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Takeda Grabs Shire At Last After Long Pursuit

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Shire PLC's acceptance, as expected, of a £48.17 per share acquisition offer from determined pursuer **Takeda Pharmaceutical Co. Ltd.**, paves the way for a roughly £46bn ($62.45bn) deal that will create a new force just inside the global pharma top 10, and also marks both the biggest ever M&A transaction by the Japanese pharma sector and the largest overseas buy-out in any sector in Japan.

The combined sales of the merged group are estimated to be around $30bn, based on recent annual sales, and Takeda's doggedness may well be explained by Shire being seen as its last best chance of becoming a true global player.

The companies said the transformative tie-up – effectively a merger given Shire's larger size and current market cap – will create a group the partners claim will have leading positions in rare diseases and plasma-derivatives, along with complementary strengths in gastroenterology and neuroscience, while adding to Takeda's pipeline and cash-flow.

Geographically, the main benefits will be a strengthening of Takeda's presence in the US, while Shire meanwhile is seen gaining from Takeda's stronger existing positions in Japan, Asia and the emerging markets. The combined group will have major research hubs in Boston, Switzerland and Singapore, along with Japan.

Takeda said it was confident of delivering "substantial annual cost synergies" on a recurring pre-tax base, which it estimated could reach at least $1.4bn per annum by the end of the third fiscal year, including overlapping R&D costs, although further details of how these will be realized and whether jobs may be at stake have yet to emerge. There may also be other revenue synergies by combining infrastructure, market presence and development capabilities under the deal, which is expected to close in the the first half of calendar 2019.

Initial reaction from some analysts in Japan was positive over the planned savings, which were seen as greater than expected.

Current Takeda shareholders – which along with Shire investors still need to approve the deal – will end up owning around 50% of the Japan-based combined group under the transaction structure, which will result in a dual listing in the US (NYSE) of American Depositary Shares (ADSs) comprising 0.5 Takeda shares each and primarily on the Tokyo Stock Exchange, a first for any pharma company.

TERMS, IMPACT, FINANCING

The agreement by both companies' boards on terms of the recommended offer came just after the 3pm market close in Tokyo on May 8 and just before an extended deadline of 5pm UK the same day under UK takeover code rules. It will see the Japanese firm offer $30.33 in cash and either 0.839 new Takeda shares or 1.678 Takeda ADSs per Shire share, in line with its earlier fifth revised offer, of £49 per share (based on then current share prices), which comprised £27.26 in new Takeda shares (to be issued in Japan and the US) and £21.75 in cash.

Based on Takeda's lower closing share price as of May 2, these terms imply a

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from the editor

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It's the fifth biggest pharma merger of all time: Takeda has finally snared its prey to create a combined company that will join the ranks of the top 10 firms in the sector.

On the face of it, Shire's price has risen considerably since it was last on the block. Takeda is offering the equivalent of around £46bn, whereas AbbVie won endorsement from the UK-listed firm's shareholders for a deal worth around £32bn nearly four years ago. But that 44% increase in value is sharply reduced when viewed in dollar terms thanks to the weakening of the British pound since the Brexit vote, with the dollar differential coming out at a more modest 15% ($62bn from Takeda versus $54bn from AbbVie).

Furthermore, Shire has spent a lot in the intervening years. The $1.6bn AbbVie had to pay to call off the merger following a clampdown on tax inversion by the US government doesn't come close to covering it, and nor does Shire's recently announced $2.4bn sale of its oncology business to Servier. Most notably it spent $32bn acquiring Baxalta in 2016, a year when it also bought Dyax for $5.9bn and NPS Pharmaceuticals for $5.2bn.

Was it all worth it? Over that same period, Shire's revenues have risen from $5.8bn in 2014 to $15.2bn in 2017, while net income has fluctuated, with two weak years following 2014's $3.4bn preceding a jump in 2017 to $4.3bn. It takes years to realize the value of acquisition investments, and the full potential of Shire CEO Flemming Ørnskov's bounty-gathering is now Takeda's responsibility to deliver.

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Novartis' Growth Driver Tafinlar/Mekinist Picks Up New Melanoma, Thyroid Indications
https://bit.ly/2KIqoei
New FDA labeling brings Tafinlar/Mekinist into adjuvant melanoma setting, but Bristol's competing Opdivo already has captured nearly 50% of the market and is approved regardless of genetic mutation.

China Zero Tariffs For Cancer Drugs Precede High-Stakes Trade Talks
https://bit.ly/2IrA3YE
China is opening up its domestic pharma market with an import duty exemption on 28 drugs including anticancers, effective this May. The duty cuts came ahead of the latest trade talks between the US and China, though Chinese officials have underscored that countries like India could also stand to gain.

AstraZeneca's Imfinzi, Lynparza On Track To India Debut
https://bit.ly/2jFMbaf
AstraZeneca, which recently committed to scaling up investments in India, appears on course to bringing two key new anticancers to the country, including the PD-1/L1 inhibitor Imfinzi. Pricing aspects for the products in what is a largely out-of-pocket market are, however, expected to be decisive.

A US Drug Pricing Rebellion Looms, Analyst Says
https://bit.ly/2jEF7um
Wells Fargo analyst David Maris warned biopharma investors that the US drug market is on a long-term trajectory toward price controls, which he characterized as an under-appreciated risk for the sector, ahead of President Trump's speech on drug pricing.

J&J's Mixed Phase III Data For Esketamine Highlight Challenges In Resistant Depression
https://bit.ly/2HYbMKa
Johnson & Johnson released data from the first two Phase III trials testing esketamine in patients with treatment-resistant depression, but only one study met the primary efficacy endpoint.

Tech Transfer Roundup: United Neuroscience Unveils Pair Of Collaborations In CTE, Alzheimer's
https://bit.ly/2jHFlAU
Irish biotech focused on Endobody vaccine candidates partners with Boston University in CTE and University of Texas in Alzheimer's. Lupus Research Alliance affiliate will help Bristol conduct a Phase II trial of Tyk2 inhibitor in lupus.

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Takeda/Shire Deal Stands Fifth Largest In Biopharma M&A

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Under the terms included in **Takeda Pharmaceutical Co. Ltd.'s** April 24 buyout offer, the Japanese pharma's acquisition of **Shire PLC** would be the fifth-largest biopharmaceutical M&A deal in history at an estimated value of $64.3bn.

The fifth publicly disclosed bid by Takeda to purchase the Irish specialty pharma would be eclipsed only by **Pfizer Inc.**'s successful hostile bid for **Warner-Lambert Co.**, the merger of **Glaxo Wellcome Inc.** with **SmithKline Beecham**, Pfizer's buyout of **Wyeth** and **Actavis** staving off **Valeant Pharmaceuticals International Inc.** to buy **Allergan PLC** as a "white night."

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One day before a deadline to make a formal offer under UK takeover law, Takeda got Shire to take a bid to its shareholders by offering the equivalent of £49 per share in a deal that would be comprised 44% of cash and 56% of equity according to the Japanese pharma's share price at the time of the proposal.

However, Takeda's stock price consistently has trended down during its pursuit of Shire, making the final cash-to-stock ratio of the buyout liquid until finalized.

The 10 largest biopharma take-outs by value, according to Strategic Transactions, range in dollar amount from $84.1bn to $38.8bn. Potentially an interesting coincidence, however, is that Shire's $32bn acquisition of **Baxalta Inc.** in 2016 ranks as the 11th largest biopharma deal, with the hemophilia franchise Shire got from the **Baxter International Inc.** spin-out likely driving at least some of Takeda's acquisition interest. Shire sold off the oncology business acquired in the Baxalta deal to **Servier SA**, however, while Takeda was in the process of making its bids for Shire.

Prior to the Takeda/Shire marriage, the 10 largest biopharma M&A deals by total value were:

1. Pfizer wrapped up its hostile bid for Warner-Lambert in February 2000, beating out an offer from **American Home Products** estimated at $72.5bn. To prevail, Pfizer increased its offer from 2.5 shares of its own stock for each Warner-Lambert share to 2.75 shares of its stock, coming to an estimated price of $84.1bn. However, the New York pharma ultimately also had to pay a $1.8bn termination fee to AHP that was included in the latter's merger agreement with Warner-Lambert.
2. Also right around the turn of the century, Glaxo Wellcome and SmithKline Beecham merged in January 2000 to become what is now known as **GlaxoSmithKline PLC**. A stock swap resulted in shareholders of the UK's Glaxo owning 58.75% of the new entity.
3. Once known as the "world's largest pharma," Pfizer has used the M&A route to grow its business many times, including its January 2009 buyout of Wyeth, a cash-and-stock transaction valued at $66.7bn. This deal would be the first of three biopharma mega-mergers in 2009 that still stand among the 10 biggest in the industry's history.
4. Actavis landed Allergan in November 2014 (and then took the latter firm's name) to conclude a string of consolidations that also included buyouts of **Forest Laboratories Inc.** and **Durata Therapeutics Inc.**. Allergan staved off a hostile bid from Valeant for seven months, with Actavis coming to the rescue with a bid of $65bn in cash and stock.
5. The French pharma then known as **Sanofi-Synthelabo KK** landed **Aventis SA** in a hostile process in April 2004 at an estimated price of $62bn, following an unsuccessful bid by **Novartis AG** as a white knight. Known for a while as Sanofi-Aventis, the pharma later shortened its name to Sanofi and paid roughly $17.5bn in 2010 to move strongly into rare diseases by acquiring US biotech **Genzyme Corp.**
6. Pfizer and **Pharmacia Corp.** announced their intentions to merge in a tax-free stock-for-stock deal in July 2002. When the deal closed and the two companies joined together under the Pfizer name, a process delayed by the need to divest certain products to meet Federal Trade Commission requirements, the final value attributed to the transaction was $59bn.
7. Announced in July 2008 but not finalized until nearly eight months later, **Roche**'s $43.7bn price tag to acquire the 44.1% of big biotech **Genentech Inc.** that it didn't own already became the second of three mega-mergers that closed in 2009.
8. Capping off the year of the biopharma mega-merger, **Merck & Co. Inc.** and **Schering-Plough Corp.** became a single entity just days after the closing of Roche/Genentech. The New Jersey pharma bought Schering for roughly $42bn in a deal comprised of 44% cash and 56% stock.
9. In a process that took more than two-and-a-half years, **Novartis AG** agreed in April 2008 to pay $39bn over the following three years to acquire a 77% interest in **Nestle SA**'s **Alcon Inc.** division. Initially, the Swiss pharma paid $11bn for a 25% interest in the ophthalmology company, but in August 2010 Novartis and Nestle agreed on another $28bn to bring Novartis the remaining 52% stake outlined in the original deal.
10. As part of the fallout of the Actavis/Allergan merger in 2014, Teva paid $40.5bn – nearly 80% of that amount in cash – to acquire **Actavis Generics** from what now was known publicly as Allergan. This transaction ended Teva's bid to at a hostile takeover of rival **Mylan NV**.

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Novo Nordisk: Switch To Weekly Ozempic Has Begun, Biopharma M&A Sought

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Novo Nordisk AS struggled in the first quarter of 2018 to gain traction from its insulin-based products – as US pricing pressure in diabetes continues to mount – but its GLP-1 products appeared insulated from this pressure, with *Victoza* (liraglutide) once again registering strong growth despite competition from Novo Nordisk's own new weekly GLP-1 *Ozempic* (semaglutide), and from **Eli Lilly & Co.**'s injectable rival *Trulicity* (dulaglutide).

That strong showing by the group's GLP-1 product line allowed the world's biggest maker of diabetes drugs to report first-quarter profit which was above market forecasts, and to boost the lower end of its 2018 sales and profit forecast.

The Copenhagen-based company now sees 2018 sales growing in local currencies at 3-5%, versus 2-5% previously forecast, while operating profit growth in local currencies is guided at 2-5%, from 1-5%.

Novo Nordisk's traditional insulin treatments remain under threat from rising US price pressure. The company is pinning hopes for growth on new obesity drugs like *Saxenda* (liraglutide), and its once-weekly Ozempic injection, and a tablet version of its semaglutide drug for which 10 key Pioneer Phase III trials will be reading out this year.

OZEMPIC OPTIMISM

In February Novo Nordisk launched Ozempic in the US, a new once-weekly GLP-1. The group's CEO said the initial feedback from prescribers and payers on the product "is positive" and the formulary coverage for Ozempic is progressing well.

"We're seeing a nice uptake in script numbers for Ozempic," Lars Fruergaard Jørgensen told reporters. "Most importantly, we have had success in landing the contracts with payers and we're now at the level where we have more than 50% access in the US across the channels so that's quite an attractive position to be in and still believe we'll be able generate sales of Ozempic of at least DKK1bn in 2018," he added.

While being upbeat about the launch of injectable GLP-1 Ozempic, the CEO also said

Novo Nordisk CEO Lars Fruergaard Jørgensen

Victoza's cardiovascular benefits would give rival Eli Lilly strong competition going forward.

"We have a leading once-weekly in Ozempic that can compete very well with Eli Lilly's once-weekly product, based on its clinical profile, while with Victoza we have the only product with a cardiovascular benefit on its label, and should therefore do quite well. Our sales growth in the first quarter is really driven by our GLP-1 franchise, so we're quite optimistic in our ability to compete against Eli Lilly," Jørgensen said.

VICTOZA 'CANNIBALIZATION' LATER

Eventually, though, the company will put its emphasis on Ozempic, causing the commercial decline of Victoza in the US.

"There will be a cannibalization of Victoza by Ozempic. Ozempic will become the priority in the US from a commercial point of view but there will still be a lot of physicians who prescribe Victoza because they know the product and have good experience with it, as do the patients. But to a larger and larger degree new scripts will come on Ozempic due to its clinical profile and once-weekly administration convenience," Jørgensen told reporters.

Longer-term though, the GLP-1 market will keep growing and offer expanding sales opportunities to companies and products, he said. The planned advent of an oral version of semaglutide would also expand the market.

"The GLP-1 category as a whole is growing significantly; the share of the diabetes market that GLP-1 drugs have is now 12.3% while a year ago it was 10.2%. So it's actually the growth of the class that matters more than whether one drug is losing or winning 1% market share to another," he added.

MEDICARE WOES

On the negative side, recently passed Medicare Part D legislation is likely to reduce Novo Nordisk' US sales in 2018 by between 1% and 2%.

"We're still in the process of landing contracts for 2019 onwards so it's too early to be more specific."

The CEO said the Medicare Part D legislation "probably represents a wish to pass some costs to the industry." He did not elaborate.

BIOPHARMA M&A

Novo Nordisk is in the meantime actively looking to acquire assets to boost the Danish group's flagging biopharma business.

"We want to get our biopharma segment growing; it grew only 1% in the first quarter (after declining by 17% in 2017). So we are looking for opportunities in the biopharma area where we can potentially bolt on – either in the form of a licensing agreement or an acquisition – late-stage assets which could contribute to sales growth for our biopharma within a few years."

The group is looking in areas where it can leverage its knowledge and contacts with physicians. "We also aim to leverage the experience we have in developing products as well as the commercial capabilities that we have in bringing chronic care in rare or orphan diseases."

"We are considering some possibilities at the moment, but there are not a lot of opportunities out there, so we need to work hard on those few that are meaningful. In the first quarter we did a licencing deal on a sickle cell compound, EPI01, with **EpiDestiny Inc.** which is moving into Phase II. That's an example of the type of activities that we are interested in," the CEO said.

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Merck KGaA/SFJ's Abituzumab In Left-Sided Metastatic Colon Cancer

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New ideas about how tumor location might affect responses to treatment are being taken into account by the VC-backed late-stage drug developer, **SFJ Pharmaceuticals Inc.**, which is taking on the clinical development of an investigational candidate, abituzumab, previously halted by **Merck KGAA** after Phase II studies.

SFJ plans to finance and be responsible for the Phase II/III development of abituzumab as a potential first-line treatment for metastatic colorectal cancer (mCRC), in combination with cetuximab (Merck's *Erbitux*) and chemotherapy, the companies announced on May 2, in what Merck KGaA calls a novel "risk-sharing collaboration agreement".

The clinical program will involve patients with KRAS wild-type left-sided colorectal tumors with high avß6 integrin expression, and will exploit the evolving understanding of how the location of metastatic colorectal cancer might affect the outcome of treatment. Abituzumab is an integrin-inhibiting MAb, which completed Phase II studies back in 2015; a subgroup of patients with over-expression of integrin αvβ6 was identified as potentially benefiting from the treatment.

The big pharma points to recent analyses suggesting that patients with colon tumors arising from the right side of the body have a worse prognosis than those on the left side. And such differences might extend to the response to treatment; a pooled analysis has suggested that chemotherapy plus EGFR antibody therapy has a greater effect on tumors arising from the left side of the body than chemotherapy alone, or chemotherapy combined with bevacizumab (*Annals of Oncology,* Aug. 1 2017, pp 1,713-1,729).

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The big pharma points to recent analyses suggesting that patients with colon tumors arising from the right side of the body have a worse prognosis than those on the left side

Merck KGaA says the collaboration is an example of how it is embracing novel forms of strategic partnering to diversify development risk and improve the efficiency of its pipeline development.

SFJ has entered into a series of development deals with big pharma companies over the past several years, including with **Pfizer Inc.** on the effects of the tyrosine kinase inhibitor, *Inlyta* (axitinib) as a second-line therapy in advanced renal cell carcinoma. It has also been involved in the testing of dacomitinib in lung cancer.

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CONTINUED FROM COVER

payment of £48.17 per Shire share, versus £49.01 on April 23.

According to data compiled by *Scrip*, the total value of the acquisition will make it the fifth-largest deal in pharma industry history.

Given that there have been some investor concerns in Japan over how the financing of the deal may impact Takeda's fiscal standing and dividends, the Japanese firm was careful to stress what it sees as the "compelling financial benefits". The combination is expected to be "significantly accretive" to underlying earnings per share from the first full fiscal year after completion, provide "strong combined cash flows", with the return on invested capital expected to exceed Takeda's cost of capital within the first full fiscal year.

The cash flow is also seen enabling quick de-levering and as such Takeda intends to maintain its current investment grade credit rating, with a mid-term target net debt to EBITDA ratio of 2.0x or less, the partners said. Addressing another worry for existing Takeda shareholders in Japan, Takeda said it intends to maintain its established dividend policy.

A consortium of banks including J.P Morgan Chase, Sumitomo Mitsui, and MUFG Bank has set up a $30.85bn bridge loan to help fund the cash portion of the deal, but Takeda sees its reliance on this being reduced prior to completion through the use of a mix of long-term debt, available cash and other resources.

PIPELINE

Takeda CEO Christophe Weber described the two companies' portfolios and pipelines as "highly complementary", with Takeda noting in particular Shire's development assets in large molecules along with gene therapy and recombinant proteins. Notably, given Takeda's so far relatively weak late-stage pipeline, Shire will bring a number of Phase III assets including SHP621 for eosinophilic esophagitis, SHP647 for ulcerative colitis and maribavir for cytomegalovirus.

Commercially, Shire's marketed ADHD drug *Vyanse* (lisdexamfetamine dimesylate) will provide the main immediate boost for Takeda in the neurology area.

Takeda said it would also continue to position oncology as a key area, helped by the recent acquisition of **Ariad Pharmaceuticals Inc.**; Shire has separated and sold its oncology business to **Servier SA** for $2.4bn.

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Bayer Focuses On Pipeline To Deflect From 1Q Financial Misses

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Bayer AG will not pursue development of one its significant cancer therapies, *Aliqopa* (copanlisib), in diffuse large B-cell lymphoma (DLBCL) despite completing Phase II trials, the company noted in its first quarter financial report for 2018.

Included in Bayer's Q1 2018 report was a list of "important" pipeline assets currently in Phase II and Phase III trials (*see table below*).

While Aliqopa was included in the company's list of critical development programs as a treatment for indolent non-Hodgkin lymphoma (NHL), Bayer noted that it would not initiate a Phase III study in patients with relapsed or refractory DLBCL. This is despite the company reporting positive topline Phase II data for the product at ASCO in June 2017.

When topline data were published last year, Biomedtracker analysts said the drug had shown encouraging responses in patients with relapsed or refractory DLBCL, with manageable toxicity. The Phase II trial has since completed and Bayer has dropped development of the drug in this indication. DLBCL is one of the most common subtypes of NHL.

The company told *Scrip*, "We currently do not plan a Phase III study in this indication for strategic reasons… Bayer continues to explore the potential of copanlisib in other NHL indications as well as solid tumors."

Aliqopa received conditional approval in the US in September 2017; the US FDA granted accelerated approval to Aliqopa for the treatment of adults with relapsed follicular lymphoma who have received at least two prior treatments. Still, a series of Phase III studies ongoing for the drug in indolent NHL.

Aliqopa is a kinase inhibitor that works by blocking several enzymes that promote cell growth. The drug was filed with the FDA in March 2017 and granted priority review designation in follicular lymphoma. Pivotal Phase III trials that are yet to readout in indolent NHL include the CHRONOS-2, CHRONOS-3 and CHRONOS-4 trials.

In its Q1 2018 report, Bayer also noted that it had discontinued joint development of *Sivextro* (torezolid phosphate) for treatment of infections of the skin and subcutaneous tissue. Bayer had licensed Sivextro from **Merck & Co. Inc.** in July 2011 for emerging markets and Japan. Merck will continue to develop and market Sivextro in a number of these countries.

Bayer also noted it had discontinued *Stivarga* (regorafenib), before a Phase III trial, as an adjuvant therapy in colon carcinoma due to an insufficient number of participants. Stivarga is already approved for the treatment of colorectal cancer, gastrointestinal stromal tumor and liver cancer.

MIXED Q1 PERFORMANCE

Despite Bayer highlighting critical pipeline products that cover various therapy areas, there are still some concerns about the company's ability to produce new blockbuster drugs – especially as its best-selling products creep closer to their patent cutoffs.

The company's mixed financial performance in the first quarter of 2018 has not helped to fill investors with confidence. Analysts at Bryan, Garnier & Co. called Bayer's Q1 performance "uninspiring" in a May 3 note. Meanwhile, Deutsche Bank analysts said Bayer's 1Q sales were light, but cost-control for the company was good. Sales for the pharma unit were in-line and key drugs *Xarelto* (rivaroxaban) and *Eylea* (aflibercept) performed well, as did sales of older products in emerging markets, Deutsche Bank analysts said in a May 3 note. "However, oncology was very weak, particularly in the US due to competition," they said.

Group sales for Bayer in the first quarter of this year came in at €9.14bn, down from €9.68bn for the same period of the prior year. EBITDA before special items was €2.90bn for the quarter, versus €3.10bn in 2017. Core EPS for the group from continuing operations was €2.28, versus €2.31 in Q1 2017.

Sales for Bayer's pharma unit in Q1 2018 were €4.08bn, down from €4.27bn in the first quarter of last year.

Alongside first quarter earnings, the German drug and crop chemicals maker said it was lowering its forecast for 2018 as a whole. The group now expects sales to fall by a low single-digit percentage to less than €35bn this year; it previously predicted sales of about €35bn.

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Selected Clinical-Stage Pipeline Priorities

DRUG NAME	INDICATION	DEVELOPMENT STAGE
copanlisib	non-Hodgkin lymphoma	Phase III
darolutamide	castration-resistant nonmetastatic prostate cancer	Phase III
darolutamide	hormone-sensitive metastatic prostate cancer	Phase III
finerenone	diabetic kidney disease	Phase III
molidustat	renal anemia	Phase III
radium-223 dichloride	combination treatment of castration-resistant prostate cancer	Phase III
rivaroxaban	anticoagulation in patients with chronic heart failure	Phase III
rivaroxaban	prevention of venous thromboembolism in high-risk patients after discharge from hospital	Phase III
rivaroxaban	peripheral artery disease	Phase III

Source: Bayer

More IDO Issues: NewLink Drops Pancreatic Cancer Indication For Indoximod

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NewLink Genetics Corp. has "deprioritized" pancreatic cancer and will not proceed with a planned Phase II study testing its lead product indoximod with **AstraZeneca PLC**'s *Imfinzi* (durvalumab), the company said during its first-quarter earnings announcement.

This follows on from news last month that NewLink had halted the Phase III Indigo301 study of indoximod in combination with PD-1 inhibitors for patients with advanced melanoma. NewLink plans to evaluate an alternative trial design for this Phase III program. However, Jefferies analysts said in an April 15 note that they expected NewLink to pivot away from melanoma given the low likelihood of success with IDO inhibitors in this indication.

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'We have to rank the things that we think are most important'

NewLink emphasized during its May 3 earnings call that indoximod had demonstrated encouraging clinical data in several cancer indications, and that its decision not to go ahead with studies in pancreatic cancer was due to pipeline prioritization.

After completing a review of its clinical programs, NewLink expects to substantially reduce the rate at which the company is using cash. Also through the review process NewLink aims to identify indoximod programs that it will not take forward.

"Because of the situation that we're in currently, we have to rank the things that we think are most important and most probable to hit within the budget and timeline that we have to be able to show proof of concept for indoximod in a definitive way," Charles Link, chair and CEO of the company, said during NewLink's Q1 earnings call.

"Our decision is that doing a trial in combination with another checkpoint blockade is probably not the optimal first place for us to go to look for final proof of concept," Link said.

Indoximod, an investigational, orally available small molecule targeting the IDO pathway, was in clinical development for melanoma, pancreatic cancer, acute myelogenous leukemia, brain cancer and solid tumors.

Link said the company was looking for "the easiest, most cost-effective path to validation" for indoximod. "We want to take time and be very purposeful and thoughtful about those decisions," he said.

When NewLink halted the Phase III trial in melanoma, Jefferies analysts suggested the company might focus on diffuse intrinsic pontine glioma (DIPG), a type of brain cancer, as a first indication for indoximod. A Phase II trial is expected for indoximod in DIPG, but the analysts said "if the Phase II trial design is single-arm as expected, concerns will remain as to how indoximod performance extrapolates to randomized pivotal studies."

IDO ISSUES

Indoleamine 2,3-dioxygenase (IDO1) is an enzyme that plays an important part in immune response. Despite promising early data and a rush into broad late-stage trials, the class has disappointed as more data rolls in.

Just this month, immuno-oncology giant **Bristol-Myers Squibb Co.** said it had terminated three Phase III studies for its in-house IDO inhibitor, BMS-986205, in melanoma, head and neck, and lung cancer. *(Also see "A Wake For IDO: Bristol Ends Registrational Trials Of High-Priced Flexus Drug" - Scrip, 30 Apr, 2018.)*

Furthermore, on April 6, **Incyte Corp.** and **Merck & Co. Inc.** announced the combination of *Keytruda (*pembrolizumab) and epacadostat failed against the Keytruda monotherapy comparator arm in the Phase III ECHO-201/KEYNOTE-252 study of 700 patients with metastatic melanoma. *(Also see "Incyte/Merck's ECHO-301 Failure Casts More Shadow On IDO Space" - Scrip, 6 Apr, 2018.)*

NEWLINK'S Q1 PERFORMANCE

NewLink ended the quarter on March 31, 2018, with cash and cash equivalents totaling $143.9m versus $158.7m for the year ending December 31, 2017. R&D expenses for the first three months of 2017 were $20.3m, the company noted, an increase of $4.6m from $15.7m for the same period in 2017.

Net loss for the first three months of the year was $18.3m compared to net loss of $20.9m for the same period in 2017.

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Teva Pushes CGRP Timeline Back To End Of 2018

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Teva Pharmaceutical Industries Ltd. has pushed back the timeline for launching the migraine drug fremanezumab in the US, but still expects the CGRP drug could launch by the end of the year. Management updated investors on the expectations for the launch during a first quarter earnings call May 3 after previously warning the launch could be delayed due to a manufacturing issue at **Celltrion Inc.**, which is manufacturing an active ingredient for fremanezumab.

In February, Teva said the issues at Celltrion could delay FDA action on fremanezumab beyond the June 16 user fee date, disappointing news for the company, which is facing various business challenges. The FDA is expected to inspect Celltrion's manufacturing sites within the coming months, CEO Kare Schultz told the quarterly call. "We have high confidence that both of these inspections will be passed, and that means we will be able to get approval and launch before the end of 2018," Schultz said.

Getting the drug to market quickly is particularly important, because several rival CGRP drugs are in development, including two others already pending at the FDA. **Amgen Inc./Novartis AG** are expecting FDA action on *Aimovig* (erenumab) by May 17, with the drug poised to be the first to market. **Eli Lilly & Co.** also has galcanezumab under FDA review, with action expected by Oct. 24. Teva is hoping that quarterly dosing for fremanezumab could help separate the drug from the competition.

The manufacturing issue at the South Korean biologics manufacturer has hung up two biosimilar applications for Teva as well, a biosimilar version of Roche's *Herceptin* (trastuzumab) and *Rituxan* (rituximab).

The setback with fremanezumab is just the latest in a string of disappointments for Teva that includes the launch of a generic version of the company's multiple sclerosis drug *Copaxone* (glatiramer) 40mg last year, a challenging US generics market and a mountain of debt Teva is trying to pay down.

Teva is in the midst of a massive restructuring under the direction of new CEO Schultz. Last year, the company announced it would lay off 25% of its workforce as part of an initiative to save $3bn by 2019. That initiative remains on track, Schultz said. The company has reduced its workforce by 6,200, bringing the total to 46,000 employees, since the plan was announced with a target to cut 14,000 over two years. Ten plant closings or divestments have been announced since December.

> 'Overall the quarter appears solid, the company appears to be making progress on its restructuring program and its financial positions seems more stable than before the new CEO joined the company'

COPAXONE 40MG HOLDS 85% VOLUME SHARE

Sales of the company's blockbuster specialty brand Copaxone, meanwhile, took a substantial hit in the first quarter. Sales of the multiple sclerosis drug in North America declined 40% to $476m in the quarter, with the top-line negatively impacted by the launch of the first generic version of the 40mg dose by **Mylan NV** in October. But the decline came mostly from price, not volume, according to the company.

Copaxone 40mg has been able to retain significant market share versus the generic, 85% versus 15%. "We have reduced the price by increasing rebates in connection with the generic competition," Schultz said. The launch of a second generic from **Sandoz Inc.** will intensify the competitive dynamics. The FDA approved Sandoz's 40mg version of glatiramer, *Glatopa,* in February, though the company needed to ramp up inventory ahead of the launch. *(Also see "Sandoz's Less Frequently Dosed Copaxone Generic Glatopa Hits Teva Two Months Early" - Scrip, 13 Feb, 2018.)* The 20mg version of Glatopa was the first generic version of Copaxone to launch in 2015, though Teva was able to convert most patients to the less frequently administered 40mg version.

The hit to Copaxone, along with the challenging US generics market, cut the North America segment's sales by 22% to $2.5bn in the quarter.

Generic drug pricing has come under significant pressure in the US fueled by consolidation among distributors and a high number of FDA approvals. Schultz has talked about raising the prices of some unprofitable SKUs or cutting the products altogether.

That portfolio rationalization process is underway, Exec VP-North America Commercial Brendan O'Grady said.

"Our goal here is not to create any shortage or disruptions in the market, and we pledged to do that with our customers," he said. Some unprofitable products will be moved to other suppliers, while in some cases Teva will be successful in increasing the price, he added. Discussions on this process is ongoing with the three major drug distributors.

The company made progress paying down its debt, which is critical to stabilizing the company. Its total gross debt was $30.8bn as of March 31, with $6.5bn in debt repayments in the first quarter partially offset by the issuance of $4.4bn of senior notes.

Net revenues declined 10.4% to $5.07bn in the first quarter. Non-GAAP net income was $954m versus $1.1bn in 2017. The sales and earnings beat analyst consensus estimates, however.

"Overall the quarter appears solid, the company appears to be making progress on its restructuring program and its financial positions seems more stable than before the new CEO joined the company," Credit Suisse analyst Vamil Divan said in a same-day research note.

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Yescarta One Of Few Gilead Bright Spots, And Now It Has A Competing CAR-T

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First quarter sales for **Gilead Sciences Inc.**'s flagship HIV and hepatitis C franchises were below expectations on May 1 and now one of the few bright spots in the company's earnings report has a competing T-cell therapy with a similar indication.

Sales of Gilead's chimeric antigen receptor T-cell (CAR-T) therapy *Yescarta* (axalimogene ciloleucel) came in at $40m for the first quarter of 2018, which was up from $7m in the fourth quarter of 2017 and more than doubled analyst consensus estimates of $19m. However, **Novartis AG** said in a same-day announcement that its CAR-T therapy *Kymriah* (tisagenlecleucel) – previously approved for certain pediatric leukemia patients – won US FDA approval for its second indication in non-Hodgkin lymphoma (NHL), bringing it into direct competition with Yescarta.

Kymriah was first approved in August 2017 for pediatric and young adult patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse. Yescarta's first and, to date, only approval came two months later.

The products are neck-and-neck in terms of the timing of their first approvals in the EU. Gilead's Chief Scientific Officer and Head of Research and Development John McHutchison noted, in his first earnings call since taking over from prior CSO Norbert Bischofberger, that the company expects a decision on Yescarta from the European Medicines Agency's (EMA) Committee for the Human Use of Medicinal Products (CHMP) in the second quarter and EMA approval in the third quarter.

Comparing Lymphoma Indications For Yescarta and Kymriah

YESCARTA	KYMRIAH
Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.	Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL), high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.

Though it still is early in Yescarta's launch, the CAR-T therapy's strong performance in the first quarter was important for Gilead, which paid $11.9bn to acquire the product's original developer, **Kite Pharma Inc.**, in hopes of making the CAR-T technology the center of a cell therapy platform and oncology franchise.

Gilead President and CEO John Milligan said during the company's first quarter earnings call that "we're encouraged by the response from the health care provider and patient communities," and that Gilead has "completed the authorization of 40 cancer centers and are on track to have enough centers certified to treat 80% of Yescarta-eligible patients in the United States by the middle of the year."

Novartis reported last month that Kymriah sales in the first quarter totaled $12m in the product's first indication, but relapsed/refractory pediatric ALL is a smaller indication than the adult NHL indication Yescarta held and that Kymriah will now compete in. Elizabeth Barrett, CEO of Novartis Oncology, said during the company's first quarter earnings call on April 19 that 35 hospitals and cancer centers were certified to treat patients with Kymriah. Barrett also noted that "we have not had any issues with reimbursement. That's going very smoothly."

But Gilead has its eye on a larger, earlier indication for its product and is enrolling patients now in ZUMA-7, a Phase III clinical trial comparing Yescarta to the standard-of-care – salvage chemotherapy followed by autologous stem cell transplantation – as second-line treatment of 350 patients with DLBCL.

CAR-T A SMALL BRIGHT SPOT IN LARGELY DARK PERFORMANCE

Mizuho Securities analyst Salim Syed said in a May 1 note that while sales for Gilead's HIV and hepatitis C virus (HCV) drugs were disappointing, the Yescarta sales were good and investors realize the CAR-T business – still a relatively small part of the company's portfolio – is "a long-term play."

However, the $21m in sales that Yescarta delivered above what analysts expected for the quarter pales in comparison to the hundreds of millions of dollars in sales that didn't come through for the company's HIV and hepatitis C virus (HCV) treatments.

Gilead reported $5bn in total first quarter revenue, which was down from $6.4bn for the same period in 2017 and below consensus of $5.4bn. The company maintained its guidance of $20bn-$21bn in full-year 2018 sales.

"We do believe that 2018 is a trough year for us on which we can grow. We'll have seasonality fluctuations from quarter-to-quarter, but we're very confident and reiterated our overall guidance for the year and expect to be able to grow off of our 2018 base going forward," Chief Financial Officer and Executive Vice President Robin Washington told the call. Investors appeared skeptical, however, sending the company's stock down 5.6% in after-hours trading on May 1 to $68.50 per share – a new low for 2018.

HIV, GILEAD'S BIGGEST FRANCHISE, DISAPPOINTS

HIV and hepatitis B products delivered $3.3bn in the first quarter, which was 2% higher than the $3.27bn in sales for the year-ago period but fell below consensus of $3.5bn. The top HIV product was *Genvoya* (elvitegravir, cobicistat, emtricitabine and tenofovir alafenamide (TAF)) with $1.08bn in sales versus $769m last year and analyst consensus of $1.1bn.

Closely-watched *Biktarvy* (bictegravir, emtricitabine and TAF) – the company's newest single tablet regimen for HIV containing *Descovy* (emtricitabine and TAF) – delivered $35m in first quarter sales following its Feb. 7 FDA approval, which was below consensus of $50m.

Biktarvy's approval in the EU is expected within the next few months after a recent positive CHMP opinion. The drug and Gilead's industry-leading HIV franchise are facing tough competition from the **GlaxoSmithKline PLC/Pfizer Inc./Shionogi Inc.** joint venture **ViiV Healthcare** .

However, Washington said during the earnings call that the company is "encouraged by the initial uptake among prescribers" and "Biktarvy is tracking very well against our expectations."

"With this trajectory, we anticipate over time Biktarvy will become the number one single-tablet regimen for treatment-naive and switch patients, a distinction currently held by Genvoya," Washington added. "Approximately 80% of Biktarvy's prescriptions came from switches, of which approximately one-third came from Genvoya and two-thirds from other regimens, including approximately 20% from regimens that contain dolutegravir, confirming Biktarvy's broad utility across patient types."

Tivicay (dolutegravir) is Viiv's integrase inhibitor contained in products like *Triumeq* (abacavir, dolutegravir and lamivudine), which is expected to be Biktarvy's biggest competitor.

SEASONAL ISSUE

Jefferies analyst Michael Yee was not troubled by Gilead's first quarter HIV performance, however, referring to seasonal inventory issues cited by the company, including the impact of generic versions of Gilead's legacy antiviral therapy *Viread* (tenofovir disoproxil fumarate). Yee said in a May 1 note that Gilead's first quarter usually looks relatively weak, so he expects the HIV franchise performance to improve significantly in the second quarter. While Gilead's HCV sales are expected to continue their decline this year in light of the waning market and increased competition for the largely curative treatments for hepatitis C, the company's first quarter revenue in this area came in mostly below expectations, which isn't necessarily a big surprise after **AbbVie Inc.**'s impressive first quarter HCV results.

Gilead reported $1.05bn in HCV sales for the first quarter, down from $2.58bn in the year-ago period and below consensus of $1.16bn despite revenue from top-seller *Epclusa* (sofosbuvir and velpatasvir) coming in at $536m, which was down from $892m for the like period in 2017, but beat consensus of $454m.

But AbbVie is catching up with $919m in first quarter HCV sales, which beat consensus of $572m, including $850m in *Mavyret* (glecaprevir and pibrentasvir) sales. It was anticipated that Mavyret stole considerable market share from Gilead's products.

Indeed, Gilead's newer product *Vosevi* (sofosbuvir, velpatasvir and voxilaprevir) generated sales of just $107m in the first quarter versus consensus of $142m. The drug's approval in July marked the end of Gilead's HCV drug development; the company has said it expects a declining market for hepatitis C therapies going forward and ceased R&D efforts in the space.

"Consistent with our expectations, in Q1, we observed a downward pricing and market share trend across the major geographies as a result of a more competitive environment. Price has now largely stabilized, and we expect market share to stabilize by mid-year," Washington said. "In addition, patient starts have become more predictable, and we expect a slow and steady decline moving forward. We continue to see the HCV market as durable, and albeit a smaller component of our revenues going forward, there are still many patients that remain to be treated."

Realm Finds New Ways to Attack Atopic Dermatitis

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Top-line results from a Phase II study of **Realm Therapeutics**' hypochlorous acid-containing lead product, PR022, in atopic dermatitis, are expected in the third quarter of 2018, and if positive should alleviate the disappointment felt when another of its lead products, PR013, failed in a Phase II study reported in March 2018.

"PR013 was being evaluated in allergic conjunctivitis, with a study design and immunologic pathology that were different from those involved in atopic dermatitis and acne vulgaris," explained Realm's CEO Alex Martin, in an analysts' briefing on the company's 2017 financial results, held on May 2.

Realm Therapeutics is developing a series of investigational product candidates based on proprietary, high-concentration and stabilized formulations of hypochlorous acid, that includes PR022 and its proof-of-concept Phase II study in atopic dermatitis and, at a different concentration, PR023 for use in acne.

A US IND is expected to be filed in the fourth quarter of 2018 for PR023 (also known as RLM023), with the start of Phase II expected in the first quarter of 2019. PR022 is also currently in preclinical studies in psoriasis.

"Hypochlorous acid could be a first-in-class immunomodulatory agent," noted Martin. In the body, the substance is released by cells in the innate immune system, killing bacteria and other pathogens, but when administered at higher concentrations inhibits inflammatory responses mediated by cytokines including IL-4 and IL-13. It may become an alternative to the use of steroids in various dermatology disorders, Martin remarked.

Realm Therapeutics, the UK AIM-listed but Malvern, PA-based biopharmaceutical company, was the new name given to **PuriCore PLC** in December 2016, after PuriCore sold its supermarket retail business for $13.5m in Oct. 2016. That business marketed other formulations of hypochlorous acid to improve the freshness of produce, including cut flowers.

Also on May 2, Realm announced that it had submitted a registration document to the US SEC involving a proposed listing of American Depositary Shares (ADSs) on Nasdaq. The move followed the raising of £19.3m ($25.4m) in gross proceeds from a September 2017 private placement, with new and existing investors including healthcare specialist funds based in the US and UK. Investors in Realm include OrbiMed, BVF Partners, RA Capital, Abingworth and Polar Capital. Further details about the potential ADS listing were not disclosed.

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Pfizer Plays Up Its In-house Potential, Avoids M&A Talk

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Pfizer Inc. has been expected by many to lead a wave of biopharma M&A this year, but CEO Ian Read largely sidestepped the issue during the firm's first quarter earnings call, while signaling that he didn't like the valuations of current options and that the potential market for offloading the consumer business looks dry as well.

"I don't see that we need a transformative deal, nor do I see one at appropriate values right now in the marketplace," Read told the May 1 call when pressed by an analyst. "We'll continue to use our capital wisely. I believe at this moment in time, although things can always change, marketplaces can change, I believe the best investment we have now is in our own pipeline.

Pfizer's chief exec did not mention M&A unprompted, sticking to the message that for now Pfizer's focus will be on commercial execution to grow its sales leaders and also development of what he called a deep, diverse pipeline.

Pfizer is at the center of speculation about an expected wave of mergers in biopharma, spurred by US tax reform and large cash balances. The pharma giant's own history of mega-mergers, and its decision not to divide the company into separate innovative product and mature product companies in 2016, has investors anxious for next steps.

ANCHORS PRIMED

"We continue to deliver on our strategy and believe we remain well-positioned to deliver new medicines to patients and increase value for our investors going forward," Read said. "Most of our anchor brands are primed for continuous growth. Our pipeline is as deep and focused as it's ever been. … Our strong balance sheet and disciplined approach to capital allocation will ensure we have the resources to invest in future growth opportunities."

Pfizer noted strong year-over-year sales growth for the breast cancer drug *Ibrance* (palbociclib), autoimmune therapy *Xeljanz* (tofacitinib) and anticoagulant *Eliquis* (apixaban), but analysts noted that the first two products underperformed against consensus. Pfizer explained that buying patterns and destocking held down the still-solid growth for Ibrance and Xeljanz. In all, the New York pharma posted a quarter slightly below Wall Street expectations for revenue, with net sales of $12.9bn up 1% year-over-year, but below consensus projections of $13.1bn.

Read also indicated that Pfizer's current patent cliff will lessen significantly once the loss of exclusivity for *Lyrica* (pregabalin) occurs in the US this December. Lyrica is at the center of a patent case before the US Supreme Court regarding the legal implications for generic drugs when the branded version still has patent protection on other indications. During the first quarter, Lyrica yielded flat sales of $1.13bn, with US sales up 2% to $907m, while international revenue dropped 6% to $225m.

Moving past the Lyrica loss of exclusivity "will unencumber the potential revenue growth of our key drivers, including the expected realization of our pipeline and allow us to achieve an inflection point in our top-line growth profile," Read told the call.

CONSUMER HEALTH GROWS

Pfizer reported 7% growth for its consumer health care business during the first quarter to $905m. Still, it has been considering strategic alternatives for the unit since last year, but Read indicated May 1 that no sale, spinout or other divestiture is imminent.

Although Chief Financial Officer Frank D'Amelio reiterated that a Pfizer split is off the table at present, the company is still reporting financials along the lines of the Innovative Health and Essential Health units. The Innovative Health unit – which includes Ibrance, Xeljanz and Eliquis – yielded more than $7.8bn in sales during the quarter, up 6% from one year earlier. The Essential Health unit, consisting of branded products that have gone off-patent or soon will, brought in nearly $5.1bn, down 5% year-over-year.

D'Amelio attributed the innovative unit's growth primarily to Ibrance, Xeljanz and Eliquis, with the quarter's performance overall pulled down by the European impact of *Enbrel* (etanercept) biosimilars and declining revenues for *Viagra* (sildenafil), which has been transitioned over the Essential Health business.

Ibrance, a CD kinase 4/6 inhibitor, yielded sales of $933m during the quarter, up 35% despite new recent market entries in the class by Novartis with *Kisqali* (ribociclib) and **Eli Lilly & Co.** with *Verzenio* (abemaciclib). US sales of $726m represented 19% year-over-year growth, while ex-US sales totaled $207m.

During its previous earnings call in January, Pfizer reported that EU sales of Ibrance declined sequentially from the third quarter to the fourth, but predicted that would be a short-lived impact of price adjustments. During the first quarter, Ibrance European sales ticked up a bit, similar to their third quarter level, but one analyst asked Read if a bigger increase had been expected.

Read indicated pricing pressures in Europe make the drug's performance there difficult to evaluate. "Very often, you sell under emergency protocols at a price that is not necessarily relevant to the final price you get or to the US price, for that matter," he said. "We see very robust uptake with physicians of Ibrance and we see an impact, of course, on the revenue as we adjust to the reimbursement levels of Ibrance that will give us sustained and a growing opportunity for substantial patient number increase in Europe."

BUYING PATTERNS CRUCIAL

US growth for the product was strong but missed consensus by $52m. Read said the US total was affected by "customer buying patterns." Similar rationale was offered for performance of Xeljanz, up 30% to $326m overall ($50m below consensus), and up 19% domestically to $253m.

Morningstar's Damien Conover predicted that Pfizer's overall revenue growth will accelerate in the upcoming quarters. "Destocking hurt cancer drug Ibrance and immunology drug Xeljanz, but we expect those trends to reverse later this year," the analyst wrote in a May 1 note.

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Ferring Makes Foray Into Gene Therapy With FKD Pact

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Fresh from announcing a deal to acquire the USA's **Rebiotix Inc.** and moving into the microbiome drug development space, **Ferring Pharmaceuticals AS** is also targeting the hot area of gene therapy with a late-stage licensing deal for a novel bladder cancer treatment from Finland's **FKD Therapies OY**.

The Swiss firm has taken the option, dependent on US approval, to secure global commercialization rights to rAd-IFN/Syn3 (nadofaragene firadenovec/Syn3), a gene therapy being developed by FKD for patients with high-grade non-muscle invasive bladder cancer (NMIBC), who are unresponsive to Bacillus Calmette-Guérin (BCG) therapy, the gold standard treatment. However, Ferring chief medical officer Klaus Dugi told *Scrip* that in high-grade NMIBC patients, while BCG is effective, over 60% of cases eventually recur and the outcome for such patients is poor, with total cystectomy (complete removal of the bladder) to prevent the cancer spreading to other organs generally being the next option.

'INTERFERON MICROFACTORIES'

This explains the interest in rAd-IFN/Syn3, which consists of an adenovirus containing the gene interferon alfa-2b. It is administered by catheter and the virus enters the cells of the bladder wall, turning the latter into what Ferring describes as "multiple interferon microfactories." Phase II trials, published in the *Journal of Clinical Oncology* last August, reported that 35% of BCG-unresponsive NMIBC bladder cancer patients who were given one dose of rAd-IFN/Syn3 every three months were free of high-grade disease at one year.

A Phase III trial is ongoing with up to 150 patients to be enrolled across 35 centers in the US. Dugi said that the first read-out was expected in 2019 and noted that rAd-IFN/Syn3 had been awarded fast track and breakthrough therapy designations by the FDA.

He added that FKD, which has "world-leading regulatory expertise in gene therapy," enjoys a "very collaborative, high frequency of interaction" with the FDA, which has recognized the unmet medical need. Dugi is also very impressed with the manufacturing set-up that FKD has built up in Kuopio, and given the simulations Ferring has done as to how many patients may benefit from the gene therapy, he is confident patient demand can be met, if approval is achieved.

As for gene therapy in general, Dugi, who joined Ferring last October from **Boehringer Ingelheim GMBH** (where his roles included CMO for the German group and UK managing director), told *Scrip* it had been an exciting field for him since the 1990s back when he spent four years carrying out research at the US National Institutes of Health. Then however, "it was more promise than reality," and now gene therapies have made it to the market.

However, it is a market very much in its infancy and the gene therapies that have been approved in Europe to date cater for rare diseases with very few patients – think **GlaxoSmithKline PLC**'s soon-to-be divested *Strimvelis* for adenosine deaminase severe combined immunodeficiency (ADA-SCID) and famously **uniQure NV**'s *Glybera* for familial lipoprotein lipase deficiency – the latter, a €1m drug used to treat just one patient, was withdrawn from the market. *(Also see "Orchard To Use Divested GSK Rare Disease Gene Therapies To Grow Globally" - Scrip, 12 Apr, 2018.)(Also see "White Flag Raised: UniQure Gives Up On Glybera, But Not Gene Therapies" - Scrip, 21 Apr, 2017.)*

However bladder cancer is a much bigger proposition with an estimated 430,000 new cases being reported worldwide each year and Dugi pointed out that it was also the fourth most common cancer in men in the US and was the most expensive to treat on a life-time basis. It is far too early to talk cost with regards to rAd-IFN/Syn3 but he stressed that the drug was given every three months so the pricing discussion would be different to those around one-off therapies. "It is a new field for pharma, payers and regulators," Dugi said, but it represents a very positive opportunity for Ferring.

As the Saint-Prex-headquartered company waits on rAd-IFN/Syn3, Paul Navarre, CEO of Ferring's US operations, told *Scrip* that Ferring would create a new oncology division across the Atlantic. Navarre, who joined the company in June last year, having previously been president of Allergan International, said that after growing successfully but steadily for many years, the firm had been transformed of late and was now reinventing itself, going into innovative areas. Dugi added that it is possible that in the next two years, Ferring may be the company that brings both the first microbiome product - Rebiotix's RBX2660 for recurrent *Clostridium difficile* infection - and the first bladder cancer gene therapy to the market.

No financial details were disclosed about the deal with FKD, which was formed back in 2011 when it acquired an exclusive licence to **Merck & Co. Inc.**'s gene therapy portfolio. *(Also see "Merck & Co out-licences clinical-stage gene therapy asset to new start-up" - Scrip, 20 Sep, 2011.)*

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Deaths In Esperion's Long-Term Bempedoic Acid Trial Spur Fears Of Commercial Delay

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A numerical imbalance in deaths in **Esperion Therapeutics Inc.**'s long-term safety study for the cholesterol-lowering drug bempedoic acid is raising concerns about competitive positioning and ability to file prior to having cardiovascular outcomes data, which could delay the product's launch.

Bempedoic acid is a first-in-class inhibitor of ATP citrate lyase (ACL) that upregulates the LDL-C receptor in order to reduce cholesterol synthesis. Esperion is developing the drug as an oral option that is complementary to **Merck & Co. Inc.**'s *Zetia* (ezetimibe), which is now generic. The company is developing a fixed-dose combination pill containing bempedoic acid and Zetia; combined, the drugs provide additional LDL reduction of from 40% to 50% beyond statins.

Esperion plans to file the drug in the US by the end of the first quarter of 2019 and in Europe by the end of the second quarter, which would pave the way for approvals in 2020. This timeline is based on plans to file for approval in high-risk populations, prior to having the results from an outcomes study that began in 2016.

FDA approved PCSK9 inhibitors in high-risk populations prior to outcomes study data and during a May 2 investor call Esperion reaffirmed its plan to follow the same regulatory path.

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RISK FOR REGULATORY DELAY

However, results outlined on May 2 from the long-term Study 1, also called 1002-040, cast doubt on the company's regulatory strategy and the outlook for bempedoic acid overall. The trial, which was the largest and longest trial in the development program, evaluated bempedoic acid against placebo in 2,230 high-risk patients with atherosclerotic cardiovascular disease (ASCVD) on lipid modifying therapy, including maximally-tolerated statin therapy. Patients in the study were randomized 2:1 to bempedoic acid or placebo.

The drug met the primary objective of safety and tolerability and also the key efficacy endpoint for LDL-lowering, but there was a numerical imbalance in the number of deaths.

"The modest efficacy of bempedoic acid, combined with potential questions about safety, though these may just be due to chance, as well as the drug's novel mechanism of action (though its main action is along the same pathway as the statins) does raise the risk that the FDA may want to see a cardiovascular outcomes trial prior to approval," Informa Pharma Intelligence's Biomedtracker service said on May 2.

That would significantly delay the potential approval to beyond 2022, the Biomedtracker analysis noted.

In addition to the trial data, the commercial landscape is changing rapidly in relationship to injectable PCSK9 inhibitors, which provide robust LDL-lowering – with reductions ranging from 50% to 70% on top of statins.

Sanofi and **Regeneron Pharmaceuticals Inc.** revealed on May 1 a deal with **Express Scripts Holding Co.** that will give their PCSK9 inhibitor *Praluent* (alirocumab) preference over **Amgen Inc.**'s competing PCSK9 inhibitor *Repatha* (evolocumab) in return for a big discount. This will bring Praluent's cost down from a list price of $14,600 to the low end of a range outlined by the Institute of Clinical and Economic review – $4,500 to $8,000.

Esperion has suggested a list price of about $3,300 to $3,600 per year for bempedoic acid and its pricing advantage is diminishing with greater discounting of PCSK9 inhibitors.

The company's stock price fell 35% on May 2 to close at $45.75.

WHAT THE NEW DATA SHOW

Esperion notes that it has completed Phase I, II and III studies in more than 1,600 patients to date and the drug demonstrated LDL-C lowering of up to 30% as a monotherapy and up to 50% when used with Zetia on top of statins. *(Also see "Esperion's Oral Bempedoic Acid Passes First Phase III Cholesterol Test" - Scrip, 7 Mar, 2018.)* The drug also has been tested as an add-on to PCSK9 therapy. *(Also see "PCSK9 Add-On Study Helps Esperion Cover All The Bases With Bempedoic Acid" - Scrip, 27 Mar, 2018.)* Results from three more pivotal trials will be released between now and the end of September.

In Study 1, about half of the patients were on high-intensity statins. CEO Tim Maylebon noted during the call that this is a much more rigorous setting than where

the company and key opinion leaders expect bempedoic acid to be used, that is the real world users will be less tolerant of statins and have higher LDL at baseline. In the latest study, bempedoic acid met the key efficacy endpoint with on-treatment additional LDL-C lowering of 20% at 12 and 24 weeks, and 16% at 52 weeks ($p<0.001$). Esperion also reported LDL-lowering of 18% at 12 weeks in an intent-to-treat analysis ($p<0.001$).

Maylebon said during the May 2 investor call that the efficacy results were "unequivocal" and exactly what the company expected.

Efficacy of 18% in the intent-to-treat population at 12 weeks and 16% at 52 weeks was lower than the 20% to 30% reduction reported in short Phase II studies, but this latest result was not completely unexpected and could be due to trial fatigue and lower compliance in long-term versus short term trials, Jefferies analyst Michael Yee said in a May 2 note. Such was the case in studies of PCSK9 inhibitors, he noted.

"FDA likely understands those issues and we don't think it impacts approval," Yee said.

DRILLING DOWN ON SAFETY

Esperion reported that the drug was safe and well tolerated in Study 1. The rate of adverse events was 78.5% for bempedoic acid versus 78.7% for placebo and the rates of serious adverse events were 14.5% and 14%, respectively. The discontinuation rate was 10.9% for bempedoic acid versus 7.1% for placebo.

Muscle-related adverse events have been problematic with statins. In Esperion's study, the discontinuation rate due to this type of event was 2.2% for bempedoic acid versus 1.9% for placebo.

However, there were two causes of concern for investors – a numerical increase in deaths and elevations in liver function tests. The percentage of patients with elevations in AST/ALT liver function tests (three times the upper limit of normal) was low overall, but higher in the bempedoic acid arm – 0.54 % versus 0.13% for placebo. Esperion pointed out that these results are in line with expectations for bempedoic acid and also with statins.

"The number of patients now treated with bempedoic acid in Phase II and Phase III clinical trials totals 2,434. Of these, 0.58% had elevations in liver function tests greater than three times the upper limit of normal, repeated and confirmed," the company said in a statement.

As with statins, the liver elevations returned to normal while patients were on therapy or after they dropped treatment, and no cases of increased bilirubin or Hy's Law were reported.

Esperion faced numerous questions about reported deaths during a lengthy May 2 investor call.

There were 15 deaths in the study altogether, 13 in the bempedoic acid arm and two in the placebo arm; all were deemed to not be related to treatment by study investigators. Out of the 13 deaths in the bempedoic acid arm, five were cardiovascular-related, five were related to lung cancer, one was a pancreatic gastrointestinal event, one was neurological and one was not detailed in the call.

In the placebo arm, one death was cardiovascular-related and the other was related to sepsis.

Execs explained during the call that the patients enrolled were very sick, as they had already experienced a cardiovascular event, and about two-thirds were smokers or had a history of smoking, so the lung cancer deaths were not so surprising. Given the high risk nature of the population, the overall death rate was about what you would expect, Bill Sasiella, senior vice president of clinical development, told the call.

The company noted that there had been no issues with two-year preclinical carcinogenicity studies submitted to the FDA in 2015. Also, the cancer deaths occurred during the first 60 or 90 days of Study 1 and had not been reported in previously released short-term studies, and Sasiella noted that "it's highly unlikely you are going to see anything cause a neoplasm in the first month or three of treatment."

Biomedtracker's analysts commented that "the early onset does suggest the cases were not due to the drug, so it may well not be an issue. We should mention, though, sometimes the FDA or an advisory committee is still cautious, and there can be a concern that a drug accelerates growth of a cancer."

For example, FDA delayed the approval of **AstraZeneca PLC**'s diabetes drug *Farxiga* (dapagliflozin) due to concerns about an imbalance in the number of cases of bladder cancer, the analysts noted. But in that case there was an imbalance even excluding the cases that occurred within one year. The drug was approved in early 2014 with a subdued warning about bladder cancer noting the absence of evidence for the risk, two years after the agency issued a complete response letter.

The FDA may not be as concerned about the early bempedoic cases, especially if no imbalance is seen in other studies, Biomedtracker analysts said.

Sasiella also noted that looking at non-fatal and fatal cardiovascular events overall, which were adjudicated by an independent committee, the rate was actually slightly numerically lower in the bempedoic acid arm – and though the numbers are small, this provides an additional point of comfort.

That could well be reassuring, though the FDA may still have questions, particularly in the face of modest efficacy, Biomedtracker analysts commented.

A BUYING OPPORTUNITY?

Some analysts rushed to the defense of the stock.

Jefferies analyst Yee said in his note that the comments in the call made it clear that the deaths were unrelated to the drug and that the safety was "very clean."

The 16% to 20% LDL reduction is solid, considering that patients seek oral alternatives, as evidenced by the $2.5bn brought in by Zetia at its peak and $2.8bn for Merck's *Vytorin* (ezetimibe/simivastatin), Yee concluded.

"Ultimately we think the drug appears approvable and a clean oral pill that adds 15%-20% LDL reduction and is a good option for statin intolerant [patients] is attractive to a part of a large patient population (1m) who still need options," Yee said.

JMP Securities analyst Jason Butler concluded that the results from Study 1 "reinforce the robust, safe, clinical profile of bempedoic acid" and said that the stock weakness is a "compelling buying opportunity."

Needham and Co's Chad Messer said the LDL reduction of 20% at 12 weeks was within expectations, but "apparently disappointing versus Street expectations" and also advised buying on weakness.

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Portola Finally Gets FDA OK For AndexXa

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Fears that **Portola Pharmaceuticals Inc.**'s *AndexXa* (andexanet alfa) would face further years of delay in getting approved in the US as an antidote for Factor Xa anticoagulants are unfounded now that the FDA has given the green light, albeit with a black box warning.

It has been a long time coming but the agency has granted approval for AndexXa, making it the only antidote indicated for patients treated with two big-selling Factor Xa bloodthinners – **Bristol-Myers Squibb Co./Pfizer Inc.**'s *Eliquis* (apixaban) and **Johnson & Johnson/Bayer AG**'s *Xarelto* (rivaroxaban) - when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. It has been approved under the FDA's Accelerated Approval pathway but that road has been far from smooth for Portola.

The company received a complete response letter (CRL) from the FDA in August 2016 citing manufacturing issues, and resubmitted a filing in August 2017. The agency gave Portola a Feb. 2, 2018, user fee date but that was extended by 90 days in December 2017, moving the action date to May 4.

However another spanner was thrown into the works in February this year when the company disclosed a potential request from the FDA about the possible need for a randomized trial before US approval of AndexXa would be granted. That had the effect of battering Portola's share price by 25%, amid fears that a launch could be delayed by two to even four years.

Those concerns have been allayed by the FDA approval late May 3 but there are other worries for Portola. The thumbs-up, which is restricted to the reversal of Xarelto and Eliquis, comes with a black box warning for thrombosis, ischemic events, cardiac arrest and sudden death and the label states that an improvement in hemostasis has not been established.

Furthermore, it is now clear that the study mentioned in February is in fact a post-approval randomized trial versus usual care to demonstrate an improvement in hemostasis which is required by the agency – that study will kick off in 2019 with data read-out scheduled in 2023.

ANDEXXA PRICED AT $27,500

On a conference call, Portola CEO Bill Lis said that the wholesale acquisition cost of AndexXa will be $27,500 per gram, which is the average dose per patient. Most analysts expected a price in the region of $20,000 but he claimed it reflects the innovative nature of the product and the benefit it offers to high-risk patients, ie those with a 30-day mortality rate of over 40% who typically have a 10-day hospital stay which costs in excess of $100,000.

Lis is confident that there is a sizeable opportunity for AndexXa, noting on the call that about 117,000 patients were hospitalized with Factor Xa inhibitor-related bleeds in the US in 2016 alone. Analysts at Credit Suisse share his confidence, pointing out in an investor note that Portola will focus their initial efforts on capturing the 25% of patients at highest risk of negative outcomes, including those with intracranial hemorrhage. The broker added that "success in capturing even this subgroup of patients is significant enough to make AndexXa a very successful product."

However it is going to take some time to actually get these sorts of patient numbers, as Lis noted that the initial launch in June will only be of the AndexXa product sourced from the company's 'generation 1' manufacturing process. This means that only a select number (about 30-40) of US hospitals, principally those which are involved in the ongoing ANNEXA-4 single-arm, open-label study in patients with major bleeding, will stock that product.

The CEO added that the plan is for a broader commercial launch in early 2019 upon FDA approval of the 'generation 2' manufacturing process. This will see AndexXa go into over 1,000 hospitals in the US and some in Europe. The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) communicated a positive trend vote on Portola's submission in February and a formal opinion is expected by the end of 2018.

Datamonitor Healthcare analyst Jack Allen told *Scrip* that it would be interesting to see how straightforward the regulatory path is for the Generation 2 product given the CRL in 2016 was mainly a result of manufacturing issues. As for the black box warning, he does not expect it to have much impact on take-up as patients are monitored for thromboembolic and cardiac risk anyway and AndexXa is already recommended by draft guidelines (ahead of the approval) from the American Society of Hematology and the European Society of Cardiology as first-line therapy.

POST-APPROVAL STUDY PROBLEMATIC

As for the post-approval study, Stuart Connolly of McMaster University in Hamilton, Ontario, who is leading the ANNEXA-4 trial, said "it wasn't our choice, we don't think it is necessary" but it will give the company and researchers to confirm the drug's benefit. Lis added that "this is not going to be easy…and there is going to be a lot of resistance at clinical sites."

The Credit Suisse analysts agreed with Lis, noting that "ethical and administrative challenges will lead to the post marketing study taking as much as five years to be completed, with Portola focusing on ex-US sites as being locations where it may be easier to recruit patients." They added that the post-marketing commitment would not significantly impact commercial uptake of the product.

AndexXa is the second FDA approval for Portola, which last year got the green light for its own Factor Xa inhibitor, *Bevyxxa* (betrixaban). Lis said that the process of getting the antidote product approved for the latter will be pursued but it is not a priority.

Lis concluded by saying that he expects no issues with the cost, demand, the black box warning or the post-marketing trial and "we can build a very successful franchise based on the data and the unmet medical need." Investors shared his enthusiasm and Portola shares closed May 4 at $42.44, up 25.6%.

Meantime, with arguably mischievous timing just hours after the AndexXa news, Boehringer Ingelheim gave an update on *Praxbind* (idarucizumab), the antidote to the German firm's direct thrombin inhibiting anticoagulant *Pradaxa* (dabigatran). Praxbind was granted accelerated approval by the FDA in October 2015, also without data from a randomized study, and received full approval from the agency last month.

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Regeneron Tries To Put Focus On PD-1 Program

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Perhaps because it was anticipating investor anxiety about unimpressive sales figures for three drugs partnered with **Sanofi**, **Regeneron Pharmaceuticals Inc.** used much of its first quarter earnings call on May 3 to talk up its anticipated first immuno-oncology approval later this year with cemiplimab in cutaneous squamous cell carcinoma.

The Tarrytown, N.Y.-based firm outlined its development plans for the PD-1 targeting antibody and offered details on how it expects to possibly compete with **Merck & Co. Inc.**'s *Keytruda* (pembrolizumab) and **Bristol-Myers Squibb Co.**'s *Opdivo* (nivolumab) in the non-small cell lung cancer setting. Cemiplumab is under review at the US FDA for metastatic cutaneous squamous cell carcinoma (CSCC) with an Oct. 28 action date, and also has been filed for approval in Europe, with a decision expected during the first half of 2019.

Regeneron also could boast of continued sales growth for anti-VEGF ophthalmology blockbuster *Eylea* (aflibercept), which achieved 15% year-over-year sales growth to $984m in the US. Global sales rose 20% to $1.61bn, and the company hopes to spur further growth with a sBLA to the FDA later this year to add non-proliferative diabetic retinopathy to the product's label. It's expected that success in the Phase III PANORAMA trial backing this filing will help Eylea compete better with **Roche**'s *Lucentis* (ranibizumab), which already has labeling for diabetic retinopathy.

The biotech couldn't pretty up the sales performance of *Praluent* (alirocumab), *Dupixent* (dupilumab) and *Kevzara* (sarilumab), all co-commercialized with Regeneron's long-time partner Sanofi. The anti-PCSK9 cholesterol drug Praluent has struggled out of the gate, due largely to payer resistance in the US, and brought in $60m for the quarter, with the $32m in the US at least representing a 25% uptick year-over-year. Dupixent yielded $132m, with $117m of that in the US, while recently launched Kevzara tallied $9m, including $6m domestically.

AIMING AT REMAINING OPPORTUNITY IN LUNG

CEO Leonard Schliefer and Chief Scientific Officer George Yancopoulos spent much of their presentation time on plans for and the potential of cemiplimab. Schliefer noted that anti-PD-1 therapies currently are selling at a combined $12bn annual run rate, but significant opportunity remains because only Keytruda has posted impressive data in the lucrative first-line NSCLC setting.

"The [47%] response rates we have seen [in CSCC] are amongst the highest reported for solid tumors and served as the basis for our breakthrough designation by the FDA," he said. "While CSCC is a significant opportunity by itself, non-small cell lung cancer is the largest indication where we are currently studying cemiplimab. Our positive early data from a small cohort of patients with advanced non-small cell lung cancer supports our decision to aggressively move forward in multiple settings of this disease."

Yancopoulos said cemiplimab is on track to be only the third anti-PD-1 agent okayed in the US, and if that occurs will mark Regeneron's first immuno-oncology approval after roughly three years of work in the space. "In addition to monotherapy opportunities with cemiplimab, we believe cemiplimab will be the bedrock upon which we plan to build additional combination therapies," he added.

To assess cemiplimab's potential in combination therapy, Regeneron is testing the agent as monotherapy head-to-head versus chemotherapy in NSCLC patients with PD-L1 levels of 50% of greater, Yancopoulos said. A second study is underway investigating cemiplimab with chemotherapy and with or without ipilimumab (Bristol's *Yervoy*) versus chemotherapy alone in NSCLC patients with PD-L1 50% or lower. Finally, Regeneron plans a study combining cemiplimab and ipilimumab, with or without chemotherapy, in patients with 50% or greater PD-L1 expression, with a comparator arm utilizing pembrolizumab, he said. The agent is also being studied in cervical cancer.

BTIG Equity Research analyst Dane Leone said cemiplimab's prospects in CSCC appear promising, but whether it will have a competitive advantage in larger indications is uncertain.

UNDERLYING DEMAND STRONG FOR DUPIXENT

The PD-1 enthusiasm somewhat helped offset the disappointing news about products partnered with Sanofi.

Leerink Partners' analyst Geoffrey Porges pointed out May 3 that the Praluent and Dupixent totals were significantly lower than consensus expectations. In an April 30 note extrapolating from Sanofi's first quarter investor call on April 27, Porges projected disappointing results for those products and Kevzara. However, he maintains that Dupixent's prescription trends look solid – Regeneron, meanwhile, points to its sBLA to add maintenance therapy for moderate-to-severe asthma with an Oct. 20 action as adding potential value.

Leerink has lowered its second quarter projections for Dupixent but retains a "relatively bullish" outlook on the IL-4/IL-13 inhibitor longer-term, Porges said. "The underlying demand trajectory for Dupixent appears to be strong, as volume increased more than 25% sequentially and a steady 550 patients continued to initiate Dupixent each week," his April 30 note states. Beyond the current quarter, Leerink expects the drug to "ramp strongly" through the rest of 2018 and then accelerate on the basis of the expected approval in asthma.

On Praluent, Regeneron and Sanofi made headlines with their agreement May 1 to obtain preferred formulary access from **Express Scripts Holding Co.** in exchange for reduced pricing. This formulary positioning will come at the expense of competitor **Amgen Inc.**'s *Repatha* (evolocumab).

Morgan Stanley analyst Matthew Harrison predicted in a May 1 note that patients insured under Express Scripts' plans will transition to Praluent quickly. "This will likely move market share back to 50/50 for Amgen's Repatha vs. Praluent," he wrote. "We had hoped that Amgen would be among the first to strike a deal with a payer for increased access, especially given their earlier [cardiovascular] outcomes data."

Regeneron also revealed a clinical setback on May 3, reporting that Phase III anti-nerve growth factor (NGF) candidate fasinumab will no longer be studied in high-dose regimens for osteoarthritis or lower back pain following the recommendations of an independent data monitoring committee. The anti-NGF class has faced safety concerns dating back to 2010, but FDA recommended that study with the agents resume in 2012.

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Sarepta CEO Vows To Get Exondys 51 Into EU Despite CHMP Negative Trend Vote

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Sarepta Therapeutics Inc.'s plans to get its drug *Exondys 51* (eteplirsen) approved in Europe this year have been derailed by regulatory advisors there, but the Boston, Mass.-based biotech's CEO has vowed to do what it takes to get the proposed treatment for Duchenne muscular dystrophy (DMD) re-assessed – and ultimately launched – on the European market.

Sarepta used its first-quarter earnings update on May 3 to announce that it received a negative trend vote following its oral presentation to the European Medicines Agency panel, the Committee for Medicinal Products for Human Use (CHMP), which is part of the EU regulator's drug assessment procedure.

"What we're announcing right now is a trend vote. It's not the actual vote," Sarepta's CEO Doug Ingram told investors and analysts.

"The actual vote will occur toward the end of May, 30 days after the oral explanation, but for our planning purposes, we don't envision that the final vote will be any different than the trend vote," he said.

> 'The standard is very high as set by the CHMP for this review, and that doesn't change in the re-examination. So ... I don't want to create the false impression that we don't have a significant challenge on our hands. We do'

SAREPTA TO SEEK RE-EXAMINATION

Ingram vowed on the update call to work intensely to get the CHMP's negative trend view on eteplirsen reversed.

Towards that end, the US company will ask for a re-examination of the therapy's merits and that a Scientific Advisory Group (SAG) to be convened as part of the EU process.

Ingram explained that following the final CHMP vote at the end of May, "we'll have 15 days thereafter to commence the re-examination process, and that will be approximately a four-month process."

Ingram strongly disagreed with the CHMP's stance on Sarepta's controversial drug – which the FDA approved in September 2016 despite a negative advisory panel vote, triggering a massive amounts of controversy, not least at the FDA itself.

"We firmly believe that eteplirsen should be expeditiously made available to patients in Europe," Ingram said.

"The eteplirsen presentation and discussion was impressive – and only makes us more resolute that children in Europe amenable to exon 51 skipping ought to have availability of eteplirsen," Ingram added.

An eventual SAG would be composed of DMD and neuromuscular specialists, "called to provide expert guidance and insight into, among other things, the validity of the external controls used and the importance of significantly slowing pulmonary decline in patients suffering from DMD," the CEO said.

But Sarepta's room for maneuver in the re-review process is limited.

"The re-exam doesn't permit us to provide additional evidence," Ingram said. "You're not allowed to do that in the re-exam, so this is really looking at the analysis and reanalysis of the data that we've done in the re-exam. The re-review process won't be any easier than the initial exercise."

He added: "The standard is very high as set by the CHMP for this review, and that doesn't change in the re-examination. So … I don't want to create the false impression that we don't have a significant challenge on our hands. We do."

The CEO said the "entire re-exam, including the SAG, as we understand it, ought to be complete before the end of 2018."

Analysts at Leerink say eteplirsen could still win an entry pass the EU market, but that that would come in 2020 at the earliest, compared to a previously foreseen launch there in this year's third quarter.

"Sarepta's commitment to Exondys 51 (eteplirsen) in the EU could lead to a re-examination, a process that could result in another update before the end of 2018," Leerink said in a reaction note to investors.

MYONEXUS R&D PACT SIGNED

Sarepta's CEO was able to lighten the atmosphere somewhat by announcing a collaboration with **Myonexus Therapeutics Inc.**, developing five gene therapies for limb-girdle muscular dystrophies, which would widen Sarepta's discovery and development efforts beyond DMD. "Through this collaboration, we have expanded our pipeline to 21 therapies in development," Ingram said.

"Our confidence in the Myonexus collaboration comes from the similarities between the Myonexus and Sarepta approaches to gene therapy. Both are seeking to treat rare neuromuscular disease through the AAVrh.74 vector; and both rely upon the unparalleled expertise of Dr Louise Rodino-Klapac in developing and executing gene therapy constructs."

Ingram said the new partnership with Myonexus enabled Sarepta to expand its R&D efforts beyond DMD. Under the deal's terms, Sarepta will pay $60m up front and an additional $45m in milestones, and also have a buyout option at proof of concept.

While the collaboration will explore many new therapeutic areas, Sarepta's CEO said it did not signal a strategic shift for the company.

"We are a DMD company. So, as we will expand beyond DMD, I don't want anyone to get the impression that we are leaving DMD. We are focused on - and committed to - bringing a better life to children around the world who suffer from Duchenne muscular dystrophy across, hopefully, as many exon mutations as possible," Ingram said.

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Can China Ace The CAR-T Race?

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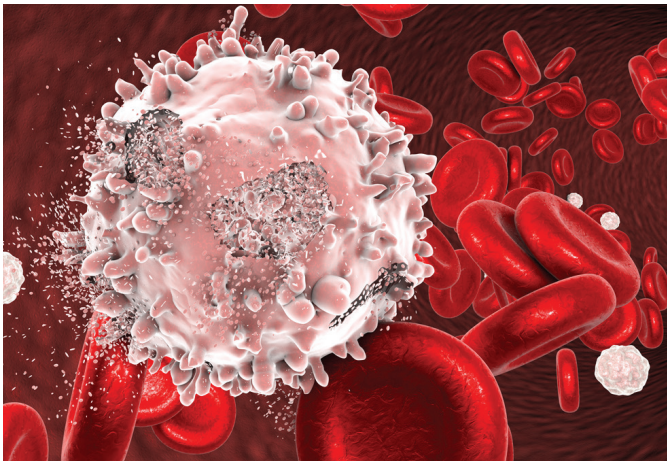
Armed with deals from a variety of multinationals and a flurry of domestic development activity, China is poised to become a major force in treating cancers using the latest CAR-T technology.

Already, the country has the highest number of ongoing CAR-T clinical studies in the world, overtaking the US by a large margin. Per data from Informa's Trialtrove, there are now a total of 237 CAR-T trials registered in China, compared to 186 in the US.

Since the US FDA approved the first CAR-T therapy, **Novartis AG**'s *Kymriah* (tisagenlecleucel) for B-cell acute lymphoma last August, and later **Kite Pharma Inc.**'s *Yescarta* (axicabtagene ciloleucel) for adult large B-cell lymphoma, the global race to commercialize CAR-T therapies has begun.

Not surprisingly, nearly half, or 106, of the Chinese CAR-T trials are for acute lymphoma, closely followed by Hodgkin's lymphoma (101) and chronic lymphoma leukemia (54).



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So far, several domestic biotechs have obtained clinical trial approvals for their CAR-T therapies, including **Nanjing Legend** with LCAR-B38M. Legend took last year's ASCO meeting by storm by announcing promising clinical results for the product, and in December **Johnson & Johnson** agreed to pay $350m upfront to develop the product, initially for multiple myeloma with B-cell maturation antigen.

TIME TO CLINIC REDUCING

Not only the sheer number of trials, but also reductions in the time needed to get to the clinical study stage, are seemingly fueling China's drive to become a major global player in the field.

It now takes a relatively shorter time for domestic developers to take projects into the clinic thanks to a government policy to encourage cutting-edge innovation, especially when it comes to treating cancers. China has high incidence rates of certain prevalent cancer types including lung, liver and colorectal, while others such as thyroid, pancreatic and prostate are increasing.

Unlike in the US, where five-year survival rates are steadily improving, China has seen slow progress in post-surgery, five-year survival figures, adding to the drive for new therapies.

In a bid to encourage the earlier introduction of CAR-T drugs to the market, the China FDA on March 16 released its first Cell Therapy Clinical Study and Review Guidelines, paving the pathway for the regulator to review and approve such products as a "living" therapy.

The rules urge developers to carefully consider pharmacology and data dossier preparations. For instance, applicants need to explain whether CAR-T cell cultures contain serum or other animal or human products, and companies also need to follow previous CFDA guidance on cell therapy Study and Review Technical Principles.

STARTING OUT

But the competitive landscape for emerging therapies is becoming more complicated, pointed out industry experts attending a recent Life Sciences Forum held in Mashan, Wuxi on April 21-22.

"CAR-T has better targets but it lacks variety, so developing combination therapies is becoming trendy," said Sun Wenjun, VP and head of Government Affairs at WuXi Juno, a joint venture devoted to developing innovative cell therapies set up between **WuXi AppTec Inc.** and **Juno Therapeutics Inc.**.

The issues facing Chinese CAR-T developers lie in several aspects, including cell manufacturing and selection, cost considerations, and safety profile. Because of a cell's complexity when multiplying inside the body, it is essential to ensure the quality of engineered T-cells - only young and thus stronger cells can ensure persistence of efficacy, noted the expert.

To that end, dosing should be carefully weighed as to whether a fixed dose or flexible dosing based on the tumor type would be better.

Additionally, safety profile has been a major issue for many CAR-T therapies. Cytokine release syndrome is a common and potentially dangerous complication of anti-T cell approaches, and Juno for its part was forced to halt trials for its lead asset JCAR015 and refocus on JCAR017. *(Also see "Juno Ends JCAR015 Development In ALL, Cementing Third Place CAR-T Position" - Scrip, 1 Mar, 2017.)*

How Chinese biotechs might mitigate the potential adverse events with their candidates over marketed and other CAR-Ts will likely decide their fate.

COST CONSIDERATIONS

Meanwhile, they must also consider the cost and time to market. Novartis's Kymriah, priced at $475,000 in the US, will be beyond the reach of most Chinese cancer patients without medical insurance coverage. The high cost may partially explain that in the first quarter of 2018, Novartis reported only $1.2m sales of the drug, a relatively low figure for the first approved CAR-T treatment.

Facing high diagnostic fees associated with the new therapies, Chinese developers must also consider end cost along with time spent during the clinical development and regulatory process. While front runner Nanjing Legend has a lead advantage, others must differentiate, in indications including solid tumors, noted Lu Jinwei, head of CAR-T at Eureka Therapeutics Inc., a China-US hybrid biotech.

"Having a cutting-edge technology may not lead to cutting-edge production and product," he said.

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Sharing Dark Data: Inside The ATOM Initiative

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How can the drug development industry and researchers get the most out of data from failed trials? John Baldoni, a senior member of **GlaxoSmithKline PLC**'s R&D team, thinks comprehensive data sharing is the answer, which led him to help set up the ATOM initiative.

A public-private consortium, ATOM (Accelerating Therapeutics for Opportunities in Medicine) aims to drastically reduce the time it takes to get from target discovery to clinical candidate: from approximately six years to just 12 months.

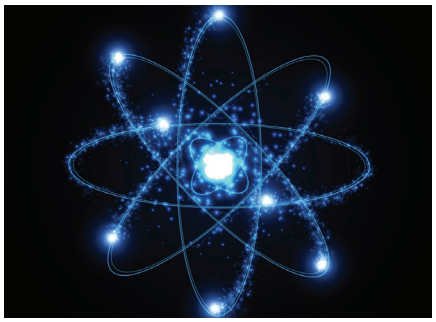
ATOM, which is focused on oncology drug discovery, wants to use supercomputers to pre-test many molecules simultaneously for safety and efficacy.

Launched in October 2017, ATOM comprises the US Department of Energy's Lawrence Livermore National Laboratory, GSK, the National Cancer Institute's Frederick National Laboratory for Cancer Research, and the University of California, San Francisco (UCSF). But the consortium is seeking additional public and private partners.

GSK has initially contributed chemical and *in vitro* biological data for more than 2 million compounds from its historic and current screening collection, as well as preclinical and clinical information on 500 molecules that failed in development in the past. The hope is data from past trials might help accelerate development of new compounds by providing knowledge about the underlying biology of candidate compounds and that of the human body.

ATOM, which has its own management team that includes Jim Brase as chief technical officer, Stacie Calad-Thomson as chief operating officer and Tom Rush as chief scientific officer, is attempting to validate a multidisciplinary approach to drug discovery that uses modern science, technology and engineering, supercomputing simulations, data science, and artificial intelligence.

From Baldoni's perspective, ATOM takes what he calls the "dark data of pharma," the data from failed studies and molecules that haven't succeeded, and makes the information available publicly. "Then anybody can develop algorithms using those data, using compounds that have not made it to the clinic, and compounds for which the industry has no interest. They can share the results within a pre-competitive consortium," he said.



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Conversations between Baldoni, a founder of ATOM and current co-chair of its governing board, and the US Department of Energy started back in 2015, with the other partners coming on board between then and the launch of ATOM in 2017.

While the ATOM team is mainly working on the data donated by GSK, Baldoni said the initiative was in negotiations with other big pharma companies, small technology companies and other national laboratories to join the consortium. "It's not a closed club," he said. "It's an open club and we want other people to join."

GETTING PHARMA INVOLVED

Baldoni said ATOM was already in negotiations with two companies about joining the initiative and adding data to the collaboration. However, he said any company joining ATOM needed to share a certain vision.

He said a company's culture must be aligned with ATOM's open data philosophy. "There are some pharma companies that have categorically said, 'There is no way we are sharing our data.' And there are other companies that have said, 'We have no interest in these molecules commercially and actually we would benefit and it could be the starting point of new drug discovery.' It depends on the culture of the company," he said.

He noted that GSK was "very forward thinking on data sharing." Baldoni, who has been with GSK for several years, highlighted that the UK big pharma was one of the first to allow individuals and researchers access to its data through a simple process. "GSK for a long time has been walking the talk of sharing data," he said.

While there are some European initiatives that have been active in data sharing for hundreds of molecules at a time, Baldoni highlighted that through ATOM, GSK had shared data for millions of molecules. "GSK sees this as its obligation to advance science by revealing the data that is not competitive anymore," he said.

Baldoni added that it was not the case that these compounds were useless, they had generated a lot of data. "The fact that the compounds didn't make it in development, doesn't negate the fact that they still find proteins, they modulate pathways, they have pharmacokinetic effects, they have toxicology effects, and they can be used to build models that would help everybody," he said.

WHAT GSK GETS OUT OF ATOM

GSK has around 10 employees involved in the ATOM project and Baldoni said these members were getting access to innovative people and technologies they had not been exposed to in the past. "Industry would never interact with the Department of Energy's computer scientists, for example, or would rarely interact with the biologists of the National Cancer Institute who have access to huge numbers of assays and data," he said.

While ATOM is still in its early stages, Baldoni said there was huge potential for growth and learning for GSK. "What they're finding is there's a synergy… There are surprises that are happening when they start talking to people," he said about GSK's members at the consortium.

Employees from GSK involved in ATOM will spend a year with the project, onsite at its offices in California, before coming back to the big pharma. "They are going to come back, and they are going to apply their learning here in GSK," said Baldoni, who runs GSK's internal artificial intelligence drug R&D unit.

Anything generated in ATOM is in the public domain, as per the bylaws of the public/private consortium. The rules of the initiative dictate that any algorithms developed, within a year of their being approved by as an algorithm by a scientific board, are available for all.

Published online 4 May 2018

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 27 April–3 May 2018

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
PHASE III RESULTS PUBLISHED			
Merck & Co. Inc.	verubecestat	Alzheimer's disease	EPOCH; *NEJM*, May 3, 2018.
Rigel Pharmaceuticals Inc.	*Tavalisse* (fostamatinib)	chronic immune thrombocytopenia	*American Journal of Hematology*, Apr. 26, 2018.
PHASE III INTERIM/TOP-LINE RESULTS			
Merck & Co. Inc.	*Keytruda* (pembrolizumab) with carboplatin, paclitaxel	metastatic squamous non-small cell lung cancer (NSCLC), first-line	KEYNOTE-407; met overall response rate secondary endpoint.
Esperion Therapeutics Inc.	bempedoic acid	dyslipidemia	CLEAR Harmony; long-term safety results.
Allergan PLC	ubrogepant	migraine	ACHIEVE II; met coprimary endpoints.
UPDATED PHASE III RESULTS			
Novartis AG	brolucizumab (RTH258)	wet age-related macular degeneration	HARRIER, HAWK; suitable for 12-week dosing.
Prometic Life Sciences Inc.	IVIG	primary immune deficiencies	Met primary and secondary endpoints.
Eli Lilly & Co.	lasmiditan	migraine	SAMURAI, SPARTAN; endpoints met.
Nektar Therapeutics	NKTR-181	chronic low back pain	SUMMIT-7; reduced pain, well tolerated.
Zogenix Inc.	ZX008 (low-dose fenfluramine)	Dravet syndrome	Study 1; Improvement in quality of life, cognitive function.
Formycon AG	FYB201 (biosimilar to ranibizumab)	wet age-related macular degeneration	COLUMBUS-AMD; comparable efficacy to *Lucentis*.
Alimera Sciences Inc.	*Yutiq* (fluocinolone acetonide) three-year insert	uveitis, chronic non-infectious	Reduced uveitis recurrences.
Alimera Sciences Inc.	*Iluvien* (fluocinolone acetonide)	uveitis, non-infectious posterior segment	Reduced macular edema.
Allergan PLC	ulipristal acetate	uterine fibroids	Venus I, II; reduced fibroid volume.
PHASE III ANNOUNCED			
Ritter Pharmaceuticals Inc.	RP-G28	food allergies	Lactose intolerance.
UPDATED PHASE II RESULTS			
Aldeyra Therapeutics Inc.	reproxalap, topical ocular formulation	dry eye disease, allergic conjunctivitis	Clinically significant activity.
Karyopharm Therapeutics Inc.	selinexor	multiple myeloma, penta-refractory	STORM; durable responses seen.
Sancilio Pharmaceuticals Co. Inc.	*Altemia* (SC411)	sickle cell disease	SCOT; signs of efficacy.
BioTime Inc.	*OpRegen* (retinal pigment epithelial cells)	dry age-related macular degeneration	Signs of cell survival and improved retinal structure.
TopiVert Ltd.	TOP1630	dry eye sydrome	Improved symptoms, well tolerated.
Endo International PLC	*Xiaflex* (*collagenase Clostridium histolyticum*)	cellulite	Initial signs of efficacy, well tolerated.
MediciNova Inc.	MN-166 (ibudilast)	amyotrophic laterial sclerosis	Initial signs of efficacy.

Source: Biomedtracker

ASLAN's Downsized US IPO Off To A Slump Start

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There was no mighty roar, nor likely even contented purring, for oncology-focused Asian venture **Aslan Pharmaceuticals Pte. Ltd.** following its US initial public offering on the Nasdaq Global Market.

The Singapore-based venture set a public price of $7.03 per American Depositary Share in the offering of six million ADSs, each comprising five ordinary shares and all sold through ASLAN. The offering is planned to close around May 8 and expected to raise gross proceeds of around $42.2m for the company, which it will use mainly to support its clinical R&D pipeline.

The ADSs starting trading on May 4, but the initial trends were not positive. While the listing price valued ASLAN at around $225m, early trading on the first day saw falls of up to 26% from the offer price, with the shares closing 20.2% down at $5.61.

The disappointing initial performance also followed a scale-back in the size of the offering, as the firm had indicated in an SEC filing some six weeks ago that it had planned to sell up to 7.5 million ADSs, eyeing a potential $86m in new funds.

The initial reasons for the poor US start were not immediately clear, given that ASLAN has a pipeline of promising molecules, but may have been linked to its similarly lackluster performance in Taiwan, where it completed a TWD992m ($33m) over-subscribed IPO on the Taipei Exchange in the middle of last year.

Since then, however, single shares there have fallen from the offer price of TWD68.92 (around $2.31 at current rates) to around TWD41.75 ($1.40, or $7 per five shares). The company has attributed the slump to wider conditions in the Taiwan investment market and some shift in investor focus away from healthcare.

Taiwan was initially seen as a good location given its strength in biotech, a supportive regulatory environment, and more investor experience with traded bioventures than home market Singapore.

ASLAN, founded in 2010 and which already has offices in China, Australia and Taiwan, indicated some time ago that it might turn to the US for further funds, given the growing financial needs of its progressing development portfolio.

The company said the actual net proceeds from the new downsized US offering, after underwriting discounts, commissions, and other offering expenses, will be used mostly "to continue to invest in the clinical development of its product candidates", as well as for general corporate development and working capital, and the development of possible manufacturing capacity.

Given that the US plans have been in train for some months and the timing of the new IPO, Nasdaq appears to have emerged as the preferred option ahead of other possibilities such as Hong Kong, which has just now introduced new, more flexible rules for the listing of bioventures, including those with no revenues.

The venture, whose top management includes several ex-**AstraZeneca** executives including CEO Dr. Carl Firth, had raised a total of around $125m since its inception up to the end of last year, from investors including BioVeda Capital and Cenova Ventures.

Its business model centers around acquiring assets for Asia-prevalent cancers and orphan disease, taking these through development using clinical expertise and sites in Asia, and then either seeking alliances or considering potential in-house commercialization.

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From the editors of PharmAsia News.

Andrew Phillips has been appointed CEO of Watertown, Mass.-based **C4 Therapeutics Inc.**, having been chief scientific officer since Jan. 2016, and president since Sept. 2016. Before joining C4T, Phillips was senior director at the Center for Development of Therapeutics at the Broad Institute of MIT and Harvard. C4's new class of drugs selectively target disease-relevant proteins for degradation.

ORIC Pharmaceuticals has named ***Jacob Chacko*** as CEO, having most recently been CFO of Ignyta. ORIC's interim CEO, ***Rich Heyman***, has become chairman. San Francisco-based ORIC is developing therapies for treatment-resistant cancer.

Eric Curtis has been named President and COO of **CytRx Corporation**, based in Los Angeles. Curtis previously served as president US commercial at Aegerion Pharmaceuticals (now Novelion Therapeutics), and in senior positions at Bayer Healthcare and GlaxoSmithKline. CytRx is developing a pipeline of ultra-high-potency oncology candidates.

Audentes Therapeutics Inc. has promoted its COO ***Natalie Holles*** to president and COO, overseeing the day-to-day operations of the company. Holles joined Audentes in 2015. Audentes is developing gene therapy products, and is conducting Phase I/II studies on lead product candidates for X-linked myotubular myopathy and for Crigler-Najjar syndrome.

Dietmar Berger, previously a senior R&D leader at Roche/Genentech, has joined **Atara Biotherapeutics Inc.** as global head of R&D. Atara is developing off-the-shelf, allogeneic, T-cell immunotherapies and its lead product is in Phase III studies. Berger was previously senior vice president and global head, product development, clinical science hematology and oncology at Roche/Genentech.

The US genome editing company **Caribou Biosciences Inc.** has appointed ***Timothy Herpin*** as chief business officer. Herpin was previously vice president and head of transactions at AstraZeneca. Berkeley, CA-based Caribou is developing off-the-shelf CAR-T candidates and microbiome-based therapies.

Sangamo Therapeutics Inc. has promoted ***Michael Holmes*** to senior vice president and chief technology officer, from vice president of research, while senior vice president and chief business officer, ***Curt Herberts***, has resigned, effective June 1, 2018, from the Richmond, CA-based firm to join a private biotech company.

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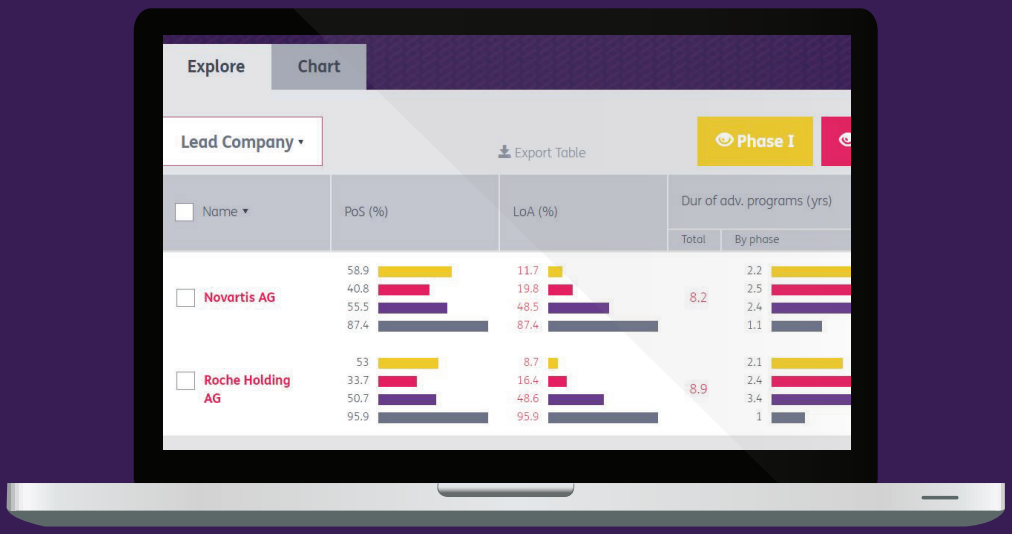

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