC study failed to show a PFS or survival benefit in advanced NSCLC patients treated with a combination of Imfinzi and AZ's CTLA-4 inhibitor tremelimumab. *(Also see "ARCTIC Chill Descends On AstraZeneca's Imfinzi/Treme Combo In NSCLC" - Scrip, 24 Apr, 2018.)*

Another study testing the combination in metastatic NSCLC, MYSTIC, disappointed when it failed to show a benefit on PFS last year, but the study is continuing, with overall survival data anticipated in the second half of the year. The trial is evaluating Imfinzi as monotherapy as well. *(Also see "MYSTIC Misses: Devastation For AstraZeneca As Imfinzi Fails PFS Endpoint In NSCLC" - Scrip, 27 Jul, 2017.)* Another Phase III study, POSEIDON, is evaluating Imfinzi with and without tremelimumab plus chemotherapy, with data expected in 2019.

The combination setback AstraZeneca has faced is not so different from what others in the industry have faced in the last year, as disappointing data has read out from IO/IO combination trials across the spectrum. One of the big themes at ASCO this year was how industry has absorbed those disappointments; IO combinations with targeted therapies and chemotherapy impressed, and companies continue to look for the next potential combinations. *(Also see "ASCO 2018: Optimism As Industry Resets And Looks To What Is Next" - Scrip, 4 Jun, 2018.)*

Fredrickson said the company is working to improve how it evaluates combinations early on before moving into large Phase III studies like it did with Imfinzi/tremelimumab. "Instead of picking one combination and moving forward with it, it's how do we get multiple different ones and pick the best ones," he said.

AstraZeneca's Head of Early Stage Oncology Susan Galbraith said the company is doing more platform-based studies and tumor sequencing work to better target potential combinations to different patients. The company is evaluating new opportunities in IO, for example, around the innate immune system and the tumor-associated macrophages in the tumor microenvironment that can inhibit tumor-infiltrating lymphocytes to attack and kill tumors.

But it is also digging in other areas as well, she said, pointing to DNA damage repair, where the company has had success with Lynparza. AstraZeneca has strategically kept a focus on small molecule cancer drugs, and thinks it has an industry-leading portfolio in DNA damage response.

"IO is a paradigm-changing, massive event in cancer that we are still riding the wave of, but it is not the only thing that is important," Galbraith said. "You don't hatch all your eggs just in that one basket, and I think we are different in that respect."

She highlighted several early-stage oncology candidates that are being studied in combination with Imfinzi, including the small molecule adenosine A2A receptor antagonist AZD4635, the anti-CD73 antibody oleclumab and anti-NKG2A antibody monalizumab.

LEADING THE WAY IN PARP

AstraZeneca and partner Merck have big expansion plans for Lynparza, which was the first PARP inhibitor approved by the FDA and is now the leading PARP inhibitor of three on the market in terms of sales. It's also the only PARP inhibitor approved in breast cancer as well as ovarian cancer, following the FDA approval in January in BRCA-positive breast cancer. *(Also see "Lynparza Gets First Mover Advantage In BRCA-Positive Breast Cancer" - Scrip, 15 Jan, 2018.)*

"I think we have the best-in-class PARP inhibitor, so that's one of the things that's most exciting, and we have the deepest and broadest development program," Galbraith said. The companies are looking toward prostate cancer next, and announced positive data from a Phase II study testing Lynparza in combination with

Johnson & Johnson's *Zytiga* (abiraterone) versus abiraterone alone, showing improvements in PFS for the first time in metastatic castration-resistant prostate cancer. *(Also see "As A New Rival Approaches, PARP Makers Look To Carve Out Their Niche" - Scrip, 7 Jun, 2018.)*

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Scrip's weekly **Pipeline Watch** tabulates the most recently reported late-stage clinical trial and regulatory developments from the more than 10,000 drug candidates currently under active research worldwide.

Click here for the entire pipeline with added commentary: http://bit.ly/2mx4jY3

Selected clinical trial developments for the week 22–28 June 2018

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
PHASE III SUSPENDED			
Aquinox Pharmaceuticals Inc.	rosiptor	interstitial cystitis/ bladder pain syndrome	LEADERSHIP 301; primary endpoint missed.
PHASE III RESULTS PUBLISHED			
Astellas PharmaInc./Pfizer Inc.	*Xtandi* (enzalutamide)	castration-resistant prostate cancer	PROSPER; *NEJM*, June 28, 2018.
Hutchison MediPharma Ltd.	fruquintinib	colorectal cancer	FRESCO; *JAMA*, June 26, 2018.
PHASE III INTERIM/TOP-LINE RESULTS			
Acceleron Pharma Inc./ Celgene Corp.	luspatercept	myelodysplastic syndorome	MEDALIST; met primary and secondary endpoints.
Global Blood Therapeutics Inc.	voxelotor	sickle cell anemia	HOPE; primary endpoint achieved.
Cara Therapeutics Inc.	*Korsuva* (difelikefalin), intravenous	pain during abdominal surgery	Met primary endpoint, reducing pain and PONV.
Boehringer Ingelheim GMBH/ Eli Lilly & Co.	*Jardiance* (empagliflozin), with insulin	diabetes, type 1	EASE-2, -3; positive top-line data.
AstraZeneca PLC	*Farxiga* (dapagliflozin), with insulin	diabetes, type 1	DEPICT-2; improved glycemic control.
Roche	*Tecentriq* (atezolizumab) plus chemo	small cell lung cancer, extensive stage	IMpower133; improved overall survival and PFS.
Amgen Inc.	*Repatha* (evolocumab), monthly	diabetes, type 2 and dyslipidemia	BANTING; reduced cholesterol.
Xeris Pharmaceuticals Inc.	glucagon, rescue pen	hypoglycemia in diabetes, type 1	Positive data.
Eli Lilly & Co.	*Taltz* (ixekizumab)	radiographic axial spondyloarthritis	COAST-W; met primary and major secondary endpoints.
Novo Nordisk AS	semaglutide, oral	diabetes, type 2	PIONEER 3; reduced weight, HbA1c levels in long-term study.
Amgen Inc.	ABP710, biosimilar infliximab	rheumatoid arthritis	Non-inferior to *Remicade*.
AstraZeneca PLC/Merck & Co. Inc.	*Lynparza* (olaparib)	ovarian cancer, first-line maintenance	SOLO 1; PFS improved.
Ferring BV/Merck & Co. Inc./WHO	*Pabal* (carbetocin), heat stable	acute hemorrhage after childbirth	CHAMPION; prevented excessive bleeding.
UPDATED PHASE III RESULTS			
Biohaven Pharmaceuticals Holding Co. Ltd.	rimegepant	migraine	Study 301, 302; relieves pain, restores function.
Edge Therapeutics Inc.	EG-1962	subarachnoid hemorrhage	NEWTON 2; clinical benefits seen.
Eli Lilly & Co.	*Emagality* (galcanezumab-gnlm)	episodic cluster headache prevention	Positive clinical results.
AstraZeneca PLC	*Farxiga* (dapagliflozin), with insulin	diabetes, type 1	DEPICT-1; reduced glycemic variability.
Lexicon Pharmaceuticals Inc./Sanofi	*Zynquista* (sotagliflozin) with insulin	diabetes, type 1	inTandem; reduced A1C levels.
Catabasis Pharmaceuticals Inc.	edasalonexent	Duchenne muscular dystrophy	MoveDMD; signs of disease slowing.
Novo Nordisk AS	semaglutide, oral	diabetes, type 2	PIONEER 2,4,7; updated clinical data.
Pfizer Inc.	*Ibrance* (palbociclib) with fulvestrant	HR+, HER2- metastatic breast cancer	PALOMA-3; positive trend in overall survival data.

Source: Biomedtracker

CONTINUED FROM PAGE 21

A large Phase III program in prostate cancer is now in the works, though AstraZeneca also said it will speak with the FDA about the Phase II results. Another Phase III program in combination with Imfinzi is also under way in ovarian cancer.

BREAKING INTO BLOOD CANCER

In hematology, the company has built a commercial team to support the launch of Calquence, which was approved by the FDA in October as a second-line option for the rare cancer mantle cell lymphoma. *(Also see "AstraZeneca's Calquence Steps Into Blood Cancer Ring With Mighty Imbruvica" - Scrip, 31 Oct, 2017.)* The launch marked AstraZeneca's entry into blood cancers, where the company will compete initially against Johnson & Johnson/AbbVie's blockbuster first-in-class BTK inhibitor *Imbruvica* (ibrutinib).

MCL is a niche indication, but it presents an opportunity for AstraZeneca to ease into the market. The company has its eye on a much larger commercial opportunity in chronic lymphocytic leukemia. Data in CLL are anticipated in 2019.

"What we really wanted to do is get quickly to market and get an opportunity for physicians to have experience with the medicine and really pave the way for what is the larger opportunity, which is the CLL market," Fredrickson said. AstraZeneca has added a new sales team and ramped up medical affairs.

"We've hired a great sales force. We've got deep hematology experience," he said. "We are well aware of the fact that people who are good at solid tumor oncology are different from those that understand hematology." He said the company is "absolutely" interested in expanding further into blood cancers, with several drugs in early development.

A second product is already poised to enter the hematology portfolio later this year, moxetumomab, an anti-CD22 antibody drug conjugate (ADC) for relapsed hairy cell leukemia, for which there are no current treatments. The BLA has been granted a priority review by the FDA and could see approval by September. Positive data from an 80-patient Phase III study presented at ASCO showed treatment resulted in a 75% objective response rate and 41% complete response rate.

Moxetumomab would also be AstraZeneca's first ADC product on the market, an area of research in which the company is investing more broadly.

AstraZeneca also made an early move to get into good position as IO extends from solid tumors into hematology, through a broad alliance with Celgene, looking to the hematology leader as a way to gain expertise as it built in the field.

It's still early days for those efforts, but AstraZeneca has made some big strides filling out its commercial cancer portfolio. Now, continuing to push its pipeline, turning new launches into blockbuster brands and uncovering the best combinations for the future will be the key to seeing how the company succeeds in building an oncology specialty from the ground up.

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Deborah Dunsire has been appointed president and CEO of **Lundbeck**, as of Sept. 1, 2018. Anders Götzsche, who had been acting as interim CEO and CFO since November 2017, will resume his position as CFO of the Danish neuroscience specialist. Most recently Dunsire was president and CEO of Xtuit Pharmaceuticals. She was previously CEO of Forum Pharmaceuticals and Millennium Pharmaceuticals, both before and after it was acquired by Takeda.

Scott Chappel has been named chief scientific officer of Belgian cancer immunotherapy firm **iTeos Therapeutics**. Previously he was a founder and chief technology of Surface Oncology, and before that was a founder and CSO of Arteaus Therapeutics (acquired by Eli Lilly) and Tokai Pharmaceuticals. The company has also appointed ***David Hallal***, former CEO of Alexion Pharmaceuticals, as chairman of its board of directors, and ***Tim Van Hauwermeiren***, CEO of argenx, as independent non-executive director.

Astellas Pharma Inc has promoted ***Yukio Mastui***, hitherto head of EMEA operations, to the position of chief commercial officer. Dirk Kosche, formerly president of Novartis Pharma KK in Japan, has joined the company to head EMEA operations.

Gene therapy developer **Orchard Therapeutics** has appointed ***Jim Geraghty*** as chairman of the board of directors, replacing Ben Auspitz, partner at F-Prime Capital. Jim held leadership positions at Genzyme, including founding president and CEO of Genzyme Transgenics, and was also senior vice president, North America strategy and business development at Sanofi.

Another former Genzyme executive, ***Andre Turenne***, has been appointed as president and CEO of **Voyager Therapeutics**. His most recent role was senior vice president, global head, business development and licensing responsible for partnering activities across all business units at Sanofi. ***Steven Paul*** is retiring as president and CEO but will continue to serve on the board of directors and science and technology committee.

Cevec Pharmaceuticals has appointed gene therapy specialist ***J. Fraser Wright***, chief technology officer, gene therapies at Axovant and scientific co-founder and former CTO at Spark Therapeutics, to its scientific advisory board.

Karen Smith, who most recently served as executive vice president, global head R&D and chief medical officer of Jazz Pharmaceuticals, has joined **Sangamo Therapeutics**' board of directors. Previously she was senior vice president, global medical affairs and global dermatology head at Allergan, and before that held leadership positions at AstraZeneca and Bristol-Myers Squibb.

Research directors from the Broad Institute, Merck Research Laboratories and Celgene have joined protein stability-focused start-up **Cedilla Therapeutics** as vice presidents. ***Dale Porter***, who most recently directed oncology drug discovery research at the William Sellers Lab of the Broad Institute of MIT and Harvard, and who previously worked at Novartis, has been appointed vice president of biology. ***Iván Cornella-Taracido*** joins as vice president of proteomics and chemical biology; he was formerly director chemical biology at Merck Research Laboratories. ***Eric Schwartz***, former executive director of chemistry at Celgene, will be vice president of drug discovery at Cedilla, which was launched in 2018 by Third Rock Ventures and is based in Cambridge, Massachusetts. The company hopes to broaden the reach of small molecules by generating therapeutics that degrade protein targets as their primary mechanism of action.

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