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Merck Exits Insulin Glargine Market, Remains Committed To Biosimilars

JESSICA MERRILL jessica.merrill@informa.com

Merck & Co. Inc. has decided that it will not commercialize its own version of **Sanofi**'s *Lantus* (insulin glargine) in the US, even though the product was already tentatively approved by the US FDA in 2017.

"After a comprehensive assessment of the current and future market environment for insulin glargine, which included an assessment of anticipated pricing and cost of production, we made the business decision to terminate our agreement on the commercialization of Lusduna pen and vial," Merck said in a statement to *Scrip*. The firm said it will reallocate resources including commercial and manufacturing capacity to other products.

The decision is surprising since the product was tentatively approved by the FDA in July 2017, though it had not launched. Tentative approval is used by the FDA when a drug is permitted to enter the market pending the resolution of ongoing patent litigation. Sanofi filed a patent infringement suit against Merck in August 2017, triggering a 30-month stay of action.

Merck is already a strong player in the diabetes market with the blockbuster *Januvia* (sitagliptin), so the company would presumably already have the commercial structure in place to market an insulin copy. However, the insulin market has become highly competitive with difficult dynamics.

The follow-on product, developed with partner **Samsung Bioepis Co. Ltd.**, would have been the third Lantus version on the market in the US behind Sanofi's original product and **Eli Lilly & Co.**'s *Basaglar*, which launched in December 2015 after Lilly reached a patent settlement agreement with Sanofi.

Both copies are technically approved under the 505(b)(2) regulatory pathway for NDAs, rather than through the biosimilar pathway, based on the way insulin is categorized at the FDA, but the agency is recategorizing insulins as biologics in a transition that will go into effect in 2020.

ANOTHER SETBACK FOR BIOSIMILARS?

Merck's decision could be another sign that the US biosimilar market isn't living up to the early hype. A handful of initial lackluster launches have raised questions about the commercial potential for biosimilars in the US in the near-term. Even FDA Commissioner Scott Gottlieb has expressed concern that slow launches could lead drug manufacturers to curtail biosimilar R&D. *(Also see "FDA's Gottlieb: 'Pricing And Reimbursement Mischief' Holding Back Biosimilar Market" - Scrip, 7 Mar, 2018.)*

Momenta announced Oct. 1 that it is exiting most biosimilar development to focus on a novel pipeline of drugs after a lengthy strategic review under which it failed to find a buyer for the business. CEO Craig Wheeler said the patent delays and market uncertainty partly contributed to the decision.

Merck is one of just a few drug makers that has experienced the challenging US biosimilar market first-hand. The company's *Renflexis* (infliximab-abda) was the second biosimilar version of **Johnson & Johnson**'s

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

Drug Price Increases
Never say never, says Regeneron (p8)

China Vs Cancer
Reimbursement for 17 cancer drugs, but pricing pressures (p10)

BMS's Checkmate-331 Failure
Analysts predict Opdivo will keep SCLC indication (p12)

from the editor

eleanor.malone@informa.com

Another week, another exit in biosimilars. Last week we reported on Momenta's decision to get out of the biosimilars game; this week it is Merck & Co that has decided not to enter the US market for insulin glargine despite having a product with tentative FDA approval (see cover story). While this decision may reflect specific challenges in the insulin market and Merck's own circumstances, it comes against a wider backdrop of uncertainty over the viability of the biosimilars space for market entrants given the effectiveness of originator company defense tactics.

In contrast to the thicket of challenges with which biosimilar companies are contending in the US, Europe is a garden of delights. Mundipharma's acquisition of Spanish biosimilar developer Cinfa Biotech bears witness to the enthusiasm for the European biosimilar market (see p5).

October 16 was a particularly noteworthy watershed moment for the EU market, as it marked the date at which the first biosimilar versions of AbbVie's *Humira* (adalimumab) were permitted to launch there (see p4). It's the third anti-TNF blockbuster to fall to the copycats, after *Remicade* (infliximab) and *Enbrel* (etanercept), but it's the biggest prize of all. Global Humira sales, at $18.9bn in 2017 including those booked by Eisai in Japan, are more than double those of of Remicade ($7.2bn) and Enbrel ($7.9bn). With four heavyweight entrants now ready to hit the ground running with biosimilar adalimumab, this is a key moment of truth for AbbVie. Will it really be able to limit ex-US erosion to 20%?

Scrip

LEADERSHIP
Phil Jarvis, Mike Ward, Karen Coleman

SUBSCRIPTIONS
Dan Simmons, Ewan Ritchie, Shinbo Hidenaga

ADVERTISING
Christopher Keeling

DESIGN SUPERVISOR
Gayle Rembold Furbert

DESIGN
Paul Wilkinson

EDITORIAL OFFICE
Christchurch Court
10-15 Newgate Street
London, EC1A 7AZ

CUSTOMER SERVICES
US Toll-Free: +1 888 670 8900
US Toll: +1 908 547 2200
UK & Europe: +44 (20) 337 73737
Australia: +61 2 8705 6907
Japan: +81 3 6273 4260
Email: clientservices@pharma.informa.com

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christopher.keeling@informa.com

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Celgene's Positive Phase III Data For Otezla In Scalp Psoriasis Could Yield Broader Label
https://bit.ly/2NNyjHE
Celgene estimates 80% of moderate-to-severe plaque psoriasis patients experience the disease in their scalps, meaning positive data in this indication could broaden the market opportunity for Otezla substantially. Novartis' Cosentyx got scalp psoriasis added to its US label in February.

Hemophilia Seen As Good Testing Ground For Commercializing Gene Therapy
https://bit.ly/2NMvwye
With a well characterized genetic driver, a clear marker to show whether it's working, and available treatments that carry high annual costs, hemophilia may be a good testing ground for commercializing gene therapy, but payers still have to work out how to reimburse the one-time medicines.

Gotham Therapeutics Raises $54M Series A To Target RNA-Modifying Proteins
https://bit.ly/2AeepCa
Versant Ventures seed company Gotham Therapeutics emerges from stealth mode to develop novel class of drugs targeting RNA-modifying proteins with backing from co-leads Versant, Forbion and SR One.

Can Lilly's Olumiant Prickle Xeljanz In India?
https://bit.ly/2RWdrRS
Lilly's Olumiant has hit the Indian market, upping the level of competition in a rheumatoid arthritis sector that already includes the fellow JAK inhibitor Xeljanz from Pfizer and at least half a dozen biosimilar versions of Humira, among other products. But could pricing cloud Olumiant's uptake?

Finance Watch: VC Tally Hits $14.5bn For 2018, Beating 2017 With A Quarter Left To Go
https://bit.ly/2RYmz8i
US VC investment in biopharma totaled $14.5bn in the first three quarters of 2018, exceeding the full-year 2017 sum of $11.9bn. UK biotech cash also is rising, benefitting new companies like Sitryx.

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Remicade (infliximab) to launch in July 2017, behind **Pfizer Inc.**'s *Inflectra* (infliximab-dyyb).

Renflexis launched at a discount to the list prices of both other infliximabs but failed to gain traction in the market. Branded Remicade has maintained a 94% share of the infliximab market two years after the first biosimilar launch, largely because of J&J's successful defensive contracting strategy. *(Also see "Exclusive Remicade Contracts Are Slowing Biosimilar Uptake" - Scrip, 1 Aug, 2017.)* Merck hasn't broken out sales of Renflexis, a sign the drug is not material to the top-line.

'Both Merck and Samsung Bioepsis remain committed to other biosimilar assets in oncology and immunology.'

Nevertheless, Merck and partner Samsung Bioepis did get a recent commercial victory when the Department of Veterans Affairs picked Renflexis as its preferred infliximab.

POSITIVE FOR LILLY

The insulin glargine decision aside, Merck said it remains committed to biosimilars. "This decision does not affect the other biosimilar assets currently in development with Samsung Bioepsis," Merck said. "Both Merck and Samsung Bioepsis remain committed to other biosimilar assets in oncology and immunology."

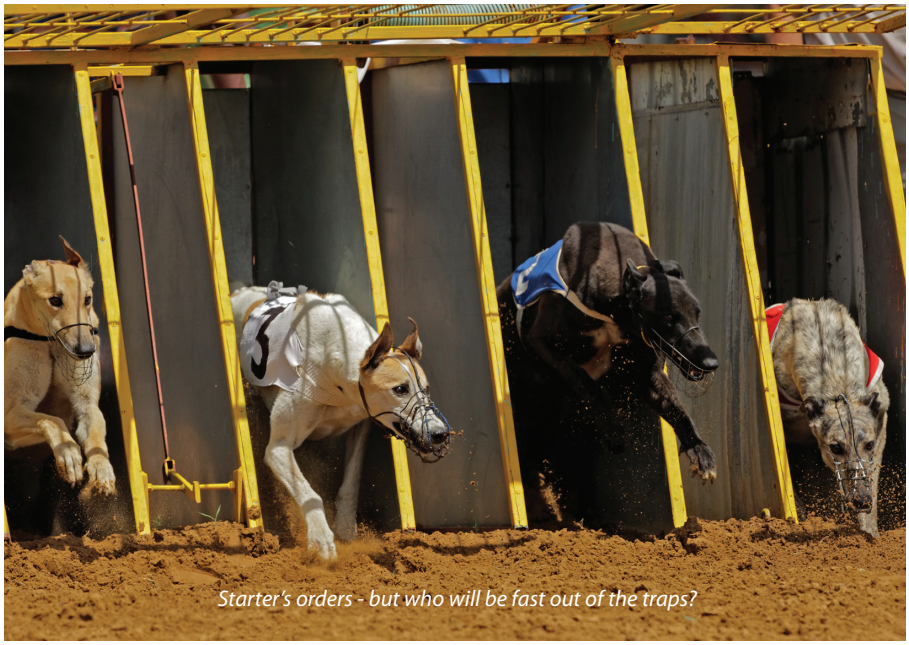
Lilly and partner **Boehringer Ingelheim GMBH** have had more success with Basaglar, which launched in late 2016 and has been a strong contributor to revenue. Basaglar generated $368.8m in the first half of 2018.

News that Merck will not now enter the market is a positive for Lilly and other biosimilar developers working on insulin glargine formulations. **Mylan NV** is one. The company's version of insulin glargine was hit by an FDA complete response letter earlier this year, but the timeline for launching is uncertain in any event due to patent issues.

Published online 11 October 2018

Sandoz And AbbVie Humira Settlement: What Does It Mean?

ELEANOR MALONE & KEVIN GROGAN



Starter's orders - but who will be fast out of the traps?

Sandoz International GMBH has settled all patent litigation with **AbbVie Inc.** over its biosimilar version of the latter's *Humira* (adalimumab), the world's best-selling medicine. The agreement will see Sandoz paying royalties and launching *Hyrimoz,* its biosimilar of the TNF inhibitor, in Europe this year and in the US in September 2023. Sandoz's deal comes after three other companies have already signed similar agreements with AbbVie.

The deal gives Sandoz a non-exclusive licence to AbbVie's Humira IP from Oct. 16 in most EU countries and other non-specified dates in other countries. The US license period begins on Sept. 30, 2023.

The US is by far the largest market for Humira: in 2017, sales of the product were $12.4bn in the US, with the five major European countries (Germany, France, the UK, Italy and Spain) generating around $4.1bn between them, as estimated by Datamonitor Healthcare. Total global sales of the product were $18.9bn.

AbbVie's CEO Rick Gonzalez has previously said that ex-US sales of Humira will fall by no more than 20% by the end of 2019. Even if this proves true, it seems unlikely that the European Humira franchise will be able to fend off the competition so effectively in subsequent years: sales of **Johnson & Johnson**'s and **Merck & Co. Inc.**'s rival branded anti-TNF drug *Remicade* (infliximab) have fallen by nearly 70%. Humira faces even more competitors, not to mention better prepared European payers increasingly determined to increase uptake of cheaper alternatives. Datamonitor Healthcare has previously forecast that adalimumab biosimilars in the EU will have a 1% negative impact on Humira sales in 2018, rising to 19% in 2019 and 36% in 2020. It expects 5EU sales of Humira to total $4.96bn in 2018, falling to $4.04bn in 2019 and $3.16bn in 2020.

In the US, Datamonitor Healthcare forecasts Humira sales to peak at $15.28bn in 2022 before falling back to $13.90bn in 2023 and $12.93bn in 2024. With the patent settlement deals being signed by AbbVie safeguarding a very large market for such a long period, there is the possibility that they will come under close scrutiny from US regulators. Biologic originator and biosimilar firms are required to report such agreements to the Federal Trade Commission and the Department of Justice. *(Also see "Biosimilar Patent Settlements: What Terms May Spur Antitrust Actions? " - Pink Sheet, 7 Oct, 2018.)*

PRIOR DEALS

In September 2017, **Amgen Inc.** and AbbVie reached a global settlement over *Amgevita/Amjevita* (adalimumab) under which Amgen said it would launch in Europe on Oct. 16, 2018, and in the US on Jan. 31, 2023.

In April 2018, **Samsung Bioepis Co. Ltd.** and AbbVie also reached a deal which would enable its partner **Biogen** to launch its biosimilar Humira, *Imraldi*, in the EU from Oct. 16, 2018 and from June 30, 2023 in the US.

The third Humira settlement deal was announced in July 2018, by AbbVie and **Mylan NV**, which gains a US license from July 31, 2018 for its product, *Hulio*. However, the deal did not cover Europe. Nevertheless, Mylan told *Scrip* it intended "to begin launching Hulio across various markets in Europe after Oct. 16," which is when a key Humira supplementary protection certificate expires. However, it did not specify precisely when and where it will launch Hulio, which is partnered with **Fujifilm** and won European approval in September 2018.

EU LAUNCH TIMINGS NOT CLEAR

Sandoz's biosimilar is one of five to have won approval from the European Commission, but the launch of the biosimilar adalimumab market in Europe will not necessarily start with five competitors on Oct. 16.

Boehringer Ingelheim GMBH, for example, which gained approval for *Cyltezo* in 2017, told *Scrip* that it would not launch its product in Europe and was concentrating on its US launch plans. The company is in talks with AbbVie, but has not reached a settlement deal. Like Mylan, Samsung Bioepis has said it would launch "after" Oct. 16, rather than "on" Oct. 16, although it seems unlikely it would delay. Amgen on the other hand said it would "launch in markets across Europe beginning on Oct. 16, 2018." It said Amgevita would be sold in all 28 EU countries plus Norway, Iceland and Liechtenstein. Amgen would not comment on pricing but said the price would vary from country to country.

SANDOZ LAUNCH BY YEAR END

When asked by *Scrip* as to whether it was ready to launch Hyrimoz on Oct. 16 and if so in which European markets, Sandoz gave nothing away, limiting itself to saying that the resolution of the AbbVie litigation paves the way for 2018 launches in key European markets. Stefan Hendriks, its global head of biopharmaceuticals, said in a statement that "in order to realize the promise of early and expanded access and healthcare savings, biosimilars must be available as soon as possible to the patients and physicians who need them. This settlement helps remove uncertainty."

Something in Sandoz' favor when it comes to the battle for Humira market is that it has a strong track record in launching biosimilars. The firm got approval in May for *Zessly*, its version of Remicade, making it the third Sandoz biosimilar to be approved in the EU in the last 12 months, and the company believes that its experience and capabilities in development, manufacturing and commercialization leaves it well-positioned to lead the biosimilars industry.

Sandoz, which is headquartered in Holzkirchen, in the Greater Munich area, derives most of its revenues in Europe. In Q2 2018, total net sales were $2.5bn and $1.2bn of that came from Europe, driven by biosimilars mainly in Germany, Italy and the UK, with the best performers being *Rixathon* (rituximab) and *Erelzi* (etanercept), biosimilars of Roche's *MabThera* and Amgen's *Enbrel* respectively, which were only launched in the second half of 2017.

Growth at Sandoz' European operations has helped offset the problems its US operations has endured of late due to price erosion. Novartis is currently finalizing the sale of its generic oral solids portfolio and the Sandoz US dermatology business to **Aurobindo Pharma Ltd.**, in a deal potentially worth $1bn, which will allow the unit to concentrate on biosimilars, value-added medicines and complex generics. *(Also see "Novartis Blows Storm Clouds Off Sandoz US In Aurobindo Sale" - Scrip, 6 Sep, 2018.)*

Published online 15 October 2018

Mundipharma Satisfies Appetite For Piece Of $4.5bn Pegfilgrastim Pie With Cinfa Biotech Buy

JO SHORTHOUSE joanne.shorthouse@informa.com

UK-based **Mundipharma International Corp. Ltd.** has added to its biosimilar basket with the acquisition of Cinfa Biotech, and with it, immediate access to revenues from the recently-approved *Pelmeg*, a biosimilar to **Amgen Inc.**'s neutropenia therapy *Neulasta* (pegfilgrastim).

While the terms of the deal were undisclosed, Mundipharma estimates the global market for Pelmeg to be up to $4.5bn, with non-US market potential of $603m.

With the EMA's drug evaluation committee, the CHMP, recommending the biosimilar less than a month ago, on Sept. 18, Mundipharma could be seen to have taken a gamble when pursuing a company whose biosimilar was not yet approved.

However, the company was suitably impressed to go ahead regardless, Warren Cook, Mundipharma's Senior Commercial Lead for Biosimilars, told *Scrip*. "There is never 100% certainty when partnering or acquiring businesses whose assets are not yet authorized by the regulatory authorities. However, we were impressed by Cinfa Biotech's robust development process and regulatory planning," he said.

"In fact, we believe Cinfa Biotech is one of the first biosimilar development companies to develop a pegfilgrastim in line with the latest CHMP guidance for development of similar biological products containing recombinant G-CSF," he continued.

Mundipharma will now work with Cinfa Biotech to ensure that post-EC approval, it brings Pelmeg to market "as quickly as feasibly possible," Cook said.

Mundipharma already owns **Napp Pharmaceutical Group Ltd.**, which distributes the **Celltrion Inc.**-manufactured *Remsima*

and *Truxima*, biosimilars of infliximab and rituximab, respectively. However, this acquisition looks to be a step forward for Mundipharma's biosimilar strategy, with the acquisition bringing in a new opportunity to develop future biosimilars, not just distribute and market existing treatments.

A Mundipharma spokesperson confirmed to *Scrip* that the company's strategy "has always been to grow and deepen our biosimilars capabilities" but that "absolutely the acquisition gives us development capabilities now beyond distribution and marketing."

There are five pegfilgrastim biosimilars approved in the EU. In addition to Cinfa's Pelmeg there are **Mylan NV**'s *Fulphila*, **Sandoz International GMBH**'s *Ziextenzo*, **Accord Healthcare Ltd.**'s *Pelgraz* and **Coherus BioSciences Inc.**'s *Udenyca*. *(Also see "EU First For Pegfilgrastim Biosimilars? EMA Decides This Week" - Pink Sheet, 24 Jul, 2018.)*

Mundipharma has bought Cinfa Biotech from Infarco. Enrique Ordieres, CEO of that parent company, said that Mundipharma was "best placed" to take Pelmeg forward because of the company's "proven track record of launching biosimilars in Europe, have built strong partnerships with payers, hospital specialists and decision makers and have the deep local understanding of complex tender environments."


Philippe Bastide

Talking to *Scrip* in 2017, Cinfa Biotech Managing Director Ruediger Jankowsky disclosed that the company was also working on a biosimilar in the autoimmune space but would not be drawn on the originator biologic.

NEW RECRUIT

In related news, Philippe Bastide has joined Mundipharma as Head of Biosimilars, reporting to Chris Surridge, European Director of Strategy and Commercial Excellence. Bastide has five years of biosimilar experience with both Amgen and **Shire PLC** in both European and global commercial roles. Philippe started the Amgen European Biosimilars organization, then led the overall **Baxalta Inc.** Biosimilars Unit. *Published online 10 October 2018*

US Drug Pricing Challenges Poised To Impact Pharma Growth, Leerink Warns

JESSICA MERRILL jessica.merrill@informa.com

An analysis of drug pricing trends in the US by Leerink suggests the pharmaceutical industry could be poised to hit a period of slower growth if the current pushback on drug pricing continues longer term. The analysis, led by analyst Geoffrey Porges and released Oct. 8, determined that net price increases have contributed a significant 61% to revenue growth of 28% for the 45 largest pharmaceutical products sold in the US over the past three years.

Industry's long-standing practice of taking double-digit price hikes on marketed drugs has been curtailed recently, as some drug makers have pledged to minimize price hikes amid public backlash. Some companies like **Pfizer Inc.** and **Novartis AG** have vowed to stop price increases altogether for a period of time, as criticism from President Trump and his administration has mounted.

Big list price increases have been used partly to offset the rebates and discounts drug makers pay to third parties, so the net price increases are significantly smaller. If the trend continues for an extended period, drug companies will feel the impact on the top-line. Certain products, for which growth has been more heavily driven by price, and the manufacturers that have relied on price for growth will be more significantly impacted than others.

"We believe investors should be anticipating that growth rates for these products will decline significantly, and the companies selling them are likely to slow accordingly," Porges said. "The most significant effect is likely to be for products in which the US market contributes the majority of sales, and in which price has significantly boosted revenue growth or meaningfully offset eroding volume in recent years."

MATURE BLOCKBUSTER POISED FOR A HIT

Some of the products Leerink expects to be most heavily impacted are **AbbVie Inc.**'s *Humira* (adalimumab), **Amgen Inc.**'s *Neulasta* (pegfilgrastim) and *Enbrel* (etanercept), and **Pfizer Inc.**'s *Lyrica* (pregabalin). The least affected products, where price has been flat or down and the product is growing based on underlying demand, are **Alexion Pharmaceuticals Inc.**'s *Soliris* (eculizumab), **Regeneron Pharmaceuticals Inc.**'s *Eylea* (aflibercept) and **Merck & Co. Inc.**'s *Keytruda* (pembrolizumab) and *Gardasil* (human papillomavirus 9-valent vaccine).

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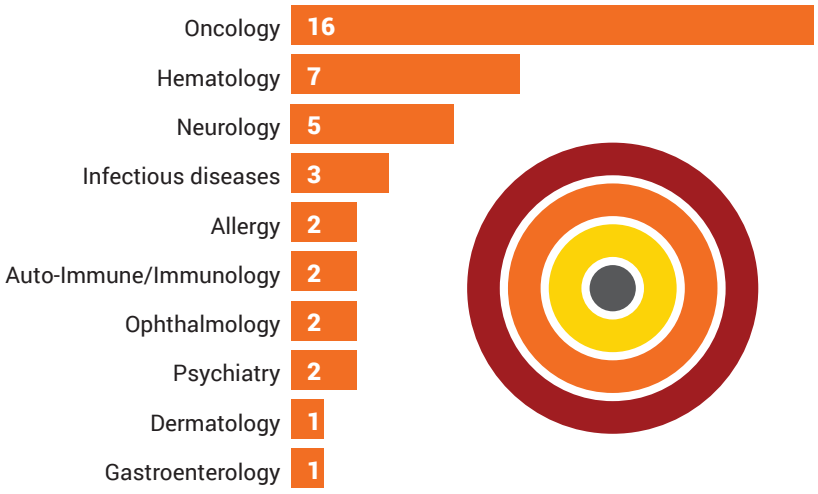
WINNERS IN 2019 DRUG LAUNCHES

Key late-stage drugs that could reach their first markets during 2019, including first-in-class products, medicines likely to become new standards of care, and products introduced for major new indications.

41

The number of key new products, or major new indications for marketed drugs, that could be launched in 2019.

THERAPEUTIC AREAS BENEFITTING FROM NEW DRUGS IN 2019:



2019 DISEASE WINNERS

Triple Negative Breast Cancer	Immunomedic's sacituzumab govitecan, Tecentriq and Keytruda could gain additional approvals
Sickle Cell Anemia	Pfizer's rivipansel and Novartis' crizanlizumab
Porphyria	Alnylam's RNAi therapeutic, givosiran
Cancer	Two CAR-T therapies, Celgene's lisocabtagene maraleucel and bluebird bio's BB2121
Thrombotic Thrombocytopenic Purpura	Johnson & Johnson's caplacizumab

NOVARTIS HAS DOUBLE THE KEY LAUNCHES OF OTHER FIRMS:

CONTINUED FROM PAGE 6

Regeneron's management has made a big talking point out of the fact that it has never raised the price of Eylea – the company's big seller – since it launched in 2011. CEO Leonard Schleifer has also been an outspoken critic of industry's practice of relying on price increases for growth.

The Leerink analysis looked at the top 45 pharmaceutical products, based on US revenues from 2014-2017. The analysts then compared changes in list price for the key products against change in product volume to determine the impact of price on growth. The analysis is flawed, Porges pointed out, because it relies on incomplete audit data for volume for many products and has limitations. Nevertheless, he said the estimates are informative for determining how dependent products or manufactures are on price for growth.

The 45 products selected for the analysis contributed $84bn in US revenue in 2014 and grew 28% to $107bn in 2017. US revenue from the group contributed 38% of US reported revenue for the group of companies in 2014, and 40% in 2017, which was 18% of global revenue for the group of companies that sell the drugs in 2014 and 22% in 2017. Drugs included in the analysis are from AbbVie, Amgen, **Celgene Corp.** Merck, **Eli Lilly & Co.**y, **Johnson & Johnson**, **Novartis AG**, Pfizer, **Biogen Inc.** Alexion, **Gilead Sciences Inc.**, **Roche**, **Sanofi**, **GlaxoSmithKline PLC** and Regeneron.

Price contributed 61%, or $14.3bn, to the $23.2bn growth in the US for these large products in aggregate over the time period, and 48% of the $29.5bn in total reported revenue growth for the group of companies. In some cases, net positive price in the US slowed revenue erosion for large products. The impact on price on individual products varied widely, however.

Products for which Leerink listed price as a 0% contribution to revenue had price or volume contribution to growth that was negative. If price made more than a 100% contribution to revenue, the product would have declined if it were not for price, so price accounted for all of the reported revenue growth. For some products like Gleevec (-71%), which had negative revenue growth, Leerink calculated how much positive price played a role in offsetting losses in volume.

For products like Neulasta, Enbrel, *Cialis*, Remicade and Novartis' *Tysabri*, positive price contributed 100% to US revenue growth from 2014-2017.

"In other words, without positive price all of these products would have had declining revenues during this period," Porges said. Products like Biogen's *Avonex* (interferon beta-1a), Lilly's *Alimta* (pemetrexed) and Novartis' *Gleevec* (imatinib) all had negative revenue growth over the period, where price partially offset negative volume. Other products like GSK's *Advair* (fluticasone/salmeterol), Sanofi's *Lantus* (insulin glargine) and Gilead's *Sovaldi/Epclusa/Harvoni* all had negative cumulative revenue growth, with loss of volume over three years and no material price contribution to offset the cumulative negative growth.

Leerink analysts also used the same methodology to evaluate how price impacted the most recent quarterly period compared to the contribution in the three prior years, looking at price and volume contributions for the second quarter of 2017 to second quarter 2018.

"It is clear that biopharma companies continued to benefit from positive price over the past year," Porges said. "Our estimate for the contribution of US price to the one-year US revenue growth of these products is $2bn, which was >100% of the total growth in these products over the past year from Q2 to Q2 (2017-2018)."

US sales of these products grew by 2% from Q2 2017 to Q2 2017, and price contributed 7%, or more than 100%, of the total reported growth.

Many drug makers became more proactive about reigning in drug price increases in July after Pfizer found itself targeted by Trump on Twitter.

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We Haven't Ruled Out Drug Price Increases, Says Regeneron's Schleifer

JO SHORTHOUSE joanne.shorthouse@informa.com

Regeneron Pharmaceuticals Inc. CEO Leonard Schleifer has been a vocal critic of the pharma industry when it comes to drug pricing, but in an interview with *Scrip* he talked about his current thinking on US drug pricing and why some price increases make sense while others do not.

"We haven't ruled out price increases. We have just ruled out price increases as a strategy for growth," he explained.

Schleifer has been openly critical of what was for many years a standard practice in the industry to raise drug prices every year by double-digits, a practice many in the industry have now started to rein in under pressure from the Trump administration and public push-back. He has argued in various public venues that industry has relied on price increases to cover gaps in innovation.

Now, he has clarified his thinking on the subject.

"Appropriate increases which match inflation when your costs are really going up, I'm not opposed or against that. I am just opposed to price increases as a growth strategy, where you raise your prices 15% or 20%. Then, you don't have to do anything except buy more products and keep doing that, and pretend that you are a research-based enterprise. That is what I object to," he told *Scrip*.

Regeneron often points to its blockbuster eye drug *Eylea* (aflibercept) as an example. The company has not raised the wholesale acquisition cost of Eylea since the drug launched in the US in 2011.

"We haven't seen a need to raise the price of Eylea. It doesn't mean we wouldn't at some point, some moderate increase if we thought it was appropriate and the market could deal with it," he explained. Eylea accounts for the majority of Regeneron's sales, generating $992m in the US in the second quarter. The drug is partnered with **Bayer AG** outside the US.

But while Regeneron hasn't increased the WAC of Eylea since launch, the company did increase the price of the atopic dermatitis drug *Dupixent* (dupilumab) this year by about 3%. Dupixent

is partnered with **Sanofi** in the US, and is pending for approval at FDA for severe asthma.

Schleifer echoed and referenced comments made by **Merck & Co. Inc.**'s CEO Ken Frazier last week at the Economic Club of New York, where Frazier took aim at the "middle men" involved in US drug pricing. "I don't understand where we live in a world where 50% of the value goes to the supply chain," Frazier said. He followed these comments by saying he expected to see "disintermediation," reducing the number of companies between product and consumer in the pharma industry.

> 'If people think they can make more money with solar panels than drugs they are going to invest in solar panels, it's just that simple.'

"There might be some rationalization in the industry where these middle men won't be taking such a big cut because we believe, as most rational people in the industry believe, there has to be adequate rewards, because capital is agnostic, it's a capital-intensive business," Schleifer said. "If people think they can make more money with solar panels than drugs they are going to invest in solar panels, it's just that simple. Because capital truly is agnostic and we want to make sure that capital flows to the industry.

"We want people to get fair rewards, we want there to be an innovation premium and so forth. We are just against taking advantage of patients, we are against egregious price increases and we are against the system that takes too much of each healthcare dollar and puts it somewhere in the middle, so the true innovators are not getting as much of a reward as they might, and that the patients are paying more than they should," he explained to *Scrip*.

Regeneron's present drug pricing challenge is reimbursement and market access for *Praluent* (alirocumab) and Dupixent. The company experienced unexpectedly high payer push-back for both drugs.

Dupixent is expected to be a big blockbuster, but initial sales have underwhelmed investors. Dupixent generated $209m in the second quarter. Datamonitor Healthcare's PharmaVitae forecasts sales of Dupixent in allergic conditions to exceed $5bn by 2023, if ongoing price negotiations are successful.

Regeneron and Sanofi took a proactive approach to pricing Dupixent, working with the Institute for Clinical and Economic Review (ICER) to determine the appropriate value. The WAC of $37,000 a year was less than some investors had anticipated, but the companies hoped to secure faster market access in return. The companies took a similar approach by lowering the price of Praluent in line with ICER's recommendations after new cardiovascular outcomes data became available. *(Also see "Praluent Pricing: Collaboration With ICER Sets A New Standard" - The Pink Sheet, 12 Mar, 2018.)*

It remains to be seen if the decision to collaborate with ICER will pay off. The next big decision will be Dupixent for asthma. ICER is currently reviewing five biologic asthma treatments for asthma and concluded in a draft report released in September that the products are overpriced and should be discounted by 50-68%.

OUTBID BIG PHARMA? "NOT OUR STYLE"

Schleifer also talked about M&A. The big biotech typically develops molecules in house and is focusing increasingly on its early genetics research to drive drug development. But as Eylea matures and Praluent and Dupixent have faced slower than expected launches, investors are getting more anxious about the company's mid-term growth outlook.

"We do our own discoveries of technologies and drugs but when we have expertise which are leverage-able and partner-able we have certainly been invested in trying to make those kinds of deals. Going out and trying to outbid Novartis or Pfizer for some drug and company is not our style."

The company has a long-standing R&D partnership with Sanofi, with which it worked on its latest approved treatment, the PD-1 inhibitor *Libtayo* (cemiplimab-rwlc) for cutaneous squamous cell carcinoma (CSCC). *(Also see "Sanofi/Regeneron's IO Springboard Libtayo Cleared For Skin Cancer " - Scrip, 28 Sep, 2018.)* Other drugs to be born out of the Sanofi partnership include Praluent, Dupixent and *Kevzara* (sarilumab). But that long-term partnership has wound down, outside of ongoing work in oncology.

Regeneron's most recent partnership is with **bluebird bio Inc.**. Regeneron will make a $100m equity investment in bluebird to collaborate on the discovery of antibodies and T cell receptors, with the hope of building out in immuno-oncology and overcoming some of the early cell therapy challenges. *(Also see "Regeneron And Bluebird Team Up In Cell Therapy "Joint Venture"-Style Deal " - Scrip, 6 Aug, 2018.)*

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The full interview with Len Schleifer and CSO George Yancopoulos can be seen in the upcoming Outlook issue of IN VIVO and Scrip.

China Vs. Cancer: Coverage For 17 Drugs Unveils Price Pressures, Commercial Battleground

BRIAN YANG brian.yang@informa.com

A new decision in China to grant reimbursement to 17 cancer drugs has been welcomed with open arms, although the move appears to be accompanied by rising official price pressures, and observers say the step is the just the first in ensuring commercial success.

Novartis AG, **Pfizer Inc.**, **Roche**, **Johnson & Johnson**, **AstraZeneca PLC**, **Takeda Pharmaceutical Co. Ltd.**, **Celgene Corp./ BeiGene Ltd.** are among the companies to have products included in the new listing.

Of the 17 oncology products to be newly covered by China's Medical Insurance Administration and listed in the National Reimbursement Drug List (NRDL), 12 are for solid tumors and five for various blood cancers. 10 new oncology drugs have been granted marketing approval since 2017, highlighting China's growing desire to introduce newer therapies, especially anticancers, to the market.

Novartis scored the most new coverage, with four of its drugs listed by the insurance agency: *Tasinga* (nilotinib), *Votrient* (pazopanib), *Zykadia* (ceritinib), and *Sandostatin LAR* (octreotide acetate microspheres for injection). The Swiss drug maker was followed by Pfizer, which had three of its oncology drugs obtaining reimbursement coverage: *Xalkori* (crizotinib), *Sutent* (sunitinib), and *Inlyta* (axitinib).

By comparison, Roche had only one product, *Zelboraf* (vemurafenib), newly listed in the NRDL this time, although the Swiss group has previously had four drugs put on the list, including *Herceptin* (trastuzumab), *Avastin* (bevacizumab) and *Tarceva* (erlotinib).

Other notable drugs included this time were AstraZeneca's *Tagrisso* (osimertinib), **Merck Serono SA**'s *Erbitux* (cetuximab), Takeda's *Velcade* (bortezomib), and J&J's *Imbruvica* (ibrutinib).

Apparently heeding repeated calls from the Chinese government to lower the prices of some life-saving cancer drugs, manufacturers' executives see the new reimbursement coverage as aiding the government's goal to have its citizens obtain real gains in terms of access to new products.

"With its patient-centered goal, Novartis actively heeds the call to work with the [Chinese] government to lower the disease burden of patients. Through the price negotiations and inclusion of the four drugs, we are helping the patients who are in need and provide access to more people, so they have feelings of real gains," Didier Dargent, head of Novartis Oncology China, said in a statement.

Two of the four newly listed Novartis drugs have been approved in China since 2017, and Zykadia gained a local approval just in May. The speedy medical insurance coverage, in this case shortened from nine years previously for some products to only five months, reflects Novartis's intention to expand patient access early on, and also underscores the government's desire to include more new therapies in insurance schemes as long as makers are willing participate in related price negotiations.

PRICE PRESSURE EVIDENT

The most recent reimbursement decisions were based on price negotiations with manufacturers, and the average price cut for the 17 newly listed drugs was 56.7%, with the deepest cut being for Beigene/Celgene's *Vidaza* (azacitidine), of 59.8%.

Compared to previous cancer drug price negotiations related to inclusion in the NRDL, the reduction range this time is slightly greater. For instance, in the first national price negotiation round, initiated in 2016, only two anticancers were affected, with AstraZeneca's *Iressa* (gefitinib) and **Betta Pharmaceuticals Co. Ltd.**'s *Conmana* (icotinib), whose prices were cut by 55% and 54%, respectively.

Roche later voluntarily reduced the price of its targeted therapy Tarceva in China.

Compared to two years ago, however, cancer drug makers now face a much different environment in China. Since the Communist Party's 19th Party Congress in 2017, when the government outlined its goal to meet increasing public demand for better lives, the pressure on manufacturers to lower the cost of life-saving therapies has been mounting.

To that end, the government has not only set up a new separate agency, the Medical Insurance and Support Agency (MISA), to speed up the reimbursement of high-priced drugs, but China Premier Li Keqiang has also been vocal about the lowering of cancer drug prices, even making this point during a past visit to Roche China in Shanghai.

"The pressure is certainly evident, especially for a cancer drug that has been approved recently and is still under patent protection in China; the pressure of lowering the price is frankly quite large," noted Yang Ruibo, a representative of companies that participated in the latest round of negotiations, quoted by China's state-run Xinhua news.

In the meantime, the government in parallel has been accelerating new drug approvals to more quickly bring novel products into China. Some notable new treatments include immuno-oncology therapies **Bristol-Myers Squibb Co.**'s *Opdivo* (nivolumab) and **Merck & Co. Inc.**'s *Keytruda* (pembrolizumab).

For the companies affected by the new listing however, reimbursement is just the beginning in China, where many see a need to further drive commercial activities by building specialized teams, commercial networks and shoring up physician education programs via online and offline tools.

While the reimbursement decision replaces a bidding process, the cancer drugs need to be included in provincial reimbursement lists issued by local health authorities. To get them into hospitals, makers must persuade hospital authorities to incorporate the products into hospital drug reimbursement lists so physicians can actually start writing prescriptions.

To that end, MISA has requested provincial authorities to strictly follow the NRDL and not to make adjustment to the prices, which are valid for three years until the end of November 2020. By the end of this October, all of the 17 newly-listed cancer drugs should be ready on the provincial platforms.

Considering this top-down approach, it is crucial for companies to build strong marketing and sales teams to actively roll out physician and patient education initiatives.

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From the editors of PharmAsia News.

Key Cancer Data To Be Unveiled At ESMO In Munich

KEVIN GROGAN kevin.grogan@informa.com

Europe's leading cancer meeting kicks off in Munich next week (Oct.19-23) and while smaller than its US counterpart ASCO, the big pharma players – and indeed the smaller ones – are increasingly using the ESMO congress to present data from major studies.

This year's meeting will see meat being put on the bones of some trials where impressive topline results have already been revealed. Chief among those will be the JAVELIN Renal 101 study of a combination of Merck KGaA and **Pfizer Inc.**'s PD-L1 inhibitor *Bavencio* (avelumab) and the latter's tyrosine kinase inhibitor *Inlyta* (axitinib) for first-line advanced kidney cancer versus Pfizer's older TKI *Sutent* (sunitinib).

Last month, the partners revealed the Bavencio arm demonstrated statistically significant better progression-free survival (PFS) than Sutent alone in previously untreated advanced renal cell carcinoma (RCC) and attendees at ESMO will be looking closely for the magnitude of that benefit. Analysts at Biomedtracker noted that the data may allow the Bavencio/Inlyta combination to quickly gain US approval in the first-line setting, "an area projected to soon become crowded with novel immunotherapy combinations," adding that it seems as though JAVELIN Renal 101 study was designed so that it could statistically support approval in either the overall population or the PD-L1+ population.

In April 2018, **Bristol-Myers Squibb Co.**'s double immuno-oncology combo of *Opdivo* (nivolumab) and *Yervoy* (ipilimumab) was approved for front-line metastatic disease, regardless of PD-L1 status. The Biomedtracker team stated that numerical data from JAVELIN Renal 101 will need to prove to be stronger than competing regimens in order for Bavencio/Inlyta to secure significant market share in this setting and uptake will be crucial for Pfizer in particular to maintain its strong position in the RCC market built through Sutent and Inlyta.

Oncology behemoth **Roche** will have a strong presence at ESMO, with the highlight being full results from its IMpassion130 study investigating *Tecentriq* (atezolizumab) plus **Celgene Corp.**'s chemotherapy *Abraxane* (nab-paclitaxel). The Swiss major announced in July that the trial was the first

Which companies will be celebrating at ESMO in Munich?

positive Phase III immunotherapy study in triple negative breast cancer (TNBC), meeting its co-primary endpoint of PFS. *(Also see "Roche's IMpassion130 Is First Positive Phase III Immunotherapy Study In Triple Negative Breast Cancer" - Scrip, 2 Jul, 2018.)*

The results will likely lead to Tecentriq being the first checkpoint inhibitor approved for breast cancer, according to Biomedtracker analysts who noted that this is "an indication where Roche has considerable expertise. Checkpoint inhibitors have focused on TNBC, they note, which accounts for 10-20% of breast cancers and is a particularly hard-to-treat form of the disease.

Another company with a strong presence at ESMO – with 54 abstracts – is **AstraZeneca PLC** and there will be a lot of interest in the full data set from the Phase III SOLO-1 trial of *Lynparza* (olaparib). Topline results from the trial disclosed in July revealed Lynparza, which is now partnered with **Merck & Co. Inc.**, to be the only PARP inhibitor to show a PFS benefit in first-line maintenance treatment of BRCA1/2-mutated ovarian cancer.

The Biomedtracker team believes that the positive readout is evidence of AstraZeneca and Merck's strong development strategy for Lynparza in ovarian cancer "and will likely move it earlier in the treatment paradigm, placing it ahead of competing PARPs - **Tesaro Inc.**'s *Zejula* (niraparib) and **Clovis Oncology Inc.**'s *Rubraca* (rucaparib)." They add that this possible label expansion, albeit limited to BRCAm patients, will increase Lynparza's available patient population and AstraZeneca has estimated that around 65,000 patients in the top eight markets alone could benefit.

Elsewhere, as is the norm at oncology meetings nowadays, Merck will be presenting more data on its checkpoint inhibitor *Keytruda* (pembrolizumab). Attendees will be keeping an eye on the first presentation of overall survival data from the Phase III KEYNOTE-048 trial investigating the drug for the first-line treatment of recurrent or metastatic head and neck squamous cell carcinoma.

Also of note will be first-time findings from the Phase II KEYNOTE-057 trial evaluating Keytruda monotherapy for advanced non-muscle invasive bladder cancer. There will also be the first presentation of Phase I for MK-1454, Merck's investigational stimulator of interferon genes (STING) agonist, as monotherapy and in combination with Keytruda, for the treatment of patients with advanced solid tumors or lymphoma.

Other studies of note include the full data set from **Novartis AG**'s Phase III SOLAR-1 trial of the PI3K inhibitor alpelisib which in combination with the estrogen receptor modulator fulvestrant has shown an improvement in PFS in patients with PIK3CA-mutated HR+/HER2- breast cancer. **Bayer AG** and partner **Loxo Oncology Inc.** will be providing updates on larotrectinib, their tropomyosin receptor kinase inhibitor for patients with locally advanced or metastatic solid tumors with a neurotrophic tyrosine receptor kinase gene fusion is currently under review by regulators on both sides of the Atlantic. *(Also see "Novartis' SOLAR-1 Study Shines on Alpelisib In Breast Cancer" - Scrip, 23 Aug, 2018.) (Also see "Bayer Files Larotrectinib In EU As LOXO-292 Hurtles Towards The Market" - Scrip, 29 Aug, 2018.)*

The ESMO organizing committee has also highlighted a number of areas that the congress will address. These include whether immunotherapy is safe for HIV patients with cancer, do women and men experience the same side effects from chemotherapy, are adolescents and young adults fairly represented in clinical trials and is Twitter a reliable source for cancer patients?

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There will be much more at the meeting – some 2,051 abstracts will be presented. Kevin Grogan will be attending ESMO for Scrip, follow him on Twitter at @kevinatgrogan

Bristol's Checkmate-331 Failure Not Likely To Endanger SCLC Labeling For Opdivo

JOSEPH HAAS joseph.haas@informa.com

The failure of **Bristol-Myers Squibb Co.**'s *Opdivo* to meet an overall survival endpoint compared to standard-of-care chemotherapy in a Phase III confirmatory trial in small-cell lung cancer is a disappointment, but several analysts predict that due to a lack of treatment options for patients, the PD-1 inhibitor will keep the third-line SCLC indication obtained less than two months ago.

Bristol reported top-line findings from the open-label Checkmate-331 study Oct. 12, showing Opdivo (nivolumab) failed to meet a primary endpoint of OS compared to SOC – either topotecan or amrubicin, where the latter is approved. Opdivo obtained accelerated approval in mid-August to treat metastatic SCLC in patients who have progressed after chemotherapy and at least one other therapeutic regimen, which was the first new SCLC approval in roughly 20 years.

SCLC is a relatively small indication compared to the much larger market opportunity in non-small cell lung cancer; SCLC accounts for about 15% of lung cancer patients, while NSCLC comprises roughly 85%. Bristol's early advantage in this space already was threatened by **Roche**'s recent Phase III success with its anti-PD-L1 *Tecentriq* (atezolizumab). The Swiss pharma has filed for a label expansion into SCLC with the US FDA.

Roche's IMpower133 study randomized 403 patients with extensive-stage SCLC – about two-thirds of the overall population – to Tecentriq or placebo. Participants received carboplatin with etoposide plus Tecentriq or placebo for 21 cycles followed by Tecentriq or placebo maintenance until the point of intolerable side effects or disease progression. The study showed a median OS of 12.3 months for Tecentriq compared to 10.3 months for placebo, a 30% reduction in risk of death, in an interim analysis.

Analysts questioned Bristol's strategy to test Opdivo monotherapy in SCLC while Roche and other competitors, such as **AstraZeneca PLC** and **Merck & Co. Inc.**, are employing combination regimens in various SCLC settings. However, they largely predicted that Opdivo would retain its SCLC labeling due to the lack of treatment alternatives in a very virulent cancer setting. SCLC patients often relapse, with a median survival of four-to-five months.

SUBGROUP ANALYSIS SUGGESTED TO PROTECT LABELING

Biomedtracker, however, took more of an outlier position on the data, saying that Opdivo's labeling for SCLC now could be at risk, and suggesting the pharma undertake subgroup analysis in a population enriched for Opdivo responders. It echoed other analysts, though, that the lack of treatment options might help keep the labeling intact and also pointed out that Bristol has another ongoing Phase III study of Opdivo in SCLC.

"A potential avenue to safeguard Opdivo's approval would be to perform a subgroup analysis in a population expected to be enriched for Opdivo responders," Biomedtracker suggested. "Indeed, in the CheckMate 032 trial that supported the accelerated approval, Opdivo showed a higher overall response rate (ORR), one-year progression-free survival (PFS), and one-year OS in patients with high tumor mutational burden (TMB). We await further company updates that will shed light on Opdivo's full approval strategy in response to this setback."

SCLC accounts for about 15% of lung cancer patients, while NSCLC comprises roughly 85%.

BMO Capital Markets analyst Alex Arfaei called the trial failure "incrementally negative" in an Oct. 12 note and questioned Bristol's logic in structuring the study. He said the outcome was not surprising due to the modest benefit Opdivo demonstrated in the Phase I/II Checkmate 032 study that supported the accelerated approval. Of 109 patients treated with Opdivo, there were 13 responses, only one of which was a complete response. The effect was not dependent on the level of PD-L1 expression.

Bristol also is investigating Opdivo in tandem with its CTLA-4 inhibitor *Yervoy* (ipilimumab) as maintenance therapy in SCLC patients who do not progress on first-line chemotherapy. Data from the Phase III Checkmate-451 study are expected during this quarter.

However, Arfaei suggested that other ongoing combination studies in SCLC may render that trial virtually meaningless even if successful. Merck and AstraZeneca both are studying combination regimens – anchored by PD-1 inhibitor *Keytruda* (pembrolizumab) and the PD-L1 inhibitor *Imfinzi* (durvalumab), respectively – in first-line SCLC that might make first-line treatment with chemotherapy obsolete, he noted. Both studies are expected to report data during the first quarter of 2019.

"The key question is whether following the first-line trials from Merck and AstraZeneca, will there be a significant portion of first-line patients that would still be treated with chemotherapy so that they would be eligible for Bristol's Opdivo + Yervoy as maintenance therapy," the analyst asked.

Regardless, Arfaei estimates that SCLC accounts for less than 5% of Opdivo's sales potential in the US. William Blair & Co. analyst Matt Phipps sees as an even smaller factor in the drug's sales – the company models $22m in US SCLC revenue for Opdivo in 2021, about 0.5% of its projected US total that year.

"While this is disappointing and unfortunate for patients, we note Opdivo and Opdivo plus Yervoy are already listed in the National Comprehensive Cancer Network (NCCN) guidelines for patients with relapsed SCLC, the recently announced success of Tecentriq plus chemotherapy in newly diagnosed patients will likely shrink IO-naïve refractory patients, and the second-line SCLC opportunity is already a relatively small patient population," Phipps wrote Oct. 12.

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Carrick Targets Ovarian Cancer With BTG Deal, Entices Celgene's Former Top Deal Maker

JO SHORTHOUSE joanne.shorthouse@informa.com

Dublin-based **Carrick Therapeutics Ltd.** has licensed exclusive worldwide rights to develop and commercialize BTG945, now known as CT900, an investigational targeted ovarian cancer drug, from **BTG PLC** for an undisclosed sum.

CT900 combines targeting folate receptor α (FRα) and inhibiting thymidylate synthase. The small-molecule compound selectively enters cancer cells that over-express folate receptor α (FRα) versus normal tissues and inhibits thymidylate synthase, leading to cell death.

Elaine Sullivan, CEO of Carrick Therapeutics, and formerly vice president for R&D functions at **Eli Lilly & Co.** and **AstraZeneca PLC** said that CT900 had "already demonstrated clinical activity in platinum-resistant/refractory high-grade serous ovarian cancer".

In addition to ovarian cancer, Carrick will be investigating CT900 in other difficult-to-treat cancers that express high levels of folate receptor α, with these patients selected via a companion diagnostic based on folate receptor α expression.

The company told *Scrip* that Carrick had no current plans to partner with big pharma on this drug, but instead would use its "highly experienced team and proven capabilities to accelerate molecules through development by utilizing our in-house capability and world-leading external network". Chair of Carrick Therapeutics' scientific advisory board is Sir John Bell, Regius Professor of Medicine at University of Oxford.

CT900 was discovered by the **Institute of Cancer Research** in London, who led its earlier development with support from Cancer Research UK and BTG.

In a Phase I study led by the ICR and The Royal Marsden NHS Foundation Trust, presented at the American Society of Clinical Oncology (ASCO) Annual Meeting in 2017, seven out of ten women with advanced ovarian cancer who had the particular molecular marker for the drug responded to treatment.

Commenting on CT900, Professor Paul Workman, CEO and president of The Institute of Cancer Research, said: "The efficacy results that we have seen so far for CT900 are very promising. The beauty of this drug is that it is targeted to the tumor cells, meaning there are fewer side effects and making it a very promising treatment for women with ovarian cancer."

There are approximately 240,000 new ovarian cancer patients per year worldwide, with 70% of patients presenting with advanced disease.

BIGGEST UNMET NEED

Treatment options for patients with platinum-resistant ovarian cancer remain limited and the prognosis for this patient group is poor, Datamonitor Healthcare said in a recent analysis of the indication.

Avastin (bevacizumab) is approved for platinum-resistant patients in the US and EU. PARP inhibitors *Lynparza* (olaparib) and *Rubraca* (rucaparib) are indicated for use in heavily pre-treated BRCA-mutated patients in the US, and are also available to platinum-resistant patients with BRCA mutations.

However, the late stage pipeline for platinum-resistant ovarian cancer, the biggest unmet need in this area, has numerous Phase III candidates. Only two of the nine candidates have same FRα target: **Eisai Co. Ltd.**'s farletuzumab, and **ImmunoGen Inc.**'s mirvetuximab soravtansine.

Of these, farletuzumab has the most clinical data but has had a bit of a tumultuous development history and is unlikely to be much of a competitor, noted Datamonitor Healthcare analyst Hardik Patel. A Phase II study of the product in platinum-resistant ovarian cancer was suspended after an interim analysis showed it was unlikely to meet PFS endpoints and a Phase III trial in platinum-sensitive patients was failed to hit its PFS endpoint, though hope remains for a patient subgroup with low CA125 biomarker levels.

Before the introduction of Avastin and PARP inhibitors, platinum-resistant ovarian cancer patients commonly received single-agent non-platinum-based chemotherapies, which are usually administered sequentially. The response rates to these single agents are low and any responses are short-lived. Single-agent non-platinum-based chemotherapies include topotecan, docetaxel, paclitaxel, gemcitabine, vinorelbine, liposomal doxorubicin, and etoposide.

There are approximately 240,000 new ovarian cancer patients per year world-

Ovarian Cancer Late Phase Pipeline

Drug	Lead Company	Target	Drug Type	Phase
Bavencio (avelumab)	Merck KGaA	PD-L1	MAb	Phase III
farletuzumab	Eisai	FRa	MAb	Phase III
mirvetuximab soravtansine	ImmunoGen	FRa	Antibody-drug conjugate	Phase III
Recentin (cediranib)	AstraZeneca	VEGFR-1, -2, and -3	Small molecule	Phase III
Tecentriq (atezolizumab)	Roche	PD-L1	MAb	Phase III
veliparib	AbbVie	PARP	Small molecule	Phase III
Vigil (gemogenovatucel-T)	Gradalis	Furin convertase	Vaccine	Phase III
Zepsyre (lurbinectedin)	PharmaMar	DNA	Small molecule	Phase III
Zybrestat (fosbretabulin tromethamine)	Mateon Therapeutics	Vascular endothelial-cadherin	Small molecule	Phase II/III

FRa = folate receptor alpha; MAb = monoclonal antibody; PARP = poly (ADP-ribose) polymerase; PD-L1 = programmed death-ligand 1; VEGFR = vascular endothelial growth factor receptor

Source: Datamonitor Healthcare

wide, with 70% of patients presenting with advanced disease. The five-year survival is around 40% and patients who become resistant to platinum-based first-line therapy have the poorest prognosis with treatment limited to single-agent salvage chemotherapy. Response rates to current second-line therapies are less than 10%.

BRING IN A BIG GUN

Meanwhile. George Golumbeski, **Celgene Corp.**'s former top deal maker, has also been appointed chairman of Carrick's board of directors. He currently serves as president of **Grail Inc.**, a company focused on early detection of cancer. At Celgene, he was responsible for all aspects of business development, including identifying and evaluating opportunities, strategic collaborations and licensing deals. *(Also see "Celgene's Partnered Pipeline Delivers Successes And Setbacks" - Scrip, 21 Nov, 2017.)*

George Golumbeski

Since its start up in 2016, Carrick is now developing two clinical assets; CT900 and CT7001, an oral CDK7 inhibitor that is progressing through Phase 1 studies, in addition to a preclinical pipeline. The company told *Scrip* that Carrick had "rapidly developed" CT7001 from a candidate drug to first-time-in-man within two years. CDK7 inhibition has emerged as a promising strategy in a range of cancer indications, including triple-negative breast cancer, hormone receptor positive breast cancer, castrate resistant prostate cancer, acute myeloid leukemia and small cell lung cancer.

Carrick has some top-name financial backers, including ARCH Ventures, Woodford Investment Management, Cambridge Enterprise, Cambridge Innovation Capital, **Evotec AG**, Google Ventures, and Lightstone Ventures.

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Merck of Germany's Hunt For MS BTKi Partner Boosted By Evobrutinib Data

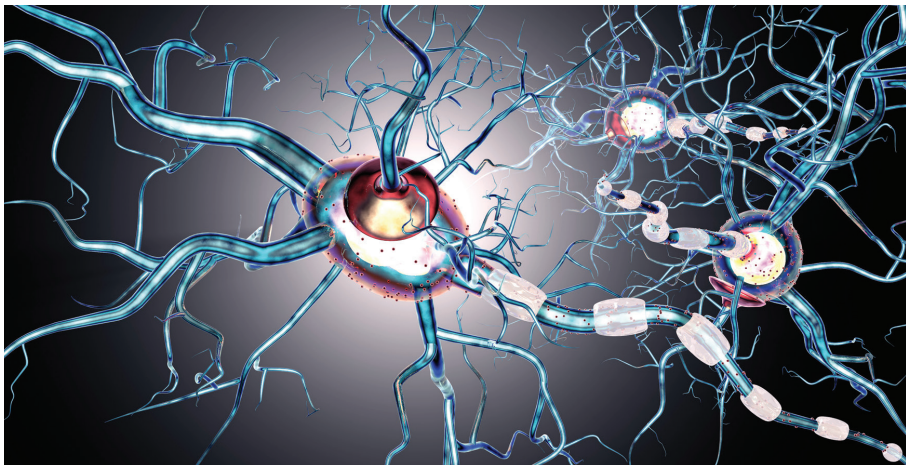
STEN STOVALL sten.stovall@informa.com

Merck KGAA's investigational Bruton's tyrosine kinase (BTK) inhibitor has generated fresh positive safety and efficacy data from a Phase IIb proof-of-concept study in multiple sclerosis which the family-owned company hopes will further help to lure a potential partner to advance the asset in MS as well as lupus and rheumatoid arthritis, executives of the German pharma company told *Scrip*.

They were speaking in Berlin where Merck presented positive Phase IIb data on its BTK inhibitor evobrutinib. It is the first study to show proof of concept for a BTK inhibitor in MS. The investigational therapy is also in Phase IIb studies in rheumatoid arthritis and systemic lupus erythematosus.

The study, for the relapsing form of the disease, met its primary endpoint, demonstrating that evobrutinib dosed at 75 mg once daily and 75 mg twice daily resulted in a significant reduction of gadolinium enhancing T1 lesions measured at weeks 12, 16, 20 and 24 in comparison to patients receiving placebo.

The data were presented Oct. 12 at the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS). It follows the publication of topline data from the trial in early March.



"This is the first demonstration of an oral therapy with the BTK inhibitor affecting the signalling of B-cells and myeloid cells to have a robust result in multiple sclerosis or in any auto-immune indication," said Luciano Rossetti, Merck's global R&D head.

"BTKi is a mechanism that has become very popular for its use in oncology, but it has never before been demonstrated in humans to have an activity in auto-immune diseases, and certainly not in MS, so this is very important from a science point-of-view," he told *Scrip*. The double-blind, placebo-controlled, 48-week, Phase IIb study assessed the safety and efficacy of evobrutinib in patients aged 18-65 years with relapsing-remitting multiple sclerosis (RRMS) or secondary progressive multiple sclerosis (SPMS) with superimposed relapses. A good safety profile was observed in the trial.

DOSE-RESPONSE TREND

Evidence of a dose-response relationship trend was also observed in the Phase IIb trial. At week 24, evobrutinib showed clinically

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Scrip Awards Finalists 2018

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Best Contract Research Organization – Full-Service Providers

The Scrip Awards for Best Contract Research Organization acknowledge the critical role that CROs play in drug development. This Award is for those companies who provide the full range of services to their clients.

CMIC Group

Japan's first CRO, CMIC Group, is now involved in nearly 80% of new drug development and filings in its home market. Over the last 25 years, it has grown to offer the full range of services encompassing the entire pharma value chain, including drug development and manufacturing, clinical research and operational support, clinical site management, and sales and marketing.

Covance

Covance has broadened its solutions for customers with a series of investments and new offerings. Its acquisition of Chiltern strengthened its clinical development offering and added new expertise in medical devices, as well as creating leading oncology expertise. Covance also opened a new Biopharm CMC unit and formed an Immunology and Immunotoxicology group.

ICON

ICON contributed to the development of 14 new drugs in 2017 in areas such as leukemia, motor neurone disease, bladder cancer, psoriasis and inflammatory bowel disease. And in early 2018, its work led to nine new drug approvals. Overall, it was involved in the development of 18 of the world's top 20 best-selling drugs.

IQVIA

Combining the strengths of its parent companies, this year IQVIA launched new offerings to further enhance protocol design, site selection, patient enrolment and data quality. It has improved enrolment rates by 60%, and IQVIA Virtual Trials now allows it to recruit patients virtually – removing geographic and logistical barriers.

PAREXEL

PAREXEL expanded its capabilities through collaboration with industry leaders and key technology enterprises in 2017, further advancing its position as a leading innovator of biopharmaceutical services. It forged a first-of-its-kind partnership with Microsoft, resulting in the launch of the Perceptive Cloud, and announced a digital health collaboration with Sanofi.

Worldwide Clinical Trials

Worldwide Clinical Trials has expanded its capabilities through strategic partnerships with Datavant and KinderPharm, as well as the acquisition of Continuum Clinical's Late Stage Research practice. It made key investments, such as implementation of the goBalto platform to shorten study startup timelines, and the Medidata Payments Cloud to shorten payment cycle times.

Best Contract Research Organization – Specialist Providers

The Scrip Awards for Best Contract Research Organization acknowledge the critical role that CROs play in drug development. This Award is for those companies who provide specialist services to their clients.

Cytel

Cytel helps its customers to improve decision-making and reduce risk across the drug product lifecycle. It increases R&D productivity through a combination of clinical trial software solutions, strategic consulting, and clinical research services. It has demonstrated its core expertise in trial design and planning as well as expertise in helping sponsors optimize their programs.

Illingworth Research Group

This niche CRO specializes in the provision of medical photography and mobile research nurses to allow patients to receive some of their clinical trial procedures away from the site – usually in their own home – increasing recruitment and retention. The past year has seen consistent expansion for Illingworth, demonstrating the increasing importance of patient-centricity.

PHASTAR

PHASTAR is a CRO with a statistical focus: it was started and continues to be managed by statisticians. The company is on target to double its headcount from 2018 to 2023 and estimates 37% revenue growth for the financial year, fuelled by continuing repeat business, as well as new customers.

Quanticate

Quanticate has become one of the world's largest CROs focused solely on the collection, analysis and reporting of clinical study data. As a biometric CRO, its niche clinical services include biostatistics, statistical programming, clinical data management, medical writing, pharmacovigilance, consultancy and statistical monitoring, and it has developed a high level of expertise for biometrics.

Simbec-Orion

This boutique CRO is focused on small/mid-size drug developers. Simbec-Orion's lean set up gives flexibility to enable complex study delivery for modular multi-arm early-phase oncology studies. Its experienced teams ensure that it can execute complex adaptive oncology studies and keep close communication with clients to allow for rapid decision making.

Tioga Research

Tioga Research is a pure-play CRO dedicated to topically-applied, small-molecule formulations, in which molecular engineering is used to modulate skin barrier function. Tioga replaces the traditional consideration of a handful of formulation compositions by a campaign in which 100-300 formulations are prepared and skin delivery assessed. This is game-changing for formulation innovation.

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CONTINUED FROM PAGE 14

relevant decreases in annualized relapse rate (ARR). A reduction in ARR was seen with evobrutinib dosed at 75 mg daily (0.13; p=0.09) and at 75 mg twice daily (0.08; p=0.06) versus placebo (0.37).

"From a statistical point of view there was dose-response relationship in both the primary and secondary endpoint," Rossetti explained. "We see two doses are active and we see some initial trend for the highest does of 75mg once-daily was more effective, at least on some parameters."

> 'This is the first demonstration of an oral therapy with the BTK inhibitor affecting the signalling of B-cells and myeloid cells to have a robust result in multiple sclerosis or in any auto-immune indication' – Luciano Rossetti

"We also had a dosing that wasn't effective, and that was evobrutinib 25 mg once-a-day, which was very close to placebo in effect in the trial," he added.

Observation of a dose-response trend in the Phase IIb should help Merck in coming regulatory discussions on future trials designs. "It's very important from a regulatory point of view to be able to identify the rationale for the dose that we want to move forward in the later trial," Rossetti said.

PLACEMENT IN A CROWDED MARKET

Merck says having a unique mechanism of action and a good safety profile and convenience of use should differentiate its BTK in the therapeutic field of MS.

Rehan Verjee, Merck KGaA's global head of innovative medicine franchises told *Scrip* the German group was confident it can position its BTKi in what is already a crowded market.

"Multiple sclerosis is very diverse and most MS patients will continue to experience disease activity, so having another mechanism to address the disease is thus a very valid and useful thing for physicians because, as they seek to migrate towards an almost zero tolerance disease activity, the only way one can achieve that is by cycling through different mechanisms until one finds the right mechanism for the right patient. Having the first mechanism for BTK is therefore an important proposition," Verjee said.

Datamonitor Healthcare analyst Stephanie Yip told *Scrip* the 24-week Phase IIb data from Merck "encouragingly indicate that evobrutinib possesses strong efficacy and is a well-tolerated drug, with the most common treatment-related adverse events being reversible and asymptomatic." She said that evidence for a dose-response relationship further supports its efficacy for relapsing multiple sclerosis (RMS).

Yip noted that the absence of safety issues is especially notable as new effective drug treatments with improved safety profiles were highlighted as the third greatest unmet need in the multiple sclerosis market by Datamonitor Healthcare's 231 surveyed neurologists across the US, Japan, and five major EU markets (France, Germany, Italy, Spain, and the UK) in May 2016.

"Current disease-modifying therapies are associated with serious safety concerns from hepatotoxicity to progressive multifocal leukoencephalopathy, and evobrutinib may be positioned as an alternative option. The drug also benefits from Merck's experience in the multiple sclerosis market with *Rebif* (interferon beta-1a) and *Mavenclad* (cladribine)," Yip said. *(Also see "Mavenclad Is Merck KGaA Bright Spot As Q2 Sales Slip" - Scrip, 9 Aug, 2018.)*

Merck R&D head Rossetti said he will soon be presenting 48-week data from the BTKi Phase IIb trial. "We believe that 48-week follow-up data on this trial will give us additional critical information particularly on the annualized response rate that is ultimately going to be part of the primary end-point for any further development," he said.

"We are now getting those data and will be presenting them very soon. And those data will drive the further refinement of the dose selection and design of the eventual Phase III trial," Rossetti added.

PARTNERING PROSPECTS

Verjee said the German company is looking for a partner with which to advance evobrutinib. "Our ideal partner for evobrutinib would need to be as excited about the potential of this molecule as we are. They need to bring competence that will be truly complementary to our own," he told *Scrip*.

"We are aiming at three indication areas – multiple sclerosis, lupus and RA – and have chosen to put three foundational Phase IIb studies into place for each, simply because the biology suggests that BTK would be a valid way to address each disease. We're looking for a potential partner who has strategic interests and competences in those three areas," Verjee said.

MS'S MANY FORMS

There are several forms of MS. In most MS patients, disease usually begins as relapsing-remitting MS (RRMS), characterized by episodes of disease exacerbation (relapses) followed by periods of partial or complete recovery (remission).

Within the first decade of disease, around half of RRMS patients will develop secondary progressive MS (SPMS), which is characterized by a progressive worsening of disease between relapses.

A third form of relapsing MS is progressive relapsing MS (PRMS), which follows a progressive course of disease from onset, punctuated by relapses and partial recovery after the relapse.

The fourth main type of MS is primary progressive MS (PPMS), whereby the disease progresses from onset with no remissions.

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Scrip Awards Finalists 2018

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Best Technological Development in Clinical Trials – Clinical Sponsor-focused

The Scrip Awards for Best Technological Development in Clinical Trials recognize the promising and disruptive role that digital health technology now plays in clinical drug development. This award is for advances from clinical sponsors.

Cytel's OK GO software

Cytel's OK GO software helps sponsors to implement a quantitative go/no-go decision-making framework within their organizations by more easily creating decision criteria and communicating these criteria in a consistent, efficient way. The goal is to help sponsors make better, faster decisions within their clinical trials and programs, improve productivity, and success across their portfolio.

Novartis's Nerve Live

Nerve Live is a bespoke computing platform that connects, analyzes and provides insights from multiple internal systems and applies advanced, predictive analytics to help improve the entire global drug development enterprise at Novartis to disrupt the traditional clinical trial process and run trials in smarter, faster and more cost-effective ways.

Covance's Xcellerate CRA Dashboard

Designed from the ground up, Covance has developed the Xcellerate CRA Dashboard to help clinical research associates access to near real-time site-level data anywhere, at any time. The innovative mobile and web-enabled application gives CRAs enhanced visibility to site performance data, reducing the day-to-day complexity of site monitoring and enabling more effective management.

PAREXEL's Perceptive Cloud

This is the result of a first-of-its kind, long-term partnership between PAREXEL and Microsoft to drive the digital transformation of the biopharmaceutical industry by combining PAREXEL's industry expertise and technologies with Microsoft's intelligent cloud services. It represents an opportunity to automate and streamline workflows and provide greater access to high-quality data.

IQVIA's Mobile SVR application

In 2017, IQVIA developed a revolutionary way for its clinical research associates (CRAs) to streamline data collection and reporting through its new Mobile SVR (Site Visits Report) application to enhance study delivery quality and accelerate clinical development for clients. Six months in, CRAs are already showing faster documentation and follow-up by 20-30%.

ICON's FIRECREST Pre-Screen

This innovative digital solution improves the speed and accuracy of the pre-screening process compared with other current paper-based and eScreen methods. The systematic and step-by-step mechanism for site staff also allows aggregation of the data collected into actionable insights into the key drivers of success and failure to give sponsors full transparency.

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Best Technological Development in Clinical Trials – Tech Sponsor-focused

The Scrip Awards for Best Technological Development in Clinical Trials recognize the promising and disruptive role that digital health technology now plays in clinical drug development. This award is for developments from tech companies.

Phesi's real-time data collection and analysis

Phesi's dynamic clinical trials database uses more than 70,000 data sources, with access to over 200,000 clinical trials, 50 million records on investigator performance, and 1.8 million clinical research projects. It enables real-time data collection and analysis to effectively inform the right indication target, number and location of sites, inclusion/exclusion criteria, and timeframes.

CluePoints' Intelligent Central Statistical Monitoring Solution

CluePoints has broken new ground in the clinical arena with its introduction of a Central Statistical Monitoring solution that enables sponsors and CROs to objectively and independently determine the quality and integrity of their clinical trial data. The first-of-its-kind cloud-based architecture provides an effective and pragmatic solution to risk-based monitoring.

Bioclinica's Bioclinica Clinical Adjudication

Bioclinica has developed an adjudication technology that enables location and schedule-independent auto-management of all persons and steps in the data collection/review processes. It enables sponsors to electronically manage the complete process around safety endpoints – from notification of an endpoint at a site through central review by therapeutic experts.

ERT's Advanced Imaging Technology Solution

This technology was specifically built for clinical trials, enabling sponsors to improve imaging data quality and run more efficient studies. Using ERT's advanced technology imaging solution, sponsors can overcome the challenges of traditional imaging approaches and generate accurate, objective and quantitative imaging data, which mitigates risks and uncertainties and supports better, faster decisions.

Ergomed/PrimeVigilance/Automation Anywhere's robotic process automation software

Ergomed and pharmacovigilance subsidiary PrimeVigilance, in partnership with Automation Anywhere, launched last December a robotic process automation (RPA) system that uses software to operate applications. This allows employees in a company to configure the computer software to execute tasks automatically. The pharma industry is full of daily repetitive tasks ideal for RPA.

Medidata's Medidata Rave Engage

Medidata Rave Engage is at the forefront of clinical trial virtualization, providing a novel trial platform to enable large, virtual clinical trials, with huge cost savings. Rave Engage allows for flexibility and scalability in trial design and is currently being used in the15,000-patient aspirin study, ADAPTABLE – the largest virtual trial ever conducted.

Akcea Expects Convenience Edge For Tegsedi, Despite Monitoring Requirements

JOSEPH HAAS joseph.haas@informa.com

Akcea Therapeutics Inc. has reached the market with *Tegsedi*, its RNA-interference (RNAi) therapy for hereditary transthyretin-mediated amyloidosis (hATTR) related polyneuropathy, just a couple months after **Alnylam Pharmaceuticals Inc.** received US FDA approval for its similar drug *Onpattro* for the same indication. The similarities will extend to pricing, as Akcea announced it will price Tegsedi roughly on par with Onpattro.

Tegsedi (inotersen) cleared the US FDA Oct. 5 for hATTR polyneuropathy, after Alnylam's Onpattro (patisiran) got the okay on Aug. 10 as the first drug therapy for the rare disease.

Akcea, an **Ionis Pharmaceuticals Inc.** spinout focused on cardiometabolic RNAi therapies, announced that a single, prefilled syringe of Tegsedi will cost $8,650 wholesale, which would come to $449,800 over a full year if taken once-weekly as the label instructs. Alnylam set a wholesale acquisition cost of $450,000 annually for Onpattro, an intravenous infusion with thrice-weekly administration recommended. Tegsedi can be self-administered once the patient is certified, which Akcea views as a key convenience advantage and allows for reimbursement under pharmacy benefits rather than medical.

"One of the advantages with Tegsedi, because it's a weekly injection [rather than intravenous], it's on pharmacy benefit and that's much easier for payers to administer. There's no administration cost and there's no wastage with it either," Akcea President Sarah Boyce told *Scrip*.

BETTING ON CONVENIENCE OF SELF-ADMINISTRATION

Stressing that amyloidosis patients face significant life disruption, Akcea executives are betting that their convenience of administration advantage will be welcomed by patients and physicians alike, even though Tegsedi's label requires both doctors and patients to be certified for a pair of monitoring requirements: weekly blood draws to check platelet counts, and urine samples every other week to assess kidney function. Onpattro's labeling does not include any monitoring requirements.

The Tegsedi US label includes a boxed warning about the risks of both thrombocytopenia and glomerulonephritis. The drug also has a Risk Evaluation and Mitigation Strategy (REMS) with restricted distribution in addition to the patient/physician certification. Akcea is partnering with **Express Scripts Holding Co.**'s specialty pharmacy Accredo for distribution.

Tegsedi also is approved in Europe – the first patient recently was dosed in Germany – and obtained Canadian regulatory approval on Oct. 4. In both of these markets, platelet monitoring every other week is required, as was requested by Akcea in its US filing for Tegsedi. The European and Canadian approvals also require urianalysis for kidney function once every three months.

On an Oct. 5 investor call, Akcea executives explained that they anticipated monitoring requirements, after receiving a complete response letter from the FDA in August for *Waylivra* (volanesorsen) for familial chylomicronemia syndrome (FCS) because of safety concerns about thrombocytopenia due to reduced platelet counts. Thrombocytopenia is a concern with the RNAi platform.

Akcea eventually plans to appeal to the FDA to relax the monitoring requirements in Tegsedi's labeling. Boyce said it would use real-world evidence from commercial use in Europe and Canada, as well from the US, including the ongoing open-label extension study, for the filing.

In rolling out Tegsedi, Akcea is launching the Akcea Connect program which will provide each patient with a nurse case manager who will get the patient enrolled in platelet and kidney monitoring to be provided by **Quest Diagnostics Inc.** under a contract with Akcea. Patients will have the option of having a Quest phlebotomist visit them each week to draw blood, or going to one of Quest's more than 2,200 locations in the US, Boyce explained.

The executive said Akcea already has built the cost of the Quest monitoring into its economics for Tegsedi, but declined to estimate what the annual cost of paying for the monitoring might be.

While the epidemiology of hATTR is evolving, Boyce said on the investor call that Akcea estimates there are about 3,000 diagnosed patients in the US and another 12,000 not yet diagnosed. Globally, it projects an hATTR population of about 50,000 with about 60% experiencing polyneuropathy.

The monitoring protocol Akcea has set up follows the practices used in both an open-label extension of its Phase III NEURO-TTR pivotal trial and an early access program for the drug. Considering there was no approved treatment for hATTR polyneuropathy up until a few months ago, Boyce said Akcea has gotten considerable feedback indicating that the monitoring requirements are not seen as too onerous.

"In terms of having a treatment, having to do the monitoring is no issue and we've ensured that it's as simple and straightforward for patients as possible," she said. "The types of physicians who typically deal with amyloidosis patients are used to prescribing drugs that may have a monitoring requirement or a REMS, so that's nothing new to them either. So, in context of the benefits versus the severity of the disease, this is something that we hear people saying will be very manageable. The key thing is establishing a routine and that's one of things we're doing as much as we can to help with that."

ANALYSTS CONCERNED MONITORING REQUIREMENTS BURDENSOME

While market analysts hailed the approval, they expressed skepticism that the monitoring requirements would affect Tegsedi's ability to build market share. BMO Capital Markets analyst Do Kim asserted in an Oct. 7 note that the black box warning might deter some physicians and patients, adding that Alnylam must overcome the need to pre-medicate Onpattro patients with steroids plus a more burdensome route of administration.

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Entry and General Enquiries:
Natalie Cornwell
Tel: +44 (0) 7827 993 776 | Email: natalie.cornwell@informa.com

Sponsorship and Table Booking Enquiries:
Christopher Keeling
Tel: +44 (0) 20 3377 3183 | Email: christopher.keeling@informa.com

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"We believe Akcea's efforts to minimize the inconvenience of weekly platelet monitoring and biweekly urinalysis should aid in adoption," Kim wrote. "We believe sufficient preference for weekly self-injections, versus eight-hour I.V. infusions every three weeks should enable Tegsedi to capture a 25% market share." Laidlaw & Co. analyst Yale Jen pointed out in an Oct. 8 note that there have been few incidences of thrombocytopenia since Akcea adopted platelet monitoring in its clinical trials and predicted a modest ramp-up that will build over time for Tegsedi. "Tegsedi adoption could accelerate once patients and physicians feel more comfortable about the thrombocytopenia concern and like to take advantage of the subcutaneous self-administrated at-home delivery benefits," he wrote. "We do not view the efficacy of the two drugs is meaningfully different in real world practice."

Morgan Stanley's David Lebowitz called the monitoring requirements "more burdensome than we had anticipated." In an Oct. 8 note, he reduced his projections for Tegsedi sales in 2025 slightly, from $422m to $405m, based on the label.

Akcea and Alnylam may soon have further competition in the hATTR space, although in a separate sub-indication. **Pfizer Inc.** has Phase III data for oral tafamidis showing reduced all-cause mortality and cardiovascular-related hospitalization in hATTR cardiomyopathy patients. The company has stressed that its indication is entirely different from hATTR polyneuropathy, but analysts generally expect some off-label usage in both directions once all three drugs are on the market.

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Ionis Catches The Eye With New Roche Alliance

KEVIN GROGAN kevin.grogan@informa.com

Ionis Pharmaceuticals Inc. has teamed up again with partner **Roche** and banked $75m upfront to develop one of the former's RNA-based drugs, one that was previously turned down by **GlaxoSmithKline PLC**, for geographic atrophy (GA) or advanced dry age-related macular degeneration.

The drug at the center of the deal is IONIS-FB-LRx, an antisense therapy that targets factor B, a key protein in the complement innate immune system. FB is predominately produced in the liver and circulates throughout the vascular system, including vessels in the eye and kidney.

PROGRESSIVE CONDITION

The deal with Roche will focus on developing IONIS-FB-LRx for a broad range of complement-mediated diseases, with an initial focus on GA. It is estimated that more than 5 million people worldwide (including 1 million in the US) have GA, a chronic, progressive condition that leads to central blind spots and permanent loss of vision. Around 40% of patients are estimated to be legally blind (20/200 or worse) and there are currently no approved therapies for GA.

A Phase I study that evaluated IONIS-FB-LRx in 54 healthy volunteers showed a reduction of plasma FB and was safe and well tolerated. Ionis noted that it would start a Phase II study in early 2019 and also explore the drug's potential in a rare severe renal indication.

On the cash front, as well as the sizeable $75m upfront, Ionis is entitled to up to $684m in milestone payments, plus tiered sales-based royalties ranging from the high teens to 20%. If Roche opts in after the Phase II study, it will be responsible for future development and commercialization.

Roche and Ionis already have an alliance in place on another antisense drug, IONIS-HTTRx (RG6042), which is being developed for Huntington's disease. A recent Phase I/II study suggested the drug can significantly reduce levels of the disease-causing mutant huntingtin protein, making it the first product to show disease-modifying potential in the progressive brain disorder.

This is the second time that a big pharma has got its hands on IONIS-FB-LRx. In August 2017, GSK decided against exercising its option for the drug as well as turning down inotersen as part of a strategy of re-prioritizing its pipeline away from rare diseases. The latter's development was not significantly affected by the GSK snub and Ionis and its commercial affiliate **Akcea Therapeutics Inc.** got FDA approval for the drug, called *Tegsedi*, earlier this month for polyneuropathy related to hereditary transthyretin amyloidosis; Tegsedi got the green light in Europe in July.

The deal has gone down well with analysts. Do Kim at BMO Capital Markets issued a note saying that the new Roche collaboration for FB-LRx "further supports large pharma's interest in Ionis's antisense platform," claiming that additional partnerships will sustain profitability as royalties on its spinal muscular atrophy blockbuster *Spinraza* (nusinersen) continue to roll in from partner **Biogen Inc.**. He said that the upfront and royalty rate from the Roche pact are healthy, adding that there is a "large opportunity in dry AMD." Wet AMD, which is less common (around 10% of patients) has multiple therapies approved, notably Roche's *Lucentis* (ranibizumab), partnered with **Novartis AG**.

Roche clearly believes dry AMD and specifically GA represents an opportunity as well and its enthusiasm for the area has seemingly not been diminished by the failure a year ago of lampalizumab. This antigen-binding fragment of a humanized monoclonal antibody targeting complement factor D failed to meet its primary endpoint in the Phase III Spectri study as it did not reduce mean change in GA lesion area compared to sham treatment after a year.

An identically designed Phase III study – Chroma – also failed to demonstrate any benefit in reducing GA lesion growth. The failure was a significant blow, given that lampalizumab was seen as its flagship ophthalmology product, with some analysts forecasting peak sales in the region of $2bn.

It is early days for IONIS-FB-LRx but there does not appear to be much competition around in the GA pipeline. The most advanced candidate seems to be **Apellis Pharmaceuticals Inc.**'s APL-2. Last month, the company said the first patient has been dosed in a Phase III trial called OAKS, evaluating APL-2, a complement 3 (C3) inhibitor in GA; an identical late-stage study, DERBY, has just begun enrolment and in total the program is looking to enrol around 600 patients.

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Mylan Head Of Biologics Chrys Kokino On Fulphila Launch And US Biosimilars

JESSICA MERRILL jessica.merrill@informa.com

Mylan NV's first biosimilar recently entered the US market, *Fulphila* (pegfilgrastim-jmbd), a launch industry is closely watching as a bellwether for the near-term prospects of the US biosimilar market. Mylan Head of Biologics Chrys Kokino talked with *Scrip* about the launch, which he called a success, but with a caveat – the commercial expectations for biosimilars need to be reset, he said.

"Do I believe Fulphila has been a success? I would say absolutely yes," Kokino said. But the expectation that a new biosimilar will enter the market and quickly take a big share of a blockbuster branded biologic's revenues is unrealistic, he added. "You've got to throw out that reference point," he said.

Mylan launched Fulphila in July as the first biosimilar version of **Amgen Inc.**'s neutropenia drug *Neulasta* (pegfilgrastim) approved in the US. *(Also see "Mylan Is First To Clear US Neulasta Biosimilar Hurdle; At-Risk Launch May Not Be Risky" - Pink Sheet, 5 Jun, 2018.)* The drug launched at a 33% discount to the reference product's wholesale acquisition cost, an aggressively lower discount relative to the first biosimilars that launched in the US.

Some of the initial biosimilars, most notably **Pfizer Inc.**'s *Inflectra* (infliximab-dyyb) and **Merck & Co. Inc.**'s *Renflexis*, both versions of **Johnson & Johnson**'s *Remicade* (infliximab), have been commercially lackluster. That's put pressure on Fulphila as a barometer to show the US market has the commercial incentives and regulatory policies in place to foster the burgeoning category.

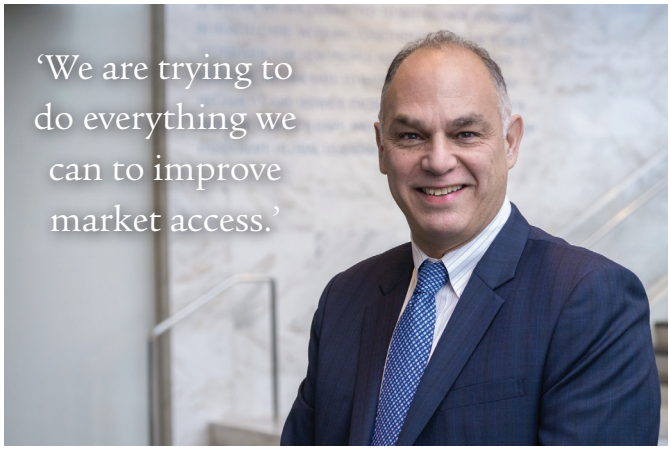
Despite Kokino's relative optimism on the launch of Fulphila, it's still early days. The company has faced a challenging environment for the launch of a generic version of **Teva Pharmaceutical Industries Ltd.**'s multiple sclerosis blockbuster *Copaxone* (glatiramer), and CEO Heather Bresch spoke at length during the company's second quarter call about "perverse incentives" that she claimed are holding back high-barrier-to-entry generics and biosimilars.

Mylan's biosimilar development partner, **Momenta Pharmaceuticals Inc.**, announced Oct. 1 that it is exiting most biosimilar drug development, another sign that biosimilar enthusiasm is waning. *(Also see "Momenta Is Exiting Biosimilars; Is That A Bellwether For Biosimilar Sentiment? " - Scrip, 2 Oct, 2018.)* Momenta and Mylan have six biosimilars in development together. Momenta will continue to co-develop one, a version of **Regeneron Pharmaceuticals Inc.**'s *Eylea* (aflibercept), but plans to end development of the other five, including a biosimilar version of **Bristol-Myers Squibb Co.**'s *Orencia* (abatacept). Mylan has not yet commented on Momenta's decision.

STEEP DISCOUNT PAVES THE WAY FOR ACCESS

Kokino credited Mylan's pricing strategy with helping to secure market access for Fulphila, which is covered by 50%-60% of US payers, Kokino said.

"That's being done without any rebates, without the incentives. Why? Because the price was favorable when it came to the comparison between our price and the average selling price of the originator price," he said.



One of the challenges in the infliximab market for biosimilar manufacturers has been securing market access, as J&J has put in place an aggressive rebating strategy for Remicade. Pfizer has called the strategy, involving exclusionary contracting, anti-competitive in a lawsuit. There are also other inherent differences between the two categories of drugs that could impact the launch trajectory of a biosimilar, like the acute versus chronic nature of the medicines.

Kokino said Mylan spent years talking to stakeholders about the best way to launch a biosimilar and one of the top responses the company heard was to enter the market with the appropriate value. That includes price, but also patient-support services, he said.

"One reason I believe Fulphila is successful today is because we did what the originator did," Kokino said. "We have the hub services, patient services, benefits verification for patients, patient assistance programs, copay cards."

Amgen's primary defensive strategy for Neulasta is focused on converting patients from the manually injected product to a newer *OnPro* version, an on-body injector that automatically delivers the Neulasta dose. Neulasta generated $4.53bn in 2017 and is the company's second-best seller, behind *Enbrel*.

Leerink Partners analyst Geoffrey Porges said in a Sept. 17 research note that Amgen has converted more than 60% of Neulasta volume to OnPro, but that adoption has been driven largely by contracting. Fulphila likely will experience relatively rapid adoption at small physician practices, and at 340B institutions, which collectively drive 46% of Neulasta's current volume, he forecast.

"Amgen's contracting around the OnPro device in our view will likely protect branded share longer than we and consensus expected, but ultimately revenue seems likely to fall below consensus beyond 2022E," Porges said. "For Mylan, we believe Fulphila could beat consensus estimates for 2019/2020 meaningfully and contribute $150m and $300m in sales in 2019E and 2020E, respectfully."

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

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

Selected clinical trial developments for the week 5–11 October 2018

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
PHASE III RESULTS PUBLISHED			
Boehringer Ingelheim/Eli Lilly	*Jardiance* (empagliflozin)	type 2 diabetes and cardiovascular disease	EMPA-REG OUTCOME; *Circulation*, Oct. 8, 2018.
Bausch Health Companies	*Altreno* (tretinoin) lotion, 0.05%	moderate-to-severe acne	*Journal of Drugs in Dermatology*, Oct. 2018.
PHASE III INTERIM/TOP-LINE RESULTS			
Johnson & Johnson	*Stelara* (ustekinumab)	ulcerative colitis	Clinical remission with single iv dose.
Roche Holding AG	*Ocrevus* (ocrelizumab)	relapsing multiple sclerosis	CHORDS; safe and effective after switch from another disease modifying therapy.
Celgene Corp.	*Otezla* (apremilast)	scalp psoriasis	STYLE; met primary endpoint.
Venus Remedies Ltd.	*Elores* (ceftriaxone/ sulbactam/EDTA)	urinary tract infections	PLEA; higher cure rates vs meropenem.
Diurnal Group PLC	*Chronocort* (hydro-cortisone)	congenital adrenal hyperplasia	DIUR-005; mixed results.
UPDATED PHASE III RESULTS			
Protalix BioTherapeutics Inc./ Chiesi Farmaceutici SpA	pegunigalsidase alfa	Fabry's disease	BRIDGE; improved renal function.
Paratek Pharmaceuticals Inc.	*Nuzyra* (omadacycline)	skin and skin structure infections	OASIS-2; improved quality of life.
Ardelyx Inc.	tenapanor	irritable bowel syndrome	T3MPO-3; safe in long-term study.
Johnson & Johnson	*Stelara* (ustekinumab)	Crohn's disease	IM-UNITI; use of concomitant immunosuppressants not necessary.
Bellerophon Therapeutics Inc.	*INOpulse* (nitric oxide)	pulmonary arterial hypertension	INOvotion-1; clinical improvements.
Roche Holding AG	*Ocrevus* (ocrelizumab)	multiple sclerosis	OPERA I, II; ORATORIO; efficacy maintained.
Evofem Biosciences Inc.	*Amphora* (L-lactic acid, citric acid, potassium bitartrate)	contraception	AMP001; patient comfort confirmed.
ObsEva SA	nolasiban (OBE001)	infertility	IMPLANT2; improved pregnancy rate.
Theravance Biopharma/Mylan	*Yupelri* (revefenacin)	chronic obstructive pulmonary disease	Positive data, safe CV profile.
Insmed Inc.	*Arikayce* (amikacin) liposome inhalation	MAC lung disease	Further clinical data collected.
PHASE III COMPLETED			
Adamas Pharmaceuticals Inc.	*Gocovri* (amantadine) extended-release	Parkinson's disease with dyskinesia	EASE LID 2; well tolerated over two years.
PHASE III INITIATED			
Strekin AG	STR001	hearing loss	RESTORE; in Europe.
Exelixis	*Cabometyx* (cabozantinib)	thyroid cancer	COSMIC-311; refractory disease.
Allergan	brazikumab	ulcerative colitis, Crohn's disease	EXPEDITION, INTREPID; versus adalimumab.
Diurnal Group PLC	*Chronocort* (hydro-cortisone)	congenital adrenal hyperplasia	RESTORE; delayed release formulation.

Source: Biomedtracker | Informa, 2018

CONTINUED FROM PAGE 21

Mylan is focused on patient and physician education about Fulphila and biosimilars more generally. The company has established a traditional field force to support the launch of Fulphila, recruiting from within Mylan's internal ranks, Kokino said. He called it a "specialty sales organization" with an emphasis in oncology.

PRODUCT TIMELINE

Fulphila is used to treat neutropenia in cancer patients, and the company's biosimilar version of **Roche**'s breast cancer blockbuster *Herceptin* (trastuzumab) has already been approved by the FDA. The timeline for launching the trastuzumab product, which Mylan has named *Ogivri*, has not been publicly disclosed but is set under a patent settlement with Roche.

Mylan is doing what it can to get the message out while keeping the commercial costs reasonable. For example, it's too early and too expensive for biosimilar manufacturers to consider consumer advertising to get the message out, according to Kokino.

"We are trying to do everything we can to improve market access, but let's not be naïve, we also have to make it affordable," Kokino said. "There is only so much investment that you can make."

The supportive cancer care setting could be a stronger therapeutic area for a new biosimilar to gain traction versus a different drug category like a chronic disease. The category, for example, doesn't face some of the same challenges around the lack of interchangeability in the US for biosimilar drugs that present a bigger hurdle in other therapy areas, Kokino said.

"Many times, the patients don't know that they are even getting this product. They get it because it has an impact on the neutrophil count," he said. "Is interchangeability absolutely necessary there? Probably not." On the other hand, interchangeability could be "highly important" for a biosimilar in a chronic immunology category, where patients administer their medicine at home, he said. Cancer drugs are a different category altogether, he added, where interchangeability could be a factor and physicians may express mixed feelings about changing a patient's treatment.

"Every molecule is different," he said.

Final guidance on interchangeability, more public education on biosimilars and combating misinformation about biosimilars were among the steps stakeholders advocated for at the FDA's recent public hearing on biosimilars. *(Also see "From Interchangeability To Exclusivity: US FDA Looks For Ways To Make Biologics Market More Competitive" - Scrip, 7 Sep, 2018.)*

The category has already experienced biosimilar entry as well, with the launch of more than one biosimilar to Amgen's *Neupogen* (filgrastim). Sandoz's *Zarxio* (filgrastim-sndz) was the first biosimilar to launch in the US three years ago and has gained substantial traction in the market. Branded Neupogen only represents about 37% of the filgrastim market, Amgen reported during its second quarter financial report.

Mylan is also ramping up to launch a biosimilar version of **AbbVie Inc.**'s *Humira* (adalimumab) in Europe later this year, at the same time as several other biosimilars. The company has a stacked pipeline of biosimilars and complex generics behind it, including generic versions of **GlaxoSmithKline PLC**'s *Advair* (fluticasone/salmeterol), Regeneron's Eylea, Roche's *Avastin* (bevacizumab) and *Rituxan* (rituximab), and **Sanofi**'s *Lantus* (insulin glargine). *(Also see "Mylan Poised To Launch Its First US Biosimilar, With A Stacked Pipeline Behind It" - Scrip, 12 Apr, 2018.)*

Published online 9 October 2018

APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
Gad Soffer	Rheos Medicines	Chief Operating Officer	Atara Biotherapeutics	Executive Vice President, Chief Strategy Officer	10-Oct-18
Ori Ben-Yehuda	CardioVascular BioTherapeutics Inc	Chief Medical Officer	Gilead Sciences	Vice President, Cardiovascular Clinical Research	2-Oct-18
Natalie R. Sacks	Harpoon Therapeutics	Chief Medical Officer	Aduro Biotech	Chief Medical Officer	3-Oct-18
Murray S. Kessler	Perrigo Company Plc	Chief Executive Officer, President and Director	Lorillard Tobacco Co	Chairman and Chief Executive Officer	8-Oct-18
Akihiro Tsujimura	SanBio Co Ltd	Chief Executive Officer, SanBio Inc and Senior Corporate Officer	Santen Pharmaceutical Co Ltd	Director	1-Oct-18
Stephane Boissel	Sangamo Therapeutics Inc	Executive Vice President, Corporate Strategy	TxCell SA	CEO	2-Oct-18
Karsten Sauer	Torque Therapeutics	Vice President, Immunology	Pfizer Inc	Director, Cancer Immunology	9-Oct-18

Click here for all appointments: https://bit.ly/2oHWRYn

Source: Medtrack | Informa, 2018

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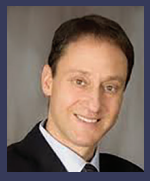

Professor Kenneth Getz, Director and Associate Professor at **CSDD**, **Tufts University School of Medicine**, *USA*

Inma Martinez, Venture Partner, Data Sciences & Product Innovation at **Deep Science Ventures**, *UK*

Daniel Prieto-Alhambra, Associate Professor & NIHR Clinician Scientist at **Oxford University**, *UK*

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