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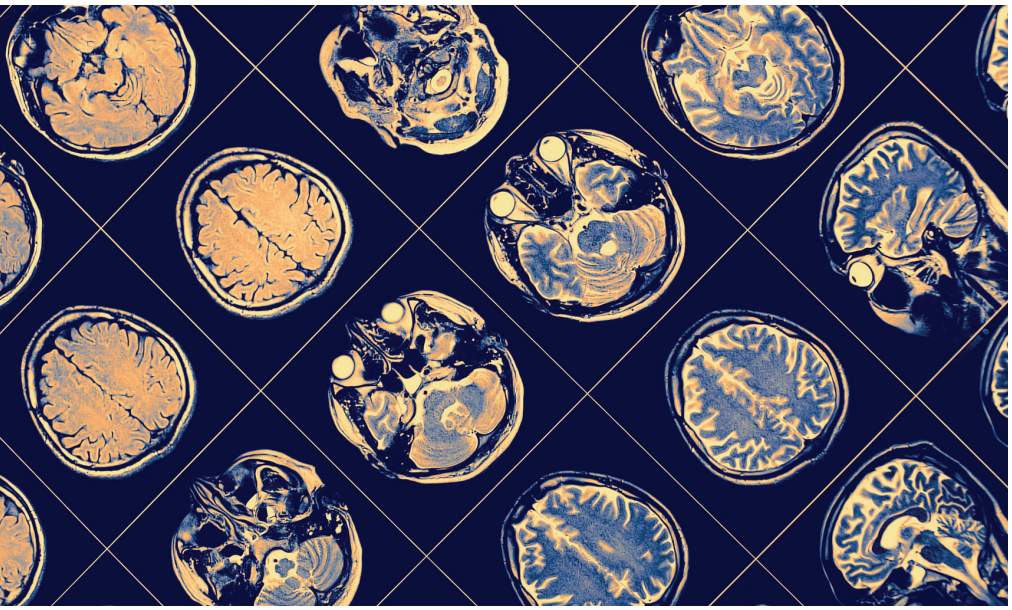

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Amgen Aims For Market Share With Aimovig's $6,900 Price

MANDY JACKSON mandy.jackson@informausa.com

Amgen Inc. and **Novartis AG** are preparing to launch *Aimovig* (erenumab-aooe), the first calcitonin gene-related peptide (CGRP) inhibitor approved for migraine prophylaxis, within the next week at a price that's designed to capture as much of the potential 8m-patient US market as possible right out of the gate.

The US FDA approved Aimovig on May 17 for the prevention of migraine headaches in adults and Amgen set a list price – before discounts negotiated with payers – of $575 per month, which comes out to $6,900 per year. That price is significantly lower than the $8,500 annual cost accessed by the Institute for Clinical and Economic Review (ICER), which estimated that only 16% of eligible patients would be treated with a CGRP inhibitor at that assumed price.

Most of the adults treated with Aimovig will be prescribed a once-monthly 70 mg dose, but a 140 mg monthly dose also will be available; both will be delivered with the *SureClick* autoinjector. Amgen notes, however, that the drug's cost will be the same regardless of the prescribed dose.

Credit Suisse analyst Vamil Divan indicated in an April 26 note that "from a public relations perspective it would be beneficial for the [CGRP] manufacturers to have lower list prices to avoid or minimize some of the negative headlines that may otherwise result from list prices that are north of $10,000 per patient per year."

Aimovig's list price appears to be at the lower end of expectations, since Jefferies analyst Michael Yee said in a May 17 note that analyst consensus was between $7,000 and $10,000. Yee expected the net price after discounts negotiated with payers to be $5,000 to $6,000, which would be competitive with **Allergan PLC**'s *Botox* (onabotulinumtoxinA) at about $6,000 annually.

"Good news is conversations with experts suggest high patient demand and awareness, but the offset is it will take some time to get contracts and on formulary and many contracts may require failure of Botox first," Yee wrote.

Divan also said low list prices, though with smaller rebates, combined with value-based contracts would help companies with CGRP inhibitors win market share among payers, since the data generated for the drugs to date have not differentiated any of the competing products.

Amgen has not disclosed whether it has negotiated any value-based or outcomes-based contracts with payers. However, Novartis Pharmaceuticals CEO Paul Hudson suggested in November that such agreements were likely for Aimovig. The partners will co-commercialize the product in the US, but Novartis will be responsible for sales in ex-US markets.

The companies have set up a program in the US called *Aimovig Ally* to help patients with health insurance coverage and to help uninsured or underinsured individuals access the drug. The *Aimovig Copay Program* will help eligible patients with commercial insurance get the medicine for as little as $5 in out-of-pocket costs.

Amgen said in its statement about the FDA approval that Aimovig's price "reflects the value it brings to patients and society,

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BROUGHT TO YOU BY THE EDITORS OF **PHARMASIA NEWS, START-UP** AND **SCRIP INTELLIGENCE**

Brexit Fears
Disruption likely to patient access (p6)

New Anticancers
What's Coming Up At Key US Meeting (p14-15)

Combating Ebola
Pharma redoubles efforts (p20-21)

from the editor

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The UK government has recently been upping its commitments to investing in health research. It has boosted its funding for brain cancer research following the death from glioblastoma of Tessa Jowell MP, who campaigned through her illness for more to be done to tackle the disease, from the way clinical trials are designed and co-ordinated, to the way patients are treated in clinical practice.

It also promised a £20m investment in CARB-X to back small companies focused on drug-resistant bacteria R&D. With the Bill & Melinda Gates Foundation also putting in a chunk of money, it is to be hoped that CARB-X will be able to attract increased funding from other new sources.

Separately, Prime Minister Theresa May outlined plans for the UK to make use of artificial intelligence to diagnose many more people with cancer at an earlier stage, with the aim of reducing annual cancer deaths by 22,000 by 2033. The government's embrace of AI in health is laudable, and could lay the ground for much progress in reducing the burden of disease. However, early diagnosis will need to go hand in hand with prompt and effective intervention with the best therapies available.

As Tessa Jowell's campaign exposed, only half of UK brain cancer centres are currently using gold standard 5-ALA dye to identify brain tumors. Achieving best practice across the continuum from diagnosis to treatment is essential. The recent UK commitments are good news for patients and developers of new therapies, but ultimately, rapid patient access to therapeutic innovations will be key to improving health outcomes. That is also in the government's gift.

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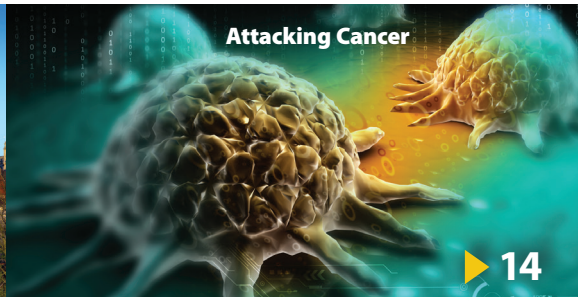

exclusive online content

Scrip Asks … What Is The Current Trend For Open Innovation In Asia?
https://bit.ly/2x0h3eY

Open innovation and global partnering are becoming one of the most frequent themes of bio conferences in South Korea and elsewhere. Scrip talked to global experts at the recent Bio Korea 2018 meeting about their views on the current climate and trends for open innovation in Asia.

Takeda And Shire - One Japan CEO's Take
https://bit.ly/2s34z0J

The planned combination of Takeda and Shire has dominated headlines in recent weeks, but how is it viewed within the industry in Japan? One CEO shares his thoughts.

Hemlibra Hits The Heights In HAVEN Hemophilia Trials
https://bit.ly/2IYiPSU

Full results from the HAVEN 3 and 4 trials suggest that Roche's hemophilia drug Hemlibra will indeed take a dominant market position in patients with or without factor VIII inhibitors although that make take some time as current therapy is already very effective and is supported by decades of safety experience.

Mehta Analysis: Trump Pricing Tempest In A Teapot Is An Opportunity For Biopharma Leaders
https://bit.ly/2wZVg7n

President Trump's much anticipated pronouncements on drug pricing reform leave a lot to be clarified. Biopharma companies and their leaders should grasp the opportunity to lead from the front and propose tangible and transformative actions that deliver benefits for all stakeholders, writes Viren Mehta, founding partner of Mehta Partners LLC.

Pharming Turns A Profit After Reclaiming Ruconest
https://bit.ly/2kh8ymR

Pharming Group, a company that has been on the drug development scene since the '80s, has recorded a quarterly net profit for the first time – two years earlier than previously forecast.

More Alzheimer's Pain As J&J Pulls Plug On BACE Inhibitor
https://bit.ly/2IEMpt3

J&J's Janssen unit is ending development of atabecestat after serious elevations of liver enzymes were seen in some patients who received the drug, increasing doubts about the BACE inhibitor mechanism as an appropriate target.

inside:

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Narasimhan Promises To Improve Novartis' Image As Top Lawyer Exits

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Novartis AG's top lawyer Felix Ehrat is taking the fall for the controversial $1.2m in payments he helped arrange to Donald Trump's attorney, as the Swiss group's newly installed CEO makes fresh promises to clean up the company's ethical act.

Ehrat – who is also an executive board member – announced May 16 that he's stepping down from his post as general counsel to take responsibility for the contract that he along with former CEO Joe Jimenez signed with lawyer Michael Cohen's Essential Consultants, saying it was a mistake.

CONTRACT WAS "AN ERROR"

"Although the contract was legally in order, it was an error. As a co-signatory with our former CEO, I take personal responsibility to bring the public debate on this matter to an end," Ehrat said in a statement.

The contract with Essential Consultants – the same firm used to pay porn star Stormy Daniels to keep her affair with Trump under wraps – has distracted from Novartis's attempts to improve its image.

CLEAN-UP DRIVE

Shannon Thyme Klinger, currently chief ethics, risk and compliance officer at Novartis, will replace Ehrat as group general counsel, effective June 1.

The board changes coincided with fresh vows by Jimenez's successor as CEO, Vas Narasimhan, to repair the company's reputation.

The Swiss group has been dogged for years by accusations of impropriety involving alleged bribery and kickbacks spanning from the US to Greece, China and Japan.

Novartis has continually brushed aside such accusations – most recently at the annual shareholders meeting in Basel in March – by saying such murky episodes related to 'the past' and not to current management.

At an investor conference entitled 'Meet Novartis Management 2018' which was held on May 15 and 16, Narasimhan outlined his five corporate priorities, the last two being trust and reputation in Novartis, and a desired culture transformation there.

Novartis CEO Vas Narasimhan

'I would rather stand here before you and miss the numbers rather than again have an instance where we compromise on our values'

The CEO told the group: "We have ongoing issues … this is going to be a long-term journey."

"The big ones on my mind [include] the Southern District of New York where there's a speaker program investigation. We have an investigation on Alcon Asia. We have an investigation that's hopefully closing in Korea. And now we have the Essential Consultants," the CEO said.

He promised to redouble efforts to improve things, and outlined steps that have already set in motion towards this end:

"We've moved ethics and risk up to the executive committee; we've put in place a new head of internal audit that will bring in a fresh perspective. We're rolling out a new professional practices policy that is principles-based that asks people to ask themselves the key questions before making a decision," Narasimhan told the investor meeting.

He said the company had established an independent ethics board to oversee all of Novartis' managed access and patient issues.

"We've tightened controls across a lot of our medical activities, and we're hopefully by the summer going to deploy a big data analytics system to continuously monitor what's going on the email traffic and other traffic in the company," he added.

Narasimhan said the company's internal culture also needed to change.

"The most important thing will be the tone from the top and from my leadership team because people look at what you say – and what you don't say."

"Let me be absolutely clear; I never want Novartis to achieve our financial performance or objectives, because we compromised on our ethical standards or our values."

"I would rather stand here before you and miss the numbers rather than again have an instance where we compromise on our values."

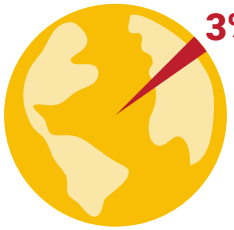
Published online 17 May 2018

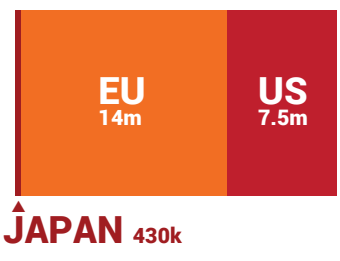
CLEAR THE WAY

A New Era Of Psoriasis Treatment

There is no cure for psoriasis but advances in drug development, moving forward from topical treatments and light therapy, mean that clear (or almost clear) skin is no longer a dream for people with the autoimmune disease.

125m
patients live with psoriatic disease, about 3% of the world's population





$63bn
Direct annual medical costs in US of psoriasis (excluding cost of co-morbidities)

$35bn
Indirect costs (lost work productivity)

THE RISE OF THE IL INHIBITORS

Following the decade-long domination of anti-TNFs, interleukin (IL) inhibitors have come to the market, with data showing they can go beyond 75% skin clearance

ANTI IL-17A AGENTS Q1 2018

$580m
Cosentyx (secukinumab)
NOVARTIS
Psoriasis, Psoriatic Arthritis, Ankylosing Spondylitis

$146.5m
Taltz (ixekizumab)
ELI LILLY
Psoriasis, PsA

$ Undisclosed
Siliq (brodalumab)
VALEANT/LEO
Psoriasis

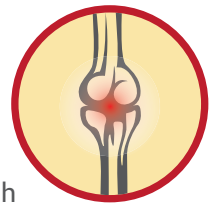
ANTI IL-12/23 AGENT Q1 2018

$1.06bn
Stelara (ustekinumab)
J&J
Psoriasis, PsA, Crohn's

ANTI IL-23 AGENT Q1 2018

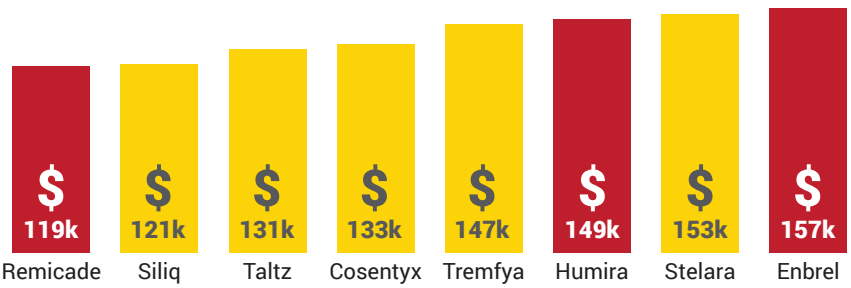
$72m
Tremfya (guselkumab)
J&J
Psoriasis

Up to 30%
of people with psoriasis also develop psoriatic arthritis (PsA)



$100k to $150k
According to ICER, this range represents good value for cost per quality-adjusted life year (QALY) gained

■ Indicates anti-TNF



Sources: International Federation of Psoriasis Associations, American Academy of Dermatology, National Psoriasis Foundation, Scrip, ICER

CONTINUED FROM COVER

including the financial impact on sufferers, caregivers and employers, while also factoring in critical issues such as patient affordability, and fair and timely access."

VEERING FROM REPATHA'S PATH

The approach taken in pricing Aimovig comes in sharp contrast to Amgen's approach in pricing the PCSK9 inhibitor *Repatha* (evolocumab) for the lowering of high LDL cholesterol in patients who can't tolerate statins or whose cholesterol isn't adequately lowered by the generic drugs.

Repatha launched with a list price of $14,100 per year, but has suffered from disappointing sales as payers pushed back on pricing in a market with potentially millions of patients eligible for treatment. Even with significant discounting since then, and label updates in the US and EU recognizing cardiovascular risk reduction observed in the large FOURIER study, the drug generated just $319m in 2017 sales and $123m in the first quarter of 2018.

Indeed, Amgen now has multiple "risk-based contracts" with payers for Repatha and the company's Executive Vice President-Global Commercial Operations Anthony Hooper said during Amgen's first quarter earnings call last month that "we're quite prepared to talk to payers about risk-based contracts with Aimovig."

During the same call, Executive Vice President-Research and Development Sean Harper noted that Aimovig stands out from its competitors as being the only monoclonal antibody in its class that targets the CGRP receptor rather than the ligand. Harper said the drug was designed that way to improve potency and he believed that the receptor-targeting differentiation also led to Aimovig's status as the only CGRP inhibitor that doesn't need a loading dose or intravenous administration.

He also said that when patients fail to see an improvement in the number of their monthly migraine headache days when treated with a CGRP inhibitor, if prescribers switch them to a different anti-CGRP product, they're likely to choose one that targets the receptor in hopes of seeing improved efficacy.

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Pharma Backs UK Parliament Report As 'No Deal Brexit' Fears Grow

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As the UK's proposed departure from the European Union draws closer, the pharmaceutical industry has again voiced its concerns about the protection of patients in terms of access to medicines and how Brexit will make the country an unattractive market for new drugs.

The arguments over Brexit and the snail-like progress that has been made so far regarding the regulation, trade and supply of medicines have been reignited by the publication on May 17 of a report published by the Business, Energy and Industrial Strategy (BEIS) Committee, called, 'The Impact of Brexit on the Pharmaceutical Sector.' The report calls on the Government to secure a post-Brexit agreement as it conducts phase 2 of the negotiations as "leaving the EU without a deal for pharmaceuticals would risk a hugely damaging effect on the sector in the UK, as access to markets diminish, including £11.9bn of exports and more than 446m potential patients and consumers in the EU."

The BEIS report points out that, "The prospect of regulatory divergence from the European Medicines Agency is the deepest concern for the industry." It notes that "any divergence could lead the need for the duplication of facilities and roles across the UK and EU to enable access to products, costing companies tens of millions to establish and millions each year to run."

A number of the bigger players such as **GlaxoSmithKline PLC** and **AstraZeneca PLC** have already begun to implement contingency plans to ensure continued access to the market. However, the report notes that "much of the sector has not."

Shutterstock: Paul Daniels

It states that a divergent regime could see extra costs of £45,000 for each new medicine released in the UK, making the country "an unattractive small market for specialised medicines, and risking the loss of access entirely to some products. Without a continued relationship, there is a significant risk of the UK being a second-tier state for new and innovative medicines." The £45,000 figure comes from a recent Confederation of British Industries report. *(Also see "What Pharma Firms Should Be Doing Now To Prepare For A 'No Deal' Brexit" - , 13 Mar, 2018.)*

MPs on the committee concluded that "there are no benefits from regulatory divergence and no prospect of the industry being able to fully manage any divergence required in the time available for transition."

In response, the Association of the British Pharmaceutical Industry and the UK BioIndustry Association – whose chief executives Mike Thompson and Steve Bates provided evidence to the committee – issued a statement saying that "every month, 45 million packs of medicine move from the UK to the EU, with 37 million moving the other way. Today's select committee report is right – a Brexit 'no deal' would significantly damage public health, patient access to medicines and the UK's leading pharmaceutical sector. This must be avoided at all costs. Securing cooperation on the regulation, trade and supply of medicines must be a priority for both the UK Government and the EU."

Haseeb Ahmad, **Novartis AG** UK country president, told *Scrip:* "Brexit is costly for business but we are not letting that stop our operations. We are working hard to ensure patients are not impacted by a disruption of supply of their medicines, and can continue to be assured in the quality and safety of their medicines – this is our priority."

He added that Novartis had "already implemented steps, incurring costs, to be ready ahead of the UK leaving the EU next March, and we're working to decide in the coming weeks which additional aspects of our contingency plans we will also need to implement." Following Brexit, Ahmad added, "We'd like to see continued cooperation between the UK and the EU on pharmaceutical regulation and this should include cooperative working between the MHRA and the EMA on medicines licensing and continued UK-EU mutual recognition of quality testing of medicines."

He acknowledged that any regulatory regime divergence could entail additional costs for manufacturers, "but more importantly, may mean new medicines' licenses would be delayed in the UK due to the need for a separate UK regulatory submissions, which would likely be prioritised only after that for the much larger EU population." Ahmad added that "already patients in France or Germany are five times more likely to get access to a medicine within its first year of launch compared to UK patients, and that picture would potentially get worse. To ensure minimised disruption to patients, free and frictionless trade between the UK and EU for pharmaceutical and medical supplies is crucial."

> 'We found no-one involved at a senior level in the sector who was prepared to make a positive case for Brexit for pharmaceuticals' – MPs report

The BEIS report also recommends that the UK and the EU pursue a deal that would enable a continued presence for EMA jobs and facilities in the country. The likelihood of this seems pretty remote, however, given European Council draft guidelines on the future relationship which say that the UK, as a third country outside the single market, will not be able to participate in any EU agencies after Brexit.

The BEIS committee went on to say, "We have sought out any potential benefits to the UK pharmaceutical sector from Brexit, but found that any small gains would be hugely outweighed by additional costs or the loss of access to existing, successful markets. The UK is already a significant part of a global industry and there is no evidence of new trade routes from which the UK could benefit."

Damningly, the MPs concluded by noting that while the sector has been "engaged and realistic since the decision to leave the EU was taken…we found no-one involved at a senior level in the sector who was prepared to make a positive case for Brexit for pharmaceuticals."

The report came out the day after the inaugural meeting of the UK Life Sciences Council, which brought together ministers and leading industry chiefs at 10 Downing Street, co-chaired by business secretary Greg Clark, health and social care secretary Jeremy Hunt and AstraZeneca CEO Pascal Soriot.

The council met as the fourth annual Life Science Competitiveness Indicators report was published which the government claimed shows that the UK continues to attract significant private equity investment, with over £660m invested in 67 UK projects in 2016. It added that the UK also accounts for 12% of total life sciences academic citations and 18% of the most-cited publications, the second highest share and "above China, Germany and Canada."

Soriot said in a statement that "with all the uncertainties of Brexit and patient access to medical innovations, the successful implementation of an ambitious industrial strategy is critical to ensure Britain remains a pioneer in life sciences and the sector continues to drive economic growth." He added that the Life Sciences Council "brings together expertise across UK life sciences to provide the strategic direction needed to thrive in the competitive global environment."

COMPETING GLOBALLY

Phil Thomson, president of global affairs at GSK, added that "bringing government, the NHS and industry together through the council is an important step in ensuring the UK remains globally competitive in life sciences.

We must all continue to work together through the Brexit negotiations to ensure the supply of medicines, regulatory alignment and the needs of patients remain priorities."

As well as Soriot and Thomson, industry representatives included Jean-Christophe Tellier and Haruo Naito, CEOs of **UCB Group** and **Eisai Co. Ltd.** respectively, as well as **Merck & Co. Inc.** R&D chief Roger Perlmutter.

Prime Minister Theresa May, who also attended, said that record turnover and foreign direct investment in the life sciences sector was "a vote of confidence in the UK."

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AstraZeneca Q1: Tagrisso Beats Expectations And Drives Oncology Performance

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During the company's first-quarter earnings call, **AstraZeneca PLC** highlighted that a fifth new cancer drug since 2014 is on target for approval this year, and recently launched Tagrisso has become the best-selling product in its oncology portfolio. Later in the day, the UK firm also announced that *Lokelma* (sodium zirconium cyclosilicate, or ZS-9) had been approved by the US FDA to treat adults with hyperkalemia, a condition characterized by elevated potassium that particularly affects patients with chronic kidney disease and those on certain heart failure medicines.

AstraZeneca's CEO Pascal Soriot made grand promises back in 2014 while fending off takeover bids for the company from US giant **Pfizer**, including a pledge of 10 new launches by 2020 – including several new cancer therapies.

Despite the positive news for the company's expanding drug pipeline, AstraZeneca missed market estimates in the first quarter of 2018. The company's stock, traded on the London Stock Exchange, was down by 2.4% in midday trading on May 18, following the publication of its first-quarter financial report.

Notably, core EPS for the first quarter came in 16% below analysts' expectations and core operating profit was lower than anticipated, predominantly caused by higher spending for recent drug launches and continued pressure on statin product *Crestor* (rosuvastatin), which faces strong generic competition in the CV market.

The company's worse than expected financial performance in the first quarter is not expected to continue throughout 2018. Deutsche Bank analysts said in a May 18 note, "1Q should be AZN's lowest profit quarter as it absorbs the tailend of generic impact, while investing aggressively in key new launches." They added that generic erosion for Crestor should ease through the year.

"We are at the maximum pressure point this year… but from 2019 onwards we expect to see the operating profit improve," Soriot also noted during the company's May 18 earnings call.

Q1 NUMBERS AT A GLANCE

- Total Revenue: $5.2bn
- Product Sales: $5bn
- Core Operating profit: $896m
- Core EPS: $0.48
- Full-year 2018 guidance reiterated: sales growth of low single-digit percentage increase; EPS range is $3.30 to $3.50

In the first quarter of 2018, AstraZeneca's newer medicines delivered $0.4bn in additional sales versus Q1 2017, particularly driven by the firm's oncology portfolio. Total oncology sales for the quarter were $1.2bn.

Deutsche Bank analysts noted that each of the company's key new oncology drugs, *Imfinzi* (durvalumab), *Lynparza* (olaparib), and *Tagrisso* (osimertinib), beat expectations (by 39%, 7%, 4% and respectively).

Tagrisso saw sales of $338m in Q1 2018, above consensus expectations of $324m. AstraZeneca highlighted that the drug was now its best-seller in oncology. In the first quarter, Lynparza saw sales of $119m (consensus of $111m) and Imfinzi brought in sales of $62m (consensus of $45m).

Following the plan laid out by Soriot in 2014, AstraZenecai's anti-CD22 recombinant immunotoxin, moxetumomab pasudotox, could be approved by regulators later this year. The drug would represent AstraZeneca's first antibody drug conjugate to get to market. The product is targeting a niche cancer indication of third-line hairy cell leukemia. A decision from the US FDA is anticipated in the third quarter of this year; the drug was granted priority review status in April.

Biomedtracker analysts have given the drug a likelihood of approval rating of 86%, 4% above the average for a similar product at the same stage of development. AstraZeneca published positive topline Phase III results for moxetumomab pasudotox at the end of 2017, followed by full data in February this year. The drug is also being explored as a treatment for non-Hodgkin's lymphoma, where Phase I/II trials are ongoing.

Also adding to AstraZenca's oncology portfolio is *Calquence* (acalabrutinib), which won approval in October 2017 in the US for use in patients with mantle cell lymphoma.

PIPELINE UPDATES

Since the final quarter of 2017, AstraZeneca has moved four drug programs for new molecular entities into Phase I trials. These include AZD9977 for cardiovascular disease (CV), Calquence plus AZD6738 for hematological malignancies, MEDI1314 for Parkinson's disease and MEDI7219 for type 2 diabetes.

The company has also initiated a Phase I study for a new immuno-oncology combination, testing its marketed checkpoint inhibitor Imfinzi in combination with danvatirsen plus chemotherapy in solid tumors. AstraZeneca has also progressed Imfinzi in combination with its own PARP inhibitor Lynparza into a Phase II trial for first-line bladder cancer, and moved AZD8601 into Phase II for CV disease.

At the later stages of development, the big pharma has initiated pivotal studies for the marketed therapy Fasenra in a new indication of nasal polyposis and for the investigational molecule roxadustat for anemia in myelodysplastic syndrome.

Despite a lot of positive activity throughout its pipeline over the last quarter, AstraZeneca has also discontinued or divested a number of programs.

Furthermore, AstraZeneca will present several data updates during the American Society of Clinical Oncology's annual meeting in June this year. The company has more than 90 abstracts included in the ASCO program, including 14 oral presentations and seven 'best of ASCO' highlights.

Notably, the company will present Phase II data for Lynparza plus abiraterone in prostate cancer, and data for Imfinzi monotherapy from the Phase III PACIFIC and the Phase II ATLANTIC trials in NSCLC.

Published online 21 May 2018

AstraZeneca's Lokelma Approved In US With Label Benefits Over Veltassa

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AstraZeneca PLC's *Lokelma* has finally won FDA approval for the treatment of adults with hyperkalemia after delays cause by manufacturing issues. But while the drug's label gives it an edge over closest rival, Vifor Pharma's *Veltassa,* being later to market may have cost AstraZeneca blockbuster status.

Lokelma (sodium zirconium cyclosilicate), previously known as ZS-9, is a highly-selective, oral potassium-removing agent. The drug previously received two complete response letters from the US FDA because of manufacturing issues at a facility in Texas. AstraZeneca's second and final CRL came in March 2017. Both letters were related to GMP issues and did not require any new clinical data, but they delayed the product's route to market.

The first CRL for the drug came in May 2016.

AstraZeneca is preparing to launch Lokelma in the US where it will compete directly with **Vifor Pharma Group**'s already marketed Veltassa (patiromer). But the US label for Lokelma includes some benefits over Vifor's existing treatment. Information about Lokelma's faster onset time (one hour versus seven hours for Veltessa), an improved drug-drug interaction profile and the ability to store it indefinitely at room temperature are included in the label for AstraZeneca's product.

The US label also suggests orally administered drugs that exhibit pH-dependent solubility be administered two hours before or after Lokelma, versus a suggested three-hour window for all drugs with Veltassa.

However, similarly to Veltassa, the drug's label warns against use for treatment of acute life-threatening hyperkalemia episodes, Deutsche Bank analysts highlighted in a May 21 note. Veltassa and Lokelma are the only approved therapeutics for hyperkalemia; there are no other candidates in clinical development but a handful are in preclinical testing from other companies.

AstraZeneca acquired Lokelma in 2015 when it bought **ZS Pharma Inc.** for $2.7bn. At that time the UK big pharma believed the drug could be a blockbuster, bringing in more than $1bn in sales. Analysts' consensus expectations though, following delays for the drug coming to market, now expect peak sales for Lokelma to be around $600m in 2022.

Deutsche Bank analysts added that "the slow launch of Veltassa and more modestly differentiated label of Lokelma than possible in best cases suggests investors are likely to remain cautious on the drug's potential for now."

Hyperkalemia is characterized by elevated potassium levels in the blood associated with cardiovascular, renal and metabolic diseases. The condition is more common in patients with chronic kidney disease and for those who take medications for heart failure, such as renin-angiotensin-aldosterone system (RAAS) inhibitors, which can increase potassium in the blood.

The FDA approval is supported by data from three double-blind, placebo-controlled trials and two open-label trials, which showed that for patients receiving Lokelma the onset of action was at 1.0 hour and the median time to achieving normal potassium levels in the blood was 2.2 hours, with 92% of patients achieving normal potassium levels within 48 hours from baseline. The treatment effect was maintained for up to 12 months.

The European Commission granted marketing authorization for Lokelma for hyperkalemia in the EU in March 2018.

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Dupixent Hits Endpoints In Adolescents, Filing Expected In Q3

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A skin condition may arguably have a greater impact on the well-being of adolescents than on adults, underlining the importance of **Sanofi** and **Regeneron Pharmaceuticals Inc.** reporting on May 16 positive Phase III results with *Dupixent* (dupilumab) in the younger age group of patients with inadequately controlled moderate-to-severe atopic dermatitis.

The interleukin-4/IL-13 inhibitor, Dupixent, is the first and only biologic to show positive results as monotherapy in adolescents aged 12 to 17 years with inadequately controlled disease, the companies say, and a US marketing submission to extend the product's indication to include such patients aged 12 to 17 years is expected in the third quarter of 2018. Atopic dermatitis is often considered a disease of childhood, and analysts at Datamonitor Healthcare are forecasting the overall market for adult and childhood therapies could grow from around $600m in 2015 to $2.7bn in 2024, driven by new products with novel mechanisms of action such as Dupixent and the unmet clinical demand for non-steroidal therapies, offset by the potential availability of generic versions to current therapies such as *Protopic* (tacrolimus) and *Elidel* (pimecrolimus).

The future growth of Dupixent is important to Sanofi, which is facing declining revenues from its mainstay diabetes franchise. The drug was approved for marketing in the US in March 2017, for the treatment of moderate-to-severe atopic dermatitis in adults whose disease is not adequately controlled with topical therapies or for whom the latter are inadvisable.

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Takeda Looks To The New As It Braces For Velcade Generics

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Takeda Pharmaceutical Co. Ltd. is bracing for "significant penetration of generic product" for its blockbuster multiple myeloma drug *Velcade* (bortezomib) in the US, particularly with the advent of the first such competitors in a subcutaneous formulation.

The proteasome inhibitor generated global sales of JPY137.3bn ($1.24bn) – including JPY113.7bn in the US – in the fiscal year ended March 31, making it the Japanese firm's number three product globally. In the US, it is approved across all lines of MM therapy and also for mantle cell lymphoma, with the more convenient SC formulation being launched in early 2012.

"We assume to lose JPY54bn [$487m] of Velcade sales, and that's about 3.5 points of [negative impact on underlying] revenue" in the current fiscal year, Takeda president and CEO Christophe Weber conceded at the company's results briefing.

> 'Entrance of a second generic will create much more pricing pressure and competition around pricing, even though they are not therapeutically equivalent'

CFO Costa Saroukos said at the same meeting that global revenues of JPY75.5bn are forecast in 2018. "Our financial assumption is based on one additional therapeutically non-equivalent [unidentified] competitor launching in September 2018 with both IV and subcutaneous administration."

The first generic entrant in the US was launched in January by Fresenius Kabi as a standard intravenous injection following a 505(b)(2) NDA, for second-line use in both indications.

SC RIVALS

Weber commented that: "We assume that the entrance of a second generic will create much more pricing pressure and competition around pricing, even though they are not therapeutically equivalent. The current product does not have a subcutaneous formulation, but we assume that the second entrant or the third, the next one [will]… which is very important to compete against Velcade."

Although Takeda is assuming the first SC product will arrive this September, the CEO admitted that "we are dealing with a lot of unknowns here" when looking at the landscape for generic competition.

PharmaVitae analyst Edward Thomason agrees Velcade "is expected to come under intense generic competition in the US with the first subcutaneous and intravenous generic version set to launch… PharmaVitae expects Velcade sales to erode by approximately 40% in FY 2018, a reduction of over $500m versus 2017," he told *Scrip*.

Datamonitor Healthcare sees global sales plunging to $272m ($103m in the US) in 2020.

COPING WITH THE LOSS

So how is Takeda planning to cope? The planned $64bn acquisition of Shire is the most obvious way in which the company is looking to boost its revenues and commercial and R&D portfolios, although the deal is not expected to close until the first half of next year, assuming shareholder approval.

More immediately, sales of the company's follow-up multiple myeloma drug *Ninlaro* (ixazomib), another proteasome inhibitor but orally administered, are also rising strongly along with another growth driver, the blockbuster for ulcerative colitis and Crohn's disease *Entyvio* (vedolizumab).

Both of these have gross margins between 15% and 20% higher than the company average, boosting overall profitability in the process. Ninlaro sales in the fiscal year were JPY46.4bn (+54%) and Entyvio surged to JPY201.4bn (+36%), and continued strong increases for both are seen this year by Takeda, which pointed to the underlying strength of such new products and business in helping to more than offset the predicted declines for Velcade.

Takeda is now expecting Entyvio – which has become its top product – to hit its initial $2bn sales target ahead of schedule early this fiscal year, helped by a launch in Japan, and to go on to $3bn the following year. Despite the expected generic competition, the company is forecasting its total company sales will fall by modest 2% to JPY1,737bn on a reported basis this fiscal year, but with underlying growth in the "low single digits."

NEW DATA FOR NINLARO

As for Ninlaro, Weber said it is too early to revise peak sales because the product has a good momentum, but "we still have a lot of data waiting", including on maintenance use, in MM, which is seen as central to future uptake. "In terms of value, it's probably even more important than the frontline data," he noted, for which the product is not yet approved in the US.)

The independent committee has reviewed the first-line indication study, but this has not yet reached statistical significance, and so has recommended continuation of the trial, delaying results by around one year. Read-out on the maintenance study is expected in the 2018 first semester.

Datamonitor Healthcare sees global Ninlaro sales reaching $992m in 2021, helped by lower peripheral neurotoxicity than Velcade and a more competitive price than **Amgen Inc.**'s MM competitor *Kyprolis* (carfilzomib).

This product also has similar toxicity benefits over Velcade and safety/efficacy improvements over that older product in relapsed/refractory MM, and Datamonitor expects US sales in this indication to reach $722m in 2020.

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From the editors of PharmAsia News.

Takeda-Shire In India: Sleeping Giant?

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Takeda Pharmaceutical Co. Ltd. has generally been keen to do more in emerging markets like India, but the Japanese major has hitherto been somewhat tentative about a sharp ramp-up in the country. The $62bn planned acquisition of **Shire PLC** may now give it just that required impetus to push things forward, adding portfolio girth and momentum for future growth in a nation that is expected to see greater focus on healthcare as it tackles the growing burden of non-communicable diseases alongside infectious ailments. India also has an estimated 70 million patients with rare diseases.

While both companies indicated that it was early days to comment on the final shape of a Takeda-Shire combine in India including whether Shire may stay standalone for now or whether a realignment in Takeda's alliances was likely, the deal could expand the duo's scope of play in India.

Takeda told *Scrip* that it was committed to making more of its products available locally, and had successfully registered some of its innovative and potentially life-saving medicines.

"We are making good progress in making them available to help meet patients' unmet medical needs," the company said.

Details on the clinical trials registry of India reflect studies for Takeda's diabetes therapy *Nesina* (alogliptin) and *Entyvio* (vedolizumab), among other products, though the regulatory status on these could not be immediately ascertained.

Takeda is also collaborating with partners to "expedite access" to potentially life-saving vaccine candidates which are expected to address some of today's most challenging infectious diseases. The Japanese company referred, in particular, to its partnership with **Zydus Cadila** to tackle chikungunya, an emerging infectious disease in the Indian sub-continent, Africa and Asia.

Takeda set up an India arm, Takeda Pharmaceuticals India Pvt. Ltd, in 2011 and also has a Nycomed legacy joint venture, Zydus Takeda Healthcare Pvt. Ltd., with Zydus Cadila. Zydus Takeda Healthcare is a 100% export-oriented unit and manufacturing activity said to be exclusively undertaken for Takeda. It has two manufacturing plants – one for active pharmaceutical ingredients and a site for manufacturing the key starting materials of pantoprazole sodium.

Takeda had also entered into licensing agreements with the Indian vaccines manufacturer **Biological E Ltd** for the transfer of technology to enable the production of affordable combination vaccines for lower income countries, though the latest on this could not be ascertained immediately.

TAKEDA'S MEASURED APPROACH, SHIRE PORTFOLIO

Nevertheless, Takeda's general tone on India, over the years, appears more measured compared to its bullish outlook in 2010 when it outlined plans with medium- to long-term strategies for business expansion in India.

"The basic plan consists of the strategies for expanding the Takeda group's presence in India which is and will be one of the fastest growing pharmaceutical markets. At the same time, Takeda will pursue innovation, productivity and cost-effectiveness as a whole within the Takeda group, by leveraging world-class capabilities at competitive costs in research, development, CMC [chemistry, manufacturing and control], toll-manufacturing services, and IT services that India offers," the Japanese group said in Oct. 2010.

Specifics on progress made in the various segments could not immediately be ascertained, but things don't appear to have played out to their full potential, at least going by what some industry observers say. Concerns around India's intellectual property policies and the still raging controversy around the disastrous **Daiichi Sankyo Co. Ltd.- Ranbaxy Laboratories Ltd.** deal may also have tempered Takeda's plans, though there's no official word on this. In 2016, Takeda "realigned" certain teams amid plans to provide sustainable access to its medicines under a new leadership in India.

For now *Tachosil* (absorbable fibrin sealant patch) is the only key product available to patients in India "via Takeda", while the Japanese company has also out-licensed pantoprazole in India, it confirmed to *Scrip*.

Shire, on the other hand, told *Scrip* it has nine products available in India – largely in the hematology segment. These are: *Advate*, *Recombinate*, *Hemofil M*, *Immunate*, *Rixubis*, *Immunine*, *FEIBA*, *Flexbumin* and *Human Albumin NG*. Shire, which is reported to have delivered strong growth in India in FY17, has been engaged alongside the non-profit Hemophilia Federation (India) in efforts to expand awareness around hemophilia and its management; there are an estimated 130,000 hemophilia patients in India, but both diagnosis and access to care are woefully inadequate in the country.

Some analysts have suggested that Shire's hematology franchise may be a potential divestment candidate, though Takeda's CEO, Christophe Weber, while acknowledging competition in hemophilia is "very tight", has underscored "good synergies" in the segment.

Shire expects the combination with Takeda to create a leading global biopharmaceutical company driven by innovative R&D with the scale to drive future development. "We believe the combined company would be well positioned to deliver highly-innovative medicines and transformative care for patients around the world," Shire told *Scrip*. The Dublin-headquartered Shire has 90 employees in India.

Both Takeda and Shire, however, said that it was early days to provide any details on the potential combine's structure in India.

Shire said that it was too early to speculate "which facilities would be affected".

"After the transaction closes, we will learn more about the integration plan and how our country organizations fit into the future structure. The acquisition is subject to shareholder approval of both companies as well as regulatory approvals and we expect it will close in H1 of 2019."

Takeda said that it is too early to comment on its proposed offer for Shire.

"Transactions like these are extremely complex and our offer is subject to an approval process that involves Takeda's and Shire's shareholders, as well as regulators and other stakeholders," Takeda said.

Besides, since Shire is a UK-listed company, it falls under the jurisdiction of the UK Takeover Code, which stipulates certain rules for how it can proceed with, and publicly communicate, developments of the transaction.

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Immuno-Oncology: What To Watch At ASCO 2018

EMILY HAYES & JESSICA MERRILL

For some years now, immunotherapy has dominated the American Society of Clinical Oncology (ASCO) annual meeting and this year is no exception as it will be a defining week for PD-1/L1 inhibitors and chimeric antigen receptor T-cell therapies.

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Drawing from a meeting preview report by Pharma Intelligence's Biomedtracker and Datamonitor Healthcare analysts following the abstract drop on May 16, we highlight the studies below as important to watch at the meeting, which will be held June 1-5 in Chicago.

[Editor's note: See our companion story for ASCO highlights outside of immuno-oncology.]

PD-1/L1 LUNG CANCER SHOWDOWN

It's already been a big year for the PD-1/L1 inhibitors in non-small cell lung cancer (NSCLC) following the combination data released at the American Association for Cancer Research (AACR) meeting in April – but ASCO 2018 will also be pivotal for the class of checkpoint inhibitors in their most valuable indication.

Late-breaker presentations include detailed results for **Merck & Co. Inc.**'s *Keytruda* (pembrolizumab) as a monotherapy vs. chemotherapy in the positive KEYNOTE-042 study (#LBA4) in first-line treatment of PD-L1-positive, non-squamous NSCLC, data that could allow expansion of labeling to patients with lower levels of PD-L1 expression. *(Also see "Merck's Keytruda Set For Expanded Use As Lung Cancer Monotherapy " - Scrip, 10 Apr, 2018.)*

Another notable late-breaker (#LBA9000) examines **Roche**'s PD-L1 inhibitor *Tecentriq* (atezolizumab) with chemotherapy in the IMpower131 study of first-line squamous NSCLC. *(Also see "Roche Gains With Tecentriq IMpower131 NSCLC Data, But For How Long? " - Scrip, 20 Mar, 2018.)* "Although the squamous population only represents approximately 30% of NSCLC patients, positive results from IMpower131 will be critical in helping Tecentriq compete with other PD-1/PD-L1 inhibitors in NSCLC," the Pharma Intelligence analysts noted.

Roche will also present the Phase III IMpower150 study (#9002), which may give Tecentriq an edge in first-line non-squamous NSCLC over Merck's Keytruda combination, currently the only checkpoint inhibitor approved for this indication. *(Also see "Roche's IMpower150 Gets AACR Applause But Merck's KEYNOTE-189 Big Winner " - Scrip, 17 Apr, 2018.)*

The ASCO abstract reports an overall survival (OS) advantage for Tecentriq in combination with Roche's VEGF inhibitor *Avastin* (bevacizumab) for all subgroups, including people with EGFR and ALK mutations, liver metastases and varying levels of PD-L1 expression. The combination is now under review at the US FDA.

"This first release of numerical OS results and subgroup analysis for IMpower150 bodes very well for Tecentriq towards becoming the second PD-1/PD-L1 inhibitor approved for the first-line treatment of NSCLC (after Keytruda). In addition to the OS data likely supporting regulatory approval of the combination, the subgroup analysis revealed that the greatest benefit was seen in EGFR/ALK mutation-positive patients. If approved, this surprising finding differentiates the Tecentriq combination from Keytruda, whose use is not supported in the first-line treatment of EGFR/ALK mutant NSCLC patients," Pharma Intelligence's report states.

Merck will be presenting data for Keytruda in the KEYNOTE-407 study in first-line squamous NSCLC, but new data on progression-free survival (PFS) and overall survival (OS) were not reported in the abstract. The company has filed for approval early based on objective response rate (ORR) data. *(Also see "Merck Files Keytruda/Chemo Combo Early With FDA In 1L Squamous Lung Cancer" - Pink Sheet, 3 May, 2018.)* According to the abstract, the ORR was 58.4% for Keytruda combined with chemo vs. 35% for chemo alone.

Bristol-Myers Squibb Co.'s combination of its PD-1 inhibitor *Opdivo* (nivolumab) with its CTLA-4 inhibitor *Yervoy* (ipilimumab) will be featured with new results from the CheckMate 227 study of first-line NSCLC, including non-squamous and squamous types (#9001). The company had released data at AACR in April for patients with high tumor-mutation burden. *(Also see "In The Hot Seat: Bristol Defends IO Position Amid Sliding Stock And Forecasts" - Scrip, 18 Apr, 2018.)* Bristol's latest dataset show better progression-free survival (PFS) in patients with less than 1% PD-L1 expression.

The data look promising and differentiate the regimen from Keytruda, which is not approved for non-PD-L1 expressing NSCLC, Pharma Intelligence analysts noted.

Regeneron Pharmaceuticals Inc. is updating data on its PD-1 late-comer cemiplimab; it is hoping to carve out a niche in cutaneous squamous cell carcinoma, an indication not carried by any of the anti-PD-1/L1s. Leerink analyst Geoffrey Porges noted that in the updated Phase I trial (#9557), "the responses have deepened (no CR in previous reports) and have become more durable, and we believe cemiplimab is well on track to receive an expedited approval in this previously overlooked indication and carve out at least an initial niche in the competitive PD-1/PDL1 field." Regeneron will also present data from the NSCLC cohort from its Phase I basket trial (#e21057).

MELANOMA COMBOS

IDO inhibitors were the toast of the town at past ASCO meetings, hailed for their potential for use in combination with PD-1/L1 inhibitors, but companies are backing away following the failure of Merck/**Incyte Corp.**'s Keytruda/epacadostat combination in the Phase III ECHO-201/KEYNOTE-252 study

in first-line metastatic melanoma in April. *(Also see "Incyte/Merck's ECHO-301 Failure Casts More Shadow On IDO Space" - Scrip, 6 Apr, 2018.)*

Data from the study will be presented at ASCO (#108), but the abstract does not indicate differences in subgroups or other data that would help shed light on why the trial failed. Investors will be interested in seeing whether any additional data are presented at the meeting that will help understand the spectacular flameout of the class. *(Also see "NewLink CEO Reflects On Golden Age And Rapid Fall Of IDO" - Scrip, 15 May, 2018.)*

Meanwhile, ASCO will be fertile hunting ground for those on the prowl for new mechanisms that may be used more successfully with PD-1/L1 inhibitors.

Dynavax Technologies Corp. will be presenting data from a Phase I/II study of its toll-like receptor 9 (TLR9) agonist SD-101 in combination with Merck's Keytruda in patients with advanced melanoma who are naïve to PD-1 inhibitors (#9513).

Data for 25 patients as of February suggest an objective response rate (ORR) of 60%, and the complete response (CR) rate was 12%, with acceptable tolerability, including no increase in the rate of immune-related adverse events, according to the abstract. Including five patients who dropped out, the ORR for SD-101/Keytruda is 50% and the CR is 10%.

Pharma Intelligence analysts described the results as encouraging. The responses in the per-protocol population compare well to historical data for Bristol's Opdivo/Yervoy combination (59% ORR and 22% CR) but without the high rate of Grade 3/4 toxicity, they said. The results also compare well to PD-1 monotherapy, they noted.

NEKTAR'S NKTR-214 RESPONSE RATES SLIDE

Nektar Therapeutics is reporting updated data for its NKTR-214, a pegylated formulation of the cytokine interleukin-2, in the Phase I/II PIVOT study of advanced solid tumors at the ASCO meeting. The PIVOT study tests the drug in combination with partner Bristol's PD-1 inhibitor Opdivo in a range of tumors, including melanoma and non-small cell lung cancer. Previously released data for 38 patients had set the immuno-oncology world on fire – the response rate was in the mid-60s for first-line metastatic melanoma and 60% in renal cell carcinoma, for example. *(Also see "Nektar's NKTR-214 IO Deal With Bristol Looks Even Sweeter With More Data" - Scrip, 2 Mar, 2018.)*

Pharma Intelligence concluded that overall the updated data reported in the ASCO abstract are positive for NKTR-214: "While response rates detailed in this abstract are slightly lower than those previously presented, small drops in response rates are to be expected as the patient cohort for each tumor type grows larger. Furthermore, these response rates still compare favorably to those observed for Opdivo monotherapy as well as Opdivo plus Yervoy."

The rate of Grade 3+ adverse events was low at 11%, which may provide an advantage over Bristol's Opdivo/Yervoy combination, the analysts added.

JOUNCE ICOS ANTIBODY UNDERWHELMS

Jounce Therapeutics Inc. delivered one of the most notable disappointments out of the ASCO abstract lineup, revealing disappointing early efficacy data for JTX-2011, a first-in-class ICOS antibody partnered with **Celgene**. The monoclonal antibody binds to and activates the InducibleT cell Co-Stimulator (ICOS), a protein on the surface of T-cells, to stimulate an immune response. Jounce's stock opened May 17 32% lower at $12.15, after the company revealed underwhelming efficacy data from the ICONIC study (#3000), including in combination with Bristol's PD-1 inhibitor Opdivo and as monotherapy.

Only one in seven gastric cancer patients treated with JTX-2011 monotherapy experienced a partial response, while two in five with triple-negative breast cancer had stable disease. Two gastric cancer patients treated with the combination experienced a partial response and two had stable disease of 19 patients. Only one triple-negative breast cancer patient, out of 15, had a partial response.

The data ruffled the feathers of some Celgene investors as well, since the big biotech paid $261m up front for an option to co-develop JTX-2011 and up to four early-stage programs associated with certain B cell, T regulatory cell and tumor-associated macrophage targets from Jounce's translational platform in 2016.

New data on CAR-T therapies including **Celgene Corp.**'s JCAR017 and **bluebird bio Inc.**'s bb2121, also partnered with Celgene, will be presented at ASCO, potentially providing more insight on the durability of the treatments and the serious side effects. Bb2121 is a second-generation CAR-T cell therapy targeting B-cell maturation antigen (BCMA) to redirect T-cells to recognize and kill malignant myeloma cells. Bluebird and Celgene reported positive data from a first-in-human study in 21 relapsed/refractory multiple myeloma patients at ASH, but will report updated safety and efficacy results in 43 patients at ASCO (#8007), as well as data from a dose-expansion arm including treatment with daratumumab. *(Also see "Celgene's CAR-T Leadership Goals Advance At ASH 2017" - , 12 Dec, 2017.)*

Celgene will also present updated long-term follow-up data from six and 12 months on JCAR017, also known as lisocabtagenemaraleucel, in patients with relapsed refractory non-Hodgkin's lymphoma (#7505). Since positive efficacy data were reported at ASH, Celgene shelled out $9bn to buy the 90% of **Juno Pharmaceuticals Pty. Ltd.** it didn't already own. *(Also see "Celgene Seeks CAR-T Leadership, Hematology Diversification With Juno Buy" - Scrip, 22 Jan, 2018.)*

Another study that could be interesting to watch is an independent third-party trial comparing the activity and safety of **Novartis AG**'s*Kymriah* and **Gilead Sciences Inc.**'s*Yescarta*, which appears to give Kymriah some advantages (#3041). The two drugs use different co-stimulatory signaling domains, 4-1BB for Kymriah and CD28 Yescarta.

The study enrolled 47 relapsed/refractory CD19-positive B-cell acute lymphoblastic leukemia patients, including 19 in the CD28 group and 28 in the 4-1BB group. The overall objective response rate of the 4-1BB group (100%) was higher than that of the CD28 group (89%). Different degrees of cytokine-release syndrome occurred in 45 of 47 patients, with five patients who had grade III-IV CRS all in the CD28 group. Meanwhile, cytokine release peak in the CD28 group was significantly higher than that of the 4-1BB group, the study showed. Five patients who had grade III-IV neurotoxicity were all in the CD28 group.

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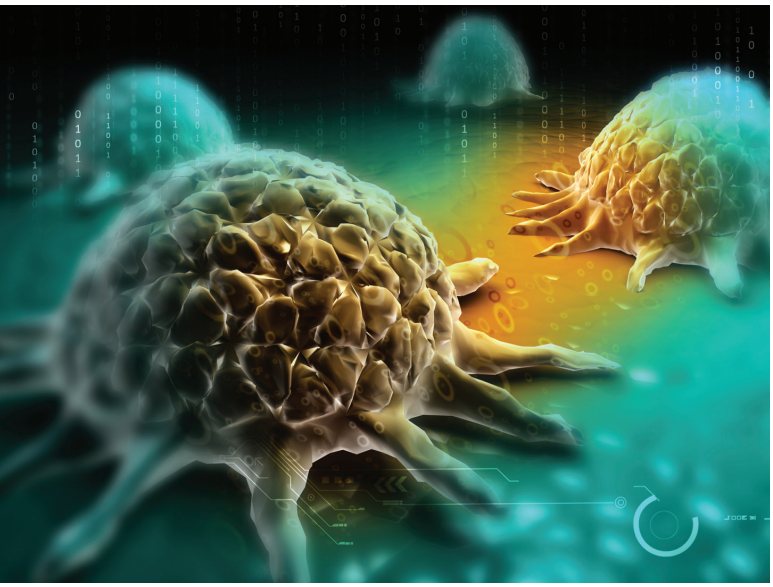
Other ASCO 2018 Highlights – It's Not All IO

EMILY HAYES & JESSICA MERRILL



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While the American Society of Clinical Oncology (ASCO) annual meeting, to be held June 1-5 in Chicago, has a long lineup of immune-oncology hits and misses, there's plenty to stay on top of outside of immunotherapy, as shown by the ASCO preview report from Pharma Intelligence's Pharma Biomedtracker and Datamonitor Healthcare analysts.

[Editor's note: See our companion piece for immuno-oncology highlights for ASCO 2018.]

Inter-class competition features heavily across several of the biggest cancer markets. In non-small cell lung cancer (NSCLC), **Pfizer Inc.**'s EGFR inhibitor dacomitinib stands to unseat **AstraZeneca PLC**'s *Iressa*. There will be commercial implications across breast cancer as a safer CDK4/6 inhibitor from **G1 Therapeutics Inc.** advances and the PI3 kinase class nears the market, with late-breaking data coming for **Roche**'s taselisib.

But **Loxo Oncology Inc.** could once again steal the show with a tissue-agnostic drug. Last year the company impressed with early data showing remarkable effects for its TRK inhibitor larotrectinib, which is now under review at the US FDA and partnered with **Bayer AG**. *(Also see "More Deals Like Loxo On The Cards As Bayer Ups Ante In Oncology" - Scrip, 6 Mar, 2018.)* This year, Loxo is unveiling the first data for its next class.

A LAYUP FOR LOXO AND RET INHIBITORS

Loxo Pharmaceuticals' RET inhibitor LOXO-292 demonstrated impressive efficacy in RET fusion-positive and RET-mutant cancers, generating enthusiasm from investors about the class of drugs. In the Phase I study reported at ASCO (#102), the overall response rate for the 32 evaluable patients was 69%, including a 65% response rate in patients with NSCLC and 83% in papillary thyroid cancer (PTC). RET fusions only occur in a small subset of patients, about 2% of NSCLC and 20% of PTC, but strong efficacy in a highly-targeted subset of patients could be a winning proposition.

Blueprint Medicines Corp. also is developing a RET inhibitor – BLU-667 – for patients with RET-altered solid tumors, but the drug demonstrated a lower objective response rate (ORR) in Phase I data released in April. The company said the ORR was 45% across all evaluable patients.

Investors rewarded Loxo for the positive data, with the stock up 20% at $167.53 on May 17. Meanwhile, Blueprint ended the day 5% lower at $81.90. Loxo was one of the winning stories out of ASCO last year, with positive data on the tropomyosin receptor kinase (TRK) fusion protein larotrectinib.

The drug met the non-inferiority endpoint for reducing severe neutropenia in 406 patients treated with myelosuppressive chemotherapy, with a numerical reduction in the duration of severe neutropenia compared with filgrastim. A second Phase III study called RECOVER is ongoing and is expected to complete later this year.

'These data are very encouraging for ivosidenib given that IDH1-mutation positive AML results in poor patient outcomes and short survival rates as compared with other molecular abnormalities in AML'

AGIOS' IVOSIDENIB UPDATE

Updated results for **Agios Pharmaceuticals Inc.**'s ivosidenib in a Phase I study of relapsed/refractory acute myeloid leukemia (AML) with IDH1 mutations are better than what has been previously reported and bode well for FDA approval; an application based on the Phase I data is under review with an Aug. 21 review deadline. *(Also see "Agios' IDH Inhibitors Show Their Mettle At ASH" - Scrip, 12 Dec, 2017.)*

The C-001 study (#7000) evaluated the drug in 258 patients. The rate of patients with a complete response (CR) or a complete response with partial hematologic recovery (CRh) was 31.8%. The median duration of CR+CRh was 8.2 months and the median duration of CR was 10.1 months. Investigators also reported that the objective response rate was 41.9%.

"Although there was no reported data on transfusion independence rates, we assume there are no drastic changes from previous results. These data are very encouraging for ivosidenib given that IDH1-mutation positive AML results in poor patient outcomes and short survival rates as compared with other molecular abnormalities in AML," Pharma Intelligence analysts said.

The ASCO meeting will also feature results for ivosidenib or Agios/**Celgene Corp.**'s *Idhifa* (enasidenib) with Celgene's *Vidaza* (azacitidine) in a Phase I/II study of newly diagnosed AML with IDH mutations. The data look promising though more patient numbers are needed to evaluate the potential.

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FDA Flags Lower Efficacy For Merck's Keytruda, Roche's Tecentriq In Frontline Bladder Cancer Trials

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The US FDA issued an alert on May 18 that said first-line monotherapy treatment with **Merck & Co. Inc.**'s *Keytruda* and **Roche**'s *Tecentriq* in metastatic urothelial cancer (mUC) trials was linked with decreased survival in patients with low expression of the PD-L1 biomarker compared with chemotherapy, though this was not due to adverse events.

Keytruda (pembrolizumab), a PD-1 inhibitor, and Tecentriq (atezolizumab), a PD-L1 inhibitor, both were cleared under the FDA's accelerated approval process for previously untreated metastatic bladder cancer in patients who are not eligible for cisplatin-based chemotherapy – about 40% to 60% of the first-line population.

Keytruda and Tecentriq as well as the three other PD-1/L1 drugs on the market – **Pfizer Inc./Merck KGAA**'s *Bavencio* (avelumab), **AstraZeneca PLC**'s *Imfinzi* (durvalumab) and **Bristol-Myers Squibb Co.**'s *Opdivo* (nivolumab) – were all approved based on response rate data for second-line use after platinum-based chemotherapy. Keytruda is the only one so far that has gone on to secure full approval in that indication after showing a survival benefit. However, Tecentriq failed to show a survival benefit in its Phase III confirmatory IMvigor211 second-line study.

Bladder cancer is a relatively modest-sized market for PD-1/L1 checkpoint inhibitors, worth an estimated $2bn versus $14.8bn for non-small cell lung cancer indications and $30bn for all tumor types in 2022, according to Morningstar Research projections. Morningstar has projected that in 2022, Merck would take a 45% share of the bladder cancer market, followed by Roche with 30% and Bristol with 12%.

DECREASED SURVIVAL IN TRIALS

The FDA issued an alert to health-care professionals, cancer trial investigators and the public about the use of the checkpoint inhibitors in first-line metastatic urothelial cancer studies following early reviews by data monitoring committees of two studies – the KEYNOTE-361 study (NCT02853305) of Keytruda and the IMvigor-130 trial (NCT02807636) for Tecentriq, both of which tested the drugs with or without platinum-based chemotherapy versus chemotherapy alone.

The agency said that in the monotherapy arms of both trials, patients with low PD-L1 had decreased survival compared to those taking cisplatin or carboplatin-based chemotherapy. This was attributed to a difference in efficacy, not a safety problem.

"There was no change in the adverse event profile of Keytruda or Tecentriq," the FDA noted.

Low PD-L1 expression is defined as immune cell staining of less than 1% in Roche's study.

Merck's study defines low PD-L1 expression as a combined positive score (CPS), the percent of tumor or infiltrating immune cells, of less than 10.

On the recommendation of data monitoring committees, Merck and Roche have stopped enrolling patients with low PD-L1 into the monotherapy arms of the studies, but low PD-L1 patients may continue to participate in the PD-1/chemo combination and standalone chemotherapy arms of the trials.

Roche subsidiary Genentech noted that participants already randomized and treated with Tecentriq monotherapy may still continue to receive treatment.

The FDA said it is reviewing the findings of the ongoing clinical trials and will communicate new information as necessary.

The agency's statement notes that the patients enrolled in the trials were eligible for platinum-based chemotherapy and therefore different from the populations tested in trials supporting accelerated approvals in first-line metastatic urothelial cancer.

"We continue to believe in the efficacy and safety of Tecentriq monotherapy in people with locally advanced or mUC who are not eligible for cisplatin-containing chemotherapy," Genentech said in a statement provided to *Scrip*.

The FDA recommended that providers select patients for treatment using criteria in the clinical studies section of drug's each label.

Keytruda's labeling in bladder cancer has no mention of PD-L1 expression status. While claims of the other PD-1/L1 drugs in bladder cancer have not specified a PD-L1 threshold in the indication, the clinical trials sections split out efficacy data by PD-L1 expression.

Merck said its KEYNOTE-361 study is ongoing and the company continues to work closely with regulatory agencies as additional data are generated in the course of the trial.

Roche's trial also continues and the company said there are no changes to other ongoing studies at this time.

Genentech is blinded to the IMvigor130 data and therefore it is challenging to extrapolate to other diseases.

FDA's statement did not reference late-stage first-line bladder cancer studies of other PD-1 inhibitors.

Bristol is testing its PD-1 inhibitor Opdivo in combination with its CTLA-4 inhibitor *Yervoy* (ipilimumab) or standard of care chemotherapy compared to the standard of care chemotherapy alone in the CheckMate 901 study of previously untreated metastatic urothelial cancer.

AstraZeneca is testing its PD-L1 inhibitor Imfinzi with or without its CTLA-4 inhibitor tremelimumab versus standard of care chemotherapy in advanced urothelial cancer.

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Syndax Sees Subgroup Efficacy For Entinostat Plus Keytruda In NSCLC

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Syndax Pharmaceuticals Inc. thinks it has identified a subgroup of non-small cell lung cancer (NSCLC) patients who respond well to treatment with entinostat and **Merck & Co. Inc.**'s *Keytruda*, and the company is designing a pivotal study it hopes to launch later this year in this biomarker-stratified patient subpopulation.

Syndax held an investor call May 17, following the release of abstracts for next month's American Society of Clinical Oncology (ASCO) meeting, to outline some of the data it will present at the conference for its selective histone deacetylase (HDAC) inhibitor with Merck's PD-1 inhibitor Keytruda (pembrolizumab) in NSCLC, melanoma and colorectal cancer (CRC).

Entinostat has a US FDA breakthrough therapy designation in advanced breast cancer and pivotal Phase III data in post-menopausal patients with hormone receptor-positive advanced breast cancer are expected this quarter. The Boston-area company is testing the entinostat/Keytruda combo in both PD-1/PD-L1 treatment-naïve and treatment-experienced NSCLC patients, under a trial collaboration agreement signed with Merck in 2015. The deal originally included melanoma and was expanded to include CRC in 2017.

The combo produced an 11% overall response rate (6/57) in a cohort of NSCLC patients who progressed after chemotherapy and anti-PD-L1 treatment in the Phase Ib/II study that will be presented at ASCO. The median duration of response among the six responders was 4.6 months, Syndax noted, with the longest response to date more than 14 months.

However, in blood sampling of 51 of the 57 enrollees, Syndax discovered that patients with high pre-treatment levels of classical monocytes appear to exhibit an enhanced benefit from the combination therapy. In these patients, it found 29% (4/14) ORR and progression-free survival (PFS) of 5.4 months, roughly double the 2.7 months seen for the overall 57-patient cohort. Patients with low baseline monocyte levels showed a 5% ORR (2/37) and PFS of 2.5 months.

Syndax CEO Briggs Morrison told the investor call that the company is planning to launch a pivotal Phase III study for the entinostat/Keytruda combination in treatment-experienced NSCLC patients with high levels of monocytes, although it still has work to do to validate the biomarker it used to identify this subgroup, which it plans to use in Phase III.

"What's tremendously exciting in this data is both the high overall response rate and particularly the PFS, which we believe is considerably longer than that observed when the standard-of-care agents are used in this population," Morrison said. "In terms of a regulatory path forward, we believe PFS is an accepted endpoint, should we conduct a randomized trial against the standard of care of chemotherapy. In the 5.4 months that we observed, it's almost twice the best estimate we have found in the current literature for PFS when standard-of-care of chemotherapy is used."

This subpopulation represents an area of growing unmet medical need, as well as a significant commercial opportunity potentially for entinostat, the exec added. Merck's KEYNOTE-189 study in newly diagnosed lung cancer patients showed that 80% of patients receiving Keytruda plus chemotherapy saw progressive disease within 18 months of starting therapy, he noted.

"There are a growing number of patients who will need therapy after their disease has progressed on both the PD-1 antagonist plus chemotherapy, and that's exactly the population of patients we studied in this cohort," Morrison said.

Syndax estimates that roughly 84,000 patients a year are candidates for second- or third-line NSCLC treatment and that approximately one-third of those will have high monocyte levels at baseline.

While it designs the Phase III study, which it hopes to initiate before the end of 2018 with a goal of top-line data in early 2020, Syndax will continue monitoring the ongoing Phase I/II trial for response rates, PFS and eventually overall survival, Morrison said.

"We are already working to validate and industrialize the monocyte assay, so that we can use it as a stratification marker in our next trials," he continued. "And we will continue to explore additional biomarkers that could improve upon the predictive value of classical monocytes."

JMP Securities analyst Konstantinos Aprilakis reiterated a "market outperform" rating for Syndax's stock in a May 18 note, although he said entinostat's current valuation is tied up in its monotherapy potential in breast cancer. Still, he called the NSCLC program a chance for significant upside and said investors may be too focused on the entinostat/Keytruda combo's middling performance in melanoma so far.

"We remind investors that patient segmentation is common in the context of NSCLC therapy, and should the combination of entinostat and pembrolizumab continue to demonstrate a meaningful clinical benefit in this [subgroup] setting going forward, the potential market opportunity would undoubtedly be sizeable, in our opinion," Aprilakis wrote.

Syndax's share price tumbled from $11.08 to $8.61 on May 17, but stabilized and rebounded slightly on May 18, closing up 2% at $8.80 a share.

MORE MATURE DATA NEEDED

Morrison told the investor call that the 18% ORR seen with the entinostat/Keytruda combo in 34 PD-1 treatment-experienced melanoma patients falls short of the 20% response rate Syndax believes would be clinically meaningful. But it plans to wait for the data in this cohort of the Phase Ib/II study to mature before making a decision for or against moving the combo into Phase III in melanoma. The data from 34 patients represent that status of the trial at the time of data cutoff for inclusion at ASCO, but the enrollment now has reached 55 patients, he added.

"Based upon continued discussions with a number of physicians, we consistently hear that response rates around 20% would be considered highly clinically relevant, especially if the median duration of response exceeds six months," Morrison said.

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Can Lilly's Cluster Headache Data Differentiate Its CGRP Inhibitor?

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Lilly Research Laboratories's galcanezumab moved into the lead in the treatment of cluster headaches with a calcitonin gene-related peptide (CGRP) inhibitor via Phase III data reported May 15, but analysts wonder how much of an impact this will have in the ultra-competitive CGRP space.

The Indianapolis pharma said that galcanezumab hit the primary endpoint in a 106-patient, Phase III study in episodic cluster headaches, but it failed to show statistical significance in a larger Phase III in chronic cluster headache. Galcanezumab is under review at the US FDA for migraine prevention with an Oct. 11 PDUFA date, but **Amgen Inc.** and **Novartis AG** are expected to have the first anti-CGRP drug approved for migraine prophylaxis with a May 17 action date for their *Aimovig* (erenumab), (see article page 1).

Lilly's only rival within the CGRP class for a cluster headache indication is **Teva Pharmaceutical Industries Ltd.**, with its Phase III antibody fremanezumab. However, the Israeli pharma, which is expected to report Phase III data in episodic and chronic cluster headaches later this year, may be falling significantly behind Lilly due to a manufacturing issue at its third-party manufacturing partner, **Celltrion Inc.**

Galcanezumab – dosed at 300 mg once a month – yielded a statistically significant reduction in overall mean episodes from baseline compared to placebo across weeks one to three in the two-month study in patients who suffer episodic cluster headaches, Lilly reported. Also, on a gated secondary endpoint, a statistically significant portion of treatment-arm patients achieved at least a 50% reduction in cluster headache episodes compared to placebo at week three.

Lilly noted that patients in this study suffered an average of 17.5 cluster headaches weekly at baseline.

The antibody's safety and tolerability profile was similar to that seen in prior studies in migraine prevention, the company said. Eight percent of patients treated with galcanezumab discontinued treatment during the trial compared to 21% in the placebo arm. Four percent discontinued galcanezumab due to adverse events and 2% discontinued due to lack of efficacy, Lilly pointed out, compared to 2% and 14%, respectively, for the placebo arm.

However, galcanezumab did not achieve statistical significance compared to placebo for reducing chronic cluster headache attacks from baseline in a separate, 237-patient, three-month trial. Lilly did not offer details of the antibody's performance in this study compared to placebo. It noted, however, that episodic cluster headaches make up an estimated 85%-90% of the overall cluster headache patient base.

The pharma said it is now in discussions with regulators to determine a best path forward in these two sub-indications.

CLUSTER HEADACHE IS A WIN, BUT HOW BIG?

In a May 15 note, Credit Suisse analyst Vamil Divan called the data "mixed," but still a net win for Lilly since the larger portion of cluster headache patients suffer episodically rather than chronically.

Biomedtracker increased galcanezumab's likelihood of approval one percentage point to 93% based on the data – 10 points higher than average for a migraine candidate under regulatory review – but also noted the high unmet need for therapies to prevent cluster headaches.

Besides galcanezumab, Aimovig and fremanezumab – all delivered via subcutaneous injections – the anti-CGRP class for migraine prophylaxis also includes the intravenous Phase III candidate eptinezumab from **Alder Biopharmaceuticals Inc.** as well as the oral drugs rimegepant from **Biohaven Pharmaceuticals Holding Co. Ltd.** and atogepant from **Allergan PLC**, which are in Phase III and Phase IIb, respectively. Allergan's lead oral CGRP inhibitor ubrogepant is being developed for acute, or on-demand, treatment of migraine headaches.

Credit Suisse's Divan said cluster headache could serve as a differentiating label claim for Lilly, but the impact on sales within the anti-CGRP class is questionable, because cluster headache represents only about 5% of his sales projections for the drug. He also wondered whether a single, positive study would be deemed sufficient by FDA for approval in episodic cluster headaches.

Divan predicted that Teva's manufacturing issues will push fremanezumab into third place behind Aimovig and galcanezumab, despite a June 16 PDUFA date, while Alder is further behind with final data from its Phase III open-label study of eptinezumab expected in mid-2018. Still, Alder could find a valuable niche in this market because eptinezumab's "rapid onset of activity and intravenous formulation could make it a differentiated competitor in the space," he wrote.

Bioomedtracker pointed out that Teva's fremanezumab could get a market advantage out of its potential to be dosed either monthly or quarterly.

MULTIPLE DRUGS MAY ACTIVATE THE MARKET

Lilly Bio-Medicines President Christi Shaw said during the company's first quarter earnings call on April 24 that several competing products entering this market at close intervals should help activate the patients and clinicians. But the competitive edge in the anti-CGRP arena, she said, likely will come down to several factors.

"The first piece is who is going to be better at the consumer-driven area, the direct-to-consumer [marketing]," Shaw told the call. "And I think our chances there are very good. We have a history of that. … And we're the only [anti-CGRP candidate] that is actually showing that 10% to 15% of the patients have the ability to really be free of migraines totally."

"The other thing we have is that [galcanezumab] is fast and durable," the exec continued. "We see results early as month one and we see the results continue through the 12 months that we've looked at." She added that successful data in the cluster headache segment would be "a huge win for patients, and obviously, then good for differentiating galcanezumab."

Galcanezumab is one part of Lilly's three-drug, late-stage pipeline for pain indications, along with oral serotonin 5HT1F receptor agonist lasmiditan for acute migraine and the nerve growth factor (NGF) inhibitor tanezumab for chronic pain.

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NewLink CEO Reflects On Golden Age And Rapid Fall Of IDO

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NewLink Genetics Corp. CEO Chuck Link says he believes the company's IDO pathway inhibitor indoximod still has potential and is differentiated from direct inhibitors of the target, even after news of **Genentech Inc.**'s exit from an IDO/TDO development deal.

Indoleamine 2,3-dioxygenase (IDO) is an enzyme that plays an important part in immune response. NewLink has developed a direct inhibitor of IDO called navoximod, as well as the unpartnered indoximod, which targets the mechanism indirectly.

Link believes there may still be a path forward for this class of drugs, although with a more measured approach to clinical development.

NewLink reported the end of its partnership with **Roche** subsidiary Genentech to develop navoximod (GDC-0919, NLG919) as well as other IDO/TDO inhibitors in a May 15 US Securities and Exchange Commission (SEC) filing. The company's stock closed down 3.5% at $5.18 following the disclosure.

Genentech paid NewLink $150m up front under their 2014 agreement to develop navoximod as well as other IDO inhibitors and tryptophan 2,3-dioxygenase (TDO) inhibitors. Genentech announced in June 2017 that it was ending an agreement to co-develop navoximod after a lackluster presentation of results at the annual American Society of Clinical Oncology annual meeting.

As NewLink noted in the SEC filing, "the agreement remained in force with respect to next-generation IDO/TDO inhibitors identified through the research program conducted under the Genentech Agreement."

The rights to the next-generation compounds now revert to NewLink, which will pay a low single-digit royalty to Genentech on any sales, should the compounds be developed and commercialized, according to the filing.

"These licenses, royalty obligations and assignments for next-generation compounds are in addition to the licenses, royalty obligations and assignments for NLG919 that went into effect in December 2017 when the Genentech Agreement terminated with respect to NLG919," the filing states.

CLASS TAKES A BEATING

IDO as a class looked enormously promising and big pharmas bought in fast and at high cost based on very early data, skipping mid-stage development. In addition to Roche, **Merck & Co. Inc.** and **Bristol-Myers Squibb Co.** started Phase III trials in a range of tumor types testing their PD-1 inhibitors in combination with **Incyte Corp.**'s epacadostat, the most advanced IDO inhibitor in the class.

The big wake-up call came in early April when Incyte and Merck announced that the combination of the PD-1 inhibitor *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.

Bristol subsequently terminated Phase III studies of its in-house IDO inhibitor BMS-986205 in melanoma, head and neck, and lung cancer – an asset acquired through a high-priced acquisition of Flexus Biosciences in 2015. And Incyte announced the end of a number of pivotal trials involving epacadostat in its first quarter earnings call, though it will press on with development in some tumor types.

NEWLINK MULLS OPTIONS

NewLink has ended plans to test indoximod in a Phase III study of melanoma and is reviewing the strategy for its programs after the wave of announcements terminating IDO development.

The company also "deprioritized" pancreatic cancer and will not proceed with a planned Phase II study of indoximod with **AstraZeneca PLC**'s PD-L1 inhibitor *Imfinzi* (durvalumab). The focus of Roche, Merck and Bristol was on building upon PD-1 blockade, but there are alternative development possibilities in combination with other types of therapies, commented NewLink CEO Chuck Link in an interview with *Scrip*.

It's not just about combinations with PD-1 inhibitors and, furthermore, indoximod functions differently than specific enzymatic inhibitors, Link said. Whereas navoximod binds directly to IDO, indoximod interacts with multiple places along the IDO pathway to elicit immune responses. At a high level, indoximod "mimics tryptophan, so the immune cells sense a normal level of tryptophan and stay active, not suppressed. Indoximod counteracts the consequences of IDO being expressed," the company has explained.

"Our viewpoint is that there is still opportunity to evaluate indoximod, since it does have such a different mechanism of action," Link said.

During the company's first-quarter earnings call on May 3, NewLink said that its indoximod program continues to show promise. At the American Association for Cancer Research annual meeting in April, NewLink presented data showing what the company views as encouraging early data from a Phase Ib study of indoximod with radiation, followed by followed by maintenance indoximod and chemotherapy in diffuse intrinsic pontine glioma (DIPG), a fatal pediatric brain tumor. NewLink views these data as supportive of indoximod's differentiated IDO mechanism. The company has also developed a new formulation of indoximod that minimizes the pill burden.

Link noted that the company has data suggesting that indoximod is complementary to specific IDO inhibitors, perhaps targeting the pathway more completely, and that the combination might have potential for use in the salvage setting after PD-1 failures, Link said. Outside of melanoma, most tumors don't respond to PD-1 therapy and in those who do respond, the majority recur, he added.

It will also be important going forward to gather biomarker data to help identify who will respond to treatment.

"Maybe you could figure out the right salvage setting in PD-1 failures," Link told *Scrip*.

Further analyses of Merck/Incyte's failed ECHO-201/KEYNOTE-252 study – the largest study every done of the mechanism – may be helpful in this regard.

With IDO, companies jumped over randomized Phase II studies and jumped into randomized Phase III trials. "Now there is clearly diminished enthusiasm for the specific enzymatic inhibitors," Link said.

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Ebola Outbreak In DR Congo: Where Are The Vaccines In Development?

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Another outbreak of Ebola, this time in the Democratic Republic of the Congo (DR Congo), could spur pharma into action once more after a quiet period since the 2014/2015 epidemic in West Africa.

The government of DR Congo declared a new outbreak of Ebola virus disease in Bikoro, Equateur Province, in early May. It is the region's ninth outbreak of Ebola since the discovery of the virus in the country in 1976. As of May 13, 39 Ebola cases had been reported, including two confirmed cases, 20 probable cases, and 19 deaths.

Ebola is endemic to DR Congo; the last Ebola outbreak in the region occurred in July 2017 in Likati Health Zone, Bas Uele Province, in the northern part of the country.

The World Health Organisation has released $2.6m from its Contingency Fund for Emergencies to kick-start rapid response to the most recent outbreak. The Wellcome Trust and UK Department for International Development (DFID) have also announced a commitment of up to £3m ($4.0m) to support efforts to contain and manage the disease. The WHO said the estimated budget for the international response was $25m for a three-month operation.

The Ebola virus causes an acute, serious illness that is often fatal if untreated – the average Ebola case fatality rate is around 50%. The virus is transmitted to people from wild animals and spreads in the human population through human-to-human transmission. The large-scale outbreak of the disease in Guinea, Liberia and Sierra Leone, which began in 2014, left more than 11,300 dead.

Merck & Co. Inc.'s investigational Phase II/III Ebola vaccine, V920, has been made available by the company for use in DR Congo and a vaccination program is set to start in the region. Merck told *Scrip* it was actively collaborating with the WHO and Médécins Sans Frontières (MSF) to support the implementation of an expanded access clinical protocol, designed to allow deployment V920 in a ring vaccination approach in response to the new outbreak. "There are 4,300 doses of our investigational V920 vaccine prepositioned with the WHO in Geneva to support rapid deployment to the outbreak area," Merck, known as MSD outside of the US and Canada, said. The company is also collaborating with the WHO to provide additional doses in Geneva to support the current response; it currently has a stockpile of more than 300,000 emergency use dose equivalents.

Merck is developing V920 in partnership with **NewLink Genetics**. The companies are expected to release top-line data for the product in the second quarter of 2018 from the Phase II/III STRIVE trial and the Phase III SAFETY study. The vaccine is experimental and not licensed, but it was tested in Guinea in 2015.

The Ebola vaccination campaign will first target health workers in DR Congo. Recent reports have noted that three nurses were among those with suspected cases of the disease, and another was one of the fatalities. The WHO told *Scrip* it has dispatched 4,000 vaccine doses to DR Congo, which arrived on May 16, and that it would deploy 4,000 more in the coming days.

As well as Merck's program, **Johnson & Johnson** and **GlaxoSmithKline PLC** also have late-stage Ebola vaccines in development.

GSK told *Scrip* that in response to the Ebola outbreak in 2014, the company progressed its candidate Ebola vaccine into Phase II trials. "However, due to the welcome drop in Ebola cases by mid-2015, the vaccine candidate did not complete Phase III efficacy testing," a spokesperson for the company said.

After the end of the 2014-15 Ebola outbreak, GSK did not submit its vaccine for licensure because its clinical efficacy had not been sufficiently established due to the reducing number of cases of the disease. "We have stockpiled doses of our Ebola candidate vaccine and are closely monitoring the current situation. We are also aware that the WHO is assessing the situation to determine how best to respond to arising needs," GSK said.

The pipeline also includes earlier stage vaccine candidates and therapeutics to treat the disease. There are also more than 10 programs against Ebola in the preclinical setting.

As well as vaccine candidates, there are a few therapeutic treatments in development for Ebola, including **Mapp Biopharmaceutical Inc.**'s *ZMapp*. The investigational biologic is composed of three humanized monoclonal antibodies manufactured in plants.

Mapp has an expanded access protocol with the FDA for ZMapp. The company told *Scrip* it would provide drug in DR Congo under this protocol once it had been requested.

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Ebola Clinical Pipeline

DRUG NAME	LEAD COMPANY	CURRENT PHASE	DRUG CLASSIFICATION
MVA-BN Filo/Ad26.ZEBOV	Johnson & Johnson	III	Vaccine
cAd3-EBO Z	GlaxoSmithKline	II/III	Vaccine
ZEBOV	Merck & Co.	II/III	Vaccine
GBV006	Globavir Biosciences	II	Non-NME
Remdesivir	Gilead Sciences	II	New Molecular Entity (NME)
ZMapp	Mapp Biopharmaceutical	I/II	Biologic
EBOV GP Vaccine	Novavax	I	Vaccine
Galidesivir	BioCryst Pharmaceuticals	I	NME
INO-4212	Inovio Pharmaceuticals	I	NME
REGN3470-3471-3479	Regeneron Pharmaceuticals	I	Biologic

Biomedtracker

Missing In Action: China's Best Shot In Ebola Vaccine Race

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Hailing it as a national priority, the China FDA has approved its first home grown Ebola vaccine in record-breaking time, but it has yet to be used in an ongoing new outbreak in Africa.

Located thousands of miles away from the affected area, China believes the approval is not only important but an urgent task, as given its 1.3 billion population, the country sees it as only a matter of time before the next epidemic could hit the nation.

So right after the abatement of the last major Ebola outbreak in 2014, which hit West Africa hard causing over 11,000 deaths, China decided to have its own vaccines ready before the next wave.

Developed by China's Academy of Military Medical Sciences, along with **CanSino Biotech**, the new vaccine is based on the Zaire strain of the virus, the same used in the one being shipped to affected Congo regions, provided by **Merck & Co. Inc.**.

The Chinese vaccine, despite having obtained CFDA approval, has yet to be assessed in a Phase III trial as the approval was given on the condition that this be conducted. This was also the first conditional approval to be granted under China's regulatory reforms to accelerate new drugs and biologics approvals.

RECORD APPROVAL TIMES

The vaccine developed in China, using an adenovirus (AAV) carrier, obtained a priority review in February 2015 and in just 10 work days the CFDA granted clinical trial approval (CTA).

In 79 work days, the agency officially approved the product last October, setting a new record for an NDA approval time. Comparatively, the standard time frames for a CTA is 90 work days and 150 for an NDA.

"To defend public well-being amid a public health crisis, we don't hesitate to stand by scientists and push forward the vaccine to the market," said Xu Jiaqi, director of the Center for Drug Evaluation (CDE), the new drug review arm of the CFDA.

To that end, eight reviewers working at the CDE's biologics division were divided into two groups and worked on the Ebola vaccine simultaneously. Given the limited reviewer resources – about 120 compared to over 1,000 at the US FDA – the agency was mustering all available effort towards the approval.

PHASE III DATA LACKING

Responding to questions from *Scrip*, World Health Organization spokesman Tarik Jaseravic said the Merck vaccine is the only one that has shown efficacy in a Phase III study, out of 12 candidates. *(Also see "Ebola Outbreak In DR Congo: Where Are The Vaccines In Development?" - Scrip, 16 May, 2018.)*

"Twelve candidate Ebola vaccines (including monovalent, bivalent and multivalent candidates) have undergone or are currently undergoing clinical development at different trial phases. The Phase III trial for an rVSV-vectored candidate vaccine (rVSVΔG-ZEBOV-GP), undertaken in Guinea, is the only study that has reported clinical efficacy and effectiveness for any candidate Ebola vaccine," he noted.

But compared to the Merck product and one approved in Russia, the Chinese vaccine shows great potential, noted the CFDA.

"The sponsor completed three clinical studies, including a randomized, double-blind Phase I study using placebo on 120 Chinese people, and a Phase II on 61 Africans residing in Hangzhou, as well as a Phase II on 500 people in Sierra Leone," noted the agency in a statement.

In comparison, the Merck vaccine has completed a Phase III study in 7,000 people in Guinea, while the locally approved Russian vaccine has only completed a Phase I program in 24 people and Phase II in 59 patients.

"Although our vaccine can produce higher levels of antibody inside a human body, due to the lack of Phase III study data, the antibody level's association with effectiveness of disease prevention is unknown," recognized the CFDA in granting the conditional approval, which also specifies only emergency use amid a public health crisis.

A freeze-dried dry power formulation, the vaccine is said to be easier to store and ship in the conditions of Africa, added the agency.

FUNDING/SUPPLY CHANNELS

So far, the new Chinese vaccine's manufacturer, CanSino, in January cleared the EU's Qualified Person's Good Manufacturing Practice rules. The company didn't disclose the current production situation, but it is expected to make stockpiles for emergency use.

Merck meanwhile has donated doses of its vaccine to the WHO, the operation to administrate these being underwritten by donations from the Vaccine Alliance, GAVI, and others, noted the WHO.

GAVI had previously entered an advanced procurement agreement for 300,000 doses of the Merck vaccine, and has approved additional funding for a global stockpile of one or more vaccines if they are licensed and recommended by the WHO.

Given the ready funding and China's desire to make domestically developed Ebola vaccines work, the path to possible global supplies should be clear. But so far, China's National Health Commission hasn't publicly disclosed any plans to send any of the Chinese product to the affected Congo regions.

Earlier this week, the WHO opened its annual meeting during which Director-General, Tedros Adhanom Ghebreysus said: "It's concerning that we now have cases of Ebola in an urban center, but we're much better placed to deal with this outbreak than we were in 2014. I am pleased to say that vaccination is starting as we speak today."

Participating Chinese Health Commissioner Ma Xiaowei told the meeting that China is willing to share its experiences with the world.

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From the editors of PharmAsia News.

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 11–17 May 2018

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
PHASE III RESULTS PUBLISHED			
AstraZeneca PLC	*Symbicort* (budesonide / formoterol) *Turbuhaler*, as-needed	asthma, mild	SYGMA 1, 2; the *NEJM*, May 17, 2018.
Novartis AG	*Ilaris* (canakinumab)	hereditary periodic fevers	CLUSTER; *NEJM*, May 17, 2018.
GW Pharmaceuticals PLC	*Epidiolex* (cannabidiol)	Lennox-Gastaut syndrome	GWPCARE3; *NEJM* online, May 17, 2018.
Johnson & Johnson/Bayer AG	*Xarelto* (rivaroxaban)	embolic stroke of undetermined source	NAVIGATE ESUS; *NEJM* online, May 16, 2018.
Teva Pharmaceutical Industries Ltd.	fremanezumab	episodic migraine	HALO; *JAMA*, May 2018.
Braeburn Pharmaceuticals Inc.	CAM2038	opioid use disorder	*JAMA Internal Medicine*, online May 14, 2018.
PHASE III INTERIM/TOP-LINE RESULTS			
Ultragenyx Pharmaceutical Inc./ Kyowa Hakko Kirin Co. Ltd.	*Crysvita* (burosumab)	X-linked hypophosphatemia in children	PIXLES; met primary endpoint.
Verastem Inc.	duvelisib	chronic lymphocytic leukemia	DUO; good overall response rate and PFS reported.
Eli Lilly & Co.	galcanezumab	cluster headache, episodic and chronic	Met primary endpoint in episodic but not in chronic.
AstraZeneca PLC	*Fasrena* (benralizumab)	chronic obstructive pulmonary disease exacerbations	GALATHEA; missed primary endpoint.
Sanofi/ Regeneron Pharmaceuticals Inc.	*Dupixent* (dupilumab)	atopic dermatitis in adolescents	Positive results.
UCB SA	*Cimzia* (certolizumab pegol)	axial spondylo-arthritis, non-radiographic	C-AXSPAND; met primary and secondary objectives.
Novartis AG	*Kisqali* (ribociclib) plus fulvestrant	breast cancer	MONALEESA-3.
Pfizer Inc.	*Lyrica* (pregabalin) oral solution CV	adjunctive therapy of partial onset seizures in infants	Met primary endpoint.
UPDATED PHASE III RESULTS			
Bristol-Myers Squibb Co.	*Opdivo* (nivolumab) versus ipilimumab	melanoma, non-small cell lung cancer (NSCLC)	CheckMate 238; improved recurrence free survival.
Bristol-Myers Squibb Co.	nivolumab	NSCLC	CheckMate 227; improved PFS.
Celgene Corp.	pomalidomide, Velcade, dexamethasone	multiple myeloma, early relapsed or refractory	OPTIMISMM; improved progression free survival.
Eli Lilly & Co.	*Cyramza* (ramucirumab)	liver cancer	REACH-2; met primary endpoint.
Incyte Corp.	epacadostat with *Keytruda* (pembrolizumab)	melanoma	ECHO-301/KeyNote-252; no added clinical benefit.
Merck & Co. Inc.	pembrolizumab with paclitaxel	gastric cancer	KeyNote-061; mixed results.
Merck & Co. Inc.	pembrolizumab with chemotherapy	NSCLC, first line	KeyNote-407; responses observed.
RedHill Biopharma Ltd.	*Bekinda* (ondansetron)	gastroenteritis	GUARD; efficacy observed.
Roche	*Alecensa* (alectinib)	NSCLC, ALK-positive	ALEX; improved PFS.
Roche	*Tecentriq* (atezolizumab) with chemotherapy	NSCLC	IMpower 150; improved overall survival.
Spectrum Pharmaceuticals Inc.	*Rolontis* (eflapegrastim)	neutropenia	ADVANCE; primary and secondary endpoints met.
Pfenex Inc.	PF708 (teriparatide biosimilar)	osteoporosis	Comparable profile to *Forteo*.

Source: Biomedtracker

Will Glenmark-Celon's 'Substitutable' Seretide Deliver In Europe?

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Glenmark Pharmaceuticals Ltd. and partner **Celon Pharma SA**'s "substitutable" generic of **GlaxoSmithKline PLC**'s *Seretide Accuhaler* (fluticasone/salmeterol) has made its debut in Denmark, putting some pressure on the innovator product, though it remains to be seen if patient endorsement for the generic will be widespread.

Glenmark said that it was the first generic company to receive regulatory approval for "substitution" in Denmark for its generic of Seretide Accuhaler – seen, among other aspects, as an important validation of the Indo-Polish alliance's technology capabilities – as they take the product into other parts of Europe.

A substitutable status could imply that detailing may not be required for Glenmark's product via a specific sales force; pharmacies are generally expected to offer the cheapest generic product to to patients, thereby underscoring the importance of pricing, though price erosion is expected to be low, industry experts told *Scrip*.

"We plan to commercialize this product across the Nordics in the near future. The grant of substitution in Denmark for this complex product affirms Glenmark's capabilities in the respiratory segment," said Achin Gupta, executive vice president and business head (Europe and Latin America) at Glenmark.

Glenmark has already received National Marketing Authorizations for its generic Seretide Accuhaler in Sweden, Finland, Norway and Iceland.

The high cost of developing a new device and bringing an inhaled combination generic to market has resulted in minimal price discounts for generic Advair/Seretide across the five major EU markets (France, Germany, Italy, Spain, and the UK), Datamonitor Healthcare noted in a report in February this year.

"In all markets, generic erosion of Advair/Seretide is forecast to be slow as physicians and patients hesitate to switch to new devices. Interviewed key opinion leaders have confirmed that patients may be concerned about the dose or efficacy equivalence between the branded drug and its generic version," the report said.

Other industry experts also explained that innovator companies submit a "lot of documentation and studies" on the benefits of the device on various parameters and generic firms do not typically invest in such elaborate studies for obvious reasons.

"Since asthma attacks can be debilitating, these devices are considered important for health outcomes and quality of patients lives and therefore governments don't take kindly to Gx claims of similar efficacy unless there are clinical studies done to prove it," one expert noted. Details on studies undertaken by Glenmark-Celon could not immediately be ascertained.

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The Gaithersburg, MD-based immuno-oncology company, **Sensei Biotherapeutics Inc.**, has appointed ***John Celebi*** as president and CEO. Celebi was most recently COO of X4 Pharmaceuticals, and was also chief business officer at Igenica Biotherapeutics Inc. Sensei's lead candidate, SNS-301, a first-in-class cancer vaccine, targets a novel embryonic self-antigen, and has completed Phase I studies, and Sensei also has a proprietary SPIRIT drug development platform that is generating novel immune-oncology therapies.

Saiid Zarrabian has been appointed president and CEO at **DelMar Pharmaceuticals Inc.**, having served as interim president and CEO since Nov. 2017. Zarrabian has previously served as chairman of La Jolla Pharmaceutical Co., and as president of the protein production division of Intrexon Corp.. DelMar is evaluating its lead anticancer candidate, VAL-083, in Phase II studies in glioblastoma multiforme.

Seattle Genetics Inc. has appointed ***Roger Dansey*** as chief medical officer. Most recently Dansey was therapeutic area head for late-stage oncology at Merck & Co, responsible for the ongoing registration efforts for *Keytruda* (pembrolizumab) across multiple tumor types, and before that was vice president, oncology clinical research at Gilead Sciences. Dansey succeeds ***Jonathan Drachman***, who remains at Seattle Genetics as a strategic adviser for innovation.

Astellas Pharma Inc. has promoted ***Bernhardt Zeiher*** to chief medical officer, effective Apr. 1, 2018. Zeiher will continue to serve as president of development, while overseeing all other functions at Astellas's medical and development organization.

Richard Marshall has been appointed chief medical officer at Denmark's **Galecto Biotech AB**, having most recently been vice president and head of the fibrosis and lung injury discovery performance unit (DPU) at GlaxoSmithKline, where he led the early clinical development of *Nucala* (mepolizumab). Galecto's lead program, TD139 is moving towards late-stage clinical studies in idiopathic pulmonary fibrosis.

Roivant Sciences has named ***Adele Gulfo*** as chief of commercial development, and ***Salomon Azoulay*** as chief medical officer. Most recently, Gulfo was executive vice president, chief strategy officer and head of global commercial development at Mylan; she has also previously served as president and general manager of Pfizer's US primary care business unit. Azoulay joins from Pfizer, where he most recently served as senior vice president and chief medical officer for Pfizer Essential Health.

Jill Jene has been appointed vice president, business development at **PDL BioPharma Inc.**, to lead the addition of healthcare assets to PDL's portfolio of products and companies. Jene was previously senior vice president, business development at twoXAR, and before that worked at Depomed, where she became vice president of business development. PDL acquires and manages a portfolio of assets in the biotech, pharma and medical device sectors.

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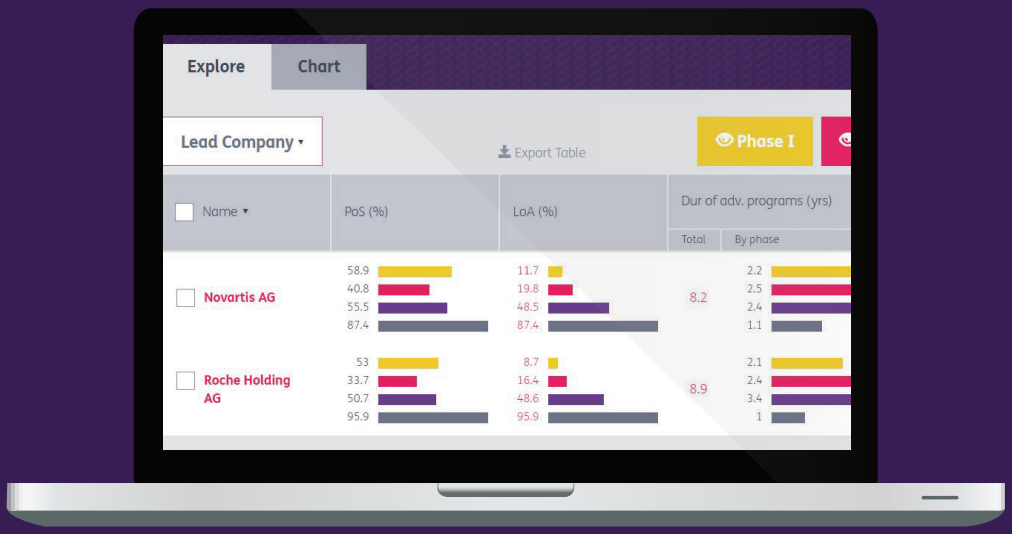

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