Scrip
Informa Pharma Intelligence
No. 3970
August 30, 2019

Amgen's $13.4bn Otezla Buy Helps Bristol/Celgene Merger Close By Year-End

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Amgen Inc. will add a revenue-generating drug with strong sales growth expectations to its portfolio via the $13.4bn purchase of Celgene Corp.'s Otezla (apremilast), the divestiture of which should pave the way for Bristol-Myers Squibb Co. to close its $74bn acquisition of Celgene by the end of 2019.

Amgen is buying the Otezla revenue stream at a crucial moment when its revenues are being hit by biosimilars and generics for some of its top-selling blockbuster products. *(Also see "Amgen's Murdo Gordon On Generating Sales Growth In A Challenging Commercial Year" - Scrip, 26 Jul, 2019.)* The transaction also comes at an important time for Bristol-Myers and Celgene, which need the US Federal Trade Commission (FTC) and other anti-competition regulators to sign off on their merger. The sale of Celgene's oral PDE4 inhibitor depends on FTC clearance of the Bristol-Celgene deal and the closing of that transaction by the end of this year. *(Also see "Bristol Values Celgene's Hematology, Immunology Portfolio At $74bn, But Does It Price In Risk?" - Scrip, 3 Jan, 2019.)*

The FTC required the sale of Otezla – approved for moderate-to-severe psoriasis, active psoriatic arthritis and oral ulcers associated with Behcet's disease – because of the drug's overlap with indications Bristol is pursuing for its small molecule inhibitor of tyrosine kinase 2 (TYK2) BMS-986165. Bristol's oral drug is in Phase III for psoriasis and Phase II for psoriatic arthritis, systemic lupus erythematosus, ulcerative colitis and Crohn's disease.

But while Amgen sells Enbrel (etanercept) and Amgevita, its Humira (adalimumab) biosimilar marketed in the EU – injectable TNF inhibitors indicated to treat psoriasis, psoriatic arthritis and other inflammatory diseases – both are biologics, not oral drugs. *(Also see "Amgen's Biosimilar Adalimumab First To EU Nod But No Launch" - Scrip, 27 Jan, 2017.)* Celgene has positioned Otezla as a post-topical, pre-biologic option for psoriasis and psoriatic arthritis, which may be enough differentiation from Enbrel and Amjevita (adalimumab-atto) for the FTC to sign off on Amgen's purchase of the drug. *(Also see "Celgene's Terrie Curran On Building, Broadening The I&I Franchise" - Scrip, 4 Apr, 2018.)*

Amjevita is the company's US Food and Drug Administration-approved Humira biosimilar, but it will not launch in the US until 2023 under a settlement with AbbVie Inc.; Amgevita launched in the EU last year. *(Also see "Biosimilar Humira Blocked Until 2023, But Time Could Clear Commercial Path" - Scrip, 28 Sep, 2017.)*

'UNIQUE' OPPORTUNITY TO BUY 'TRULY INNOVATIVE' OTEZLA

Amgen expects the net cost of its Otezla acquisition to be $11.2bn after the company realizes $2.2bn in tax benefits associated with amortizing the all-cash purchase over a 15-year period.

"As a longstanding leader in inflammation and having looked at a number of oral anti-inflammatories through time, we watched with great interest the success of Otezla, and having an opportunity to

CONTINUED ON PAGE 4

Nabriva's Antibiotic Challenge
Nabriva aims for a successful Xenleta launch (p14)

PRV Priorities
Which of AstraZeneca's upcoming drugs will take priority? (p5)

Goodwill Hunting
Pharma companies make their statement of purpose (p8)

from the editor

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The US Business Roundtable has just published new corporate governance principles overthrowing its long-standing endorsement of the supremacy of the stockholder when it comes to the purpose of the corporation. Interestingly, the writing of the updated statement, in which serving customers, employees, suppliers and communities all now share equal billing with serving shareholders, was overseen by Alex Gorsky, CEO of Johnson & Johnson (see p8). In fact, the new set of principles bears no small resemblance to J&J's famous Credo, which declares the company's first responsibility is to its customers, followed by employees and the wider community, before the "final responsibility" to stockholders.

The detailed wording of the J&J Credo has changed since it was first written in 1943, but the broad idea and the order of responsibilities have remained constant. Indeed, the company's belief in prioritizing customers and workers over stockholders set it apart from other corporations even earlier than that. During the Great Depression, its visionary president Robert Wood Johnson went against the grain of contemporary industrialist behavior, raising wages and urging others to do likewise to help the country exit the economic crisis. His 1935 pamphlet *Try Reality: A Discussion of Hours, Wages and the Industrial Future*, argued that it was "in the interest of modern industry that service to customers comes first; service to its employees and management second, and service to its stockholders last."

Will big business publicly endorsing J&J's 1930s corporate ethos lead to real change in the 2020s? Given that the principles are blandly similar to many corporations' existing mission statements, it feels unlikely.

Scrip
Informa Pharma Intelligence

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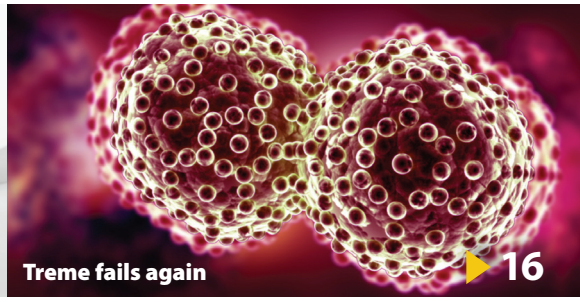

exclusive online content

NICE Head Sir Andrew Dillon To Stand Down

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Sir Andrew Dillon is to step down as chief executive of England's health technology assessment body, the National Institute for Health and Care Excellence, after 20 years in the post.

Sir Andrew will vacate his position at the end of March 2020, NICE announced on 22 August. The search for a replacement will begin shortly.

His departure will be keenly felt: Sir Andrew has led NICE since it was established in 1999. The institute, which provides guidance on whether drugs, medical devices or diagnostics should be funded through the National Health Service in England, has grown into an internationally respected and hugely influential health technology assessment organization under his leadership.

Sir Andrew said it had been "a privilege to lead the organization through its first two decades. NICE has made a significant contribution to improving outcomes for people using the health and care services, and to the efficient use of resources. I feel very proud to be associated with those achievements."

Published online 23 August 2019

To read the rest of this story go to: https://bit.ly/2zolvTl

inside:

CONTINUED FROM PAGE 1

acquire a truly innovative and established success like this now while it's still at an early stage in its global lifecycle is really unique," CEO Robert Bradway said during Amgen's 26 August call to discuss the Otezla purchase.

Otezla sales totaled $1.6bn in 2018, and Celgene forecast $1.9bn for 2019 sales; the drug brought in $882m in the first half of this year, which was up 21.2% year-over-year. Amgen said it expects annual growth of at least low single-digit percentages for the next five years with the potential for additional growth from new indications and launches in new markets.

"Otezla is the first choice therapy for [psoriasis] patients not satisfied with topical therapies given its differentiated mechanism of action and established efficacy and safety profile," Amgen executive vice president for research and development David Reese said during the company's call. "In psoriatic arthritis, Otezla is positioned for use in patients early in disease and/or with moderate joint involvement who are unsatisfied with [disease-modifying anti-rheumatic drugs (DMARDs)]."

Also, since Otezla is an oral drug, "it provides a patient-friendly alternative to injections or creams," Reese said. He noted that the drug is approved in more than 50 countries, but marketed in only 32.

INTERNATIONAL OTEZLA EXPANSION PLANNED

Amgen intends to launch Otezla in those other markets where the company already has an established presence in autoimmune and inflammatory diseases or is working to build a presence – particularly via Amgevita, since ex-US revenues from Enbrel have dwindled due to biosimilar competition.

"We've been clear that international expansion is an important strategic priority for us, and Otezla, with approvals around the world, offers yet another attractive international growth opportunity, especially in a number of large European markets and Japan," Bradway said. "The timing of this deal is attractive for us as Otezla will fit well alongside our ongoing investments in our biosimilar Amgevita business and it will contribute as well to the growth of our recently established presence in Japan."

William Blair analyst Matt Phipps pointed out in a 26 August note that the biggest competition for Otezla will come from Bristol's TYK2 inhibitor BMS-986165, which delivered "impressive" Phase II results in psoriasis last year and is in Phase III clinical trials with two comparators – placebo and Otezla. Phase III data are expected for BMS-986165 in 2020, but Phipps forecast that Otezla will maintain significant market share in the pre-biologic setting for patients with milder psoriasis.

> Amgen expects Otezla to be immediately accretive to its earnings in 2020 after the deal's late-2019 close.

"As has been seen time and again with new drug launches in the treatment of inflammatory diseases, formulary placement is essential for gaining access to newly diagnosed patients, and patients who are stable on a current therapy are unlikely to switch to a novel therapy," he said. "We continue to believe BMS-986165 has blockbuster potential, but believe it has greater likelihood to gain market share initially from patients on biologics wanting to avoid injections or those who have suboptimal responses to current therapies."

BRISTOL'S BENEFITS FROM OTEZLA DEAL ARE THREE-FOLD

While Amgen stands to benefit from bolstering its international presence in inflammatory diseases and boosting its revenue stream as sales for key franchises like Neulasta (pegfilgrastim) and Sensipar (cinacalcet) slump under the weight of biosimilar and generic competitors, Bristol also appears to benefit from the sale of the drug in multiple ways. *(Also see "Amgen Explains How Big A Hit It May Take From Biosimilars, Pricing Pressures" - Scrip, 29 Jan, 2019.)*

First, the transaction will allow for Bristol's Celgene acquisition to close before the end of 2019, which is on the earlier side of the companies' guidance of late 2019 or early 2020 based on FTC clearance of their merger.

Second, Amgen is paying more than the $10bn maximum that analysts expected for Otezla, which Mizuho securities analyst Salim Syed said in a 26 August note is a "best case" scenario for Bristol and Celgene. Syed said the deal makes sense for Amgen, but doesn't leave much room for the company to absorb the impact for Otezla if Bristol launches its TYK2 inhibitor as expected in 2022.

Third, Bristol will have more money to reduce its debt burden faster and maintain its credit rating. The company said it also will increase its stock repurchases to $7bn from a planned $5bn share buyback initiative. Even after that, it noted, Bristol still will have money to engage in further business development activities to boost its product portfolio.

A DEAL TOO LARGE OR JUST RIGHT FOR AMGEN?

SVB Leerink analyst Geoffrey Porges speculated in a same-day note that the tax benefit that lowered Amgen's net cost for Otezla paired with competitive bidding for the drug probably drove the deal's value above analyst consensus. However, he did not see the price as so high that the deal wouldn't be positive for Amgen.

"With sales of $1.6bn in 2018, $2bn+ in 2020E and $2.45bn in 2021E, Otezla should certainly be immediately profitable for Amgen," Porges said. "Investors are likely to be skeptical about Amgen's assertion of IP exclusivity for Otezla until 2028 in the US, but even with earlier generic introduction, for the total cost of the purchase (5.5x expected 2020 sales) Amgen has still secured incremental product sales, with a synergistic operational footprint. On this basis the transaction does not seem outrageously expensive to us."

Amgen's Otezla purchase, which it says comes with US patents protecting the product through at least 2028 in the US,

includes both the drug and the sales and research teams involved with the asset. Otezla also is being investigated in scalp and genital psoriasis, mild-to-moderate psoriasis and in pediatric indications. *(Also see "Celgene's Positive Phase III Data For Otezla In Scalp Psoriasis Could Yield Broader Label" - Scrip, 9 Oct, 2018.)*

Amgen anticipates that its sales expenses and its R&D costs will be higher than previously expected in 2020 based on expenditures related to Otezla. Analysts noted this could be a temporary spending spike, because the company may cut costs where Amgen's sales and R&D teams overlap with Celgene's Otezla activities. However, Bradway indicated during Amgen's call that there won't be an immediate reckoning.

"As transactions go, this has the potential to be more straightforward than most in that it doesn't entail a complex infrastructure integration or redundancy issues," the CEO said. "Teams joining us from sales and marketing, development, medical affairs and manufacturing, for example, will fit well with our existing infrastructure capabilities."

Amgen expects Otezla to be immediately accretive to its earnings in 2020 after the deal's late-2019 close. The company indicated confidence that the FTC will sign off on the deal and Wolfe Research analysts said in a note about Bristol that the parties must have gotten some indication from the regulator that their transaction would be acceptable before they consummated the deal.

While Amgen will finance the transaction with cash from its balance sheet – it had $21.8bn in cash and investments as of 30 June – the company does not expect the deal to dampen its ability to continue investing in its own R&D programs, acquire new assets or buy back shares from investors, Bradway and chief financial officer David Meline noted during the Amgen call.

Fitch Ratings left Amgen's credit rating unchanged, saying on 26 August that the all-cash deal still leaves the company with enough liquidity to maintain its BBB rating related to its $25.1bn in outstanding debt as of 30 June. Amgen's stock closed up 3.2% at $205.41 on 26 August, while Bristol rose 3.3% to $48.11 and Celgene gained 3.2% to close at $97.

Published online 26 August 2019

AstraZeneca Buys Priority Review Voucher With Two Big Filings On The Horizon

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AstraZeneca PLC has its sights set on speeding up the US Food and Drug Administration review of an upcoming new drug filing. The company revealed on 22 August that it paid $95m to buy a priority review voucher from Swedish Orphan Biovitrum AB.

An FDA priority review cuts the timeline for reviewing a new drug from 10 months to six months, excluding the two-month filing period, and AstraZeneca has two big US filings targeted in the second half of 2019: roxadustat for anemia in chronic kidney disease and trastuzumab deruxtecan in HER2+ breast cancer.

It seems likely AstraZeneca could be planning to use the voucher for one of those high-profile filings. The company's partner on trastuzumab deruxtecan, Daiichi Sankyo Co. Ltd., is taking the lead on the US filing however, under their alliance to jointly commercialize the antibody-drug conjugate. The companies announced positive Phase II data on the drug in advanced HER2-positive breast cancer patients in May and said the data would underpin a regulatory filing in the US in 2019.

AstraZeneca agreed to pay $1.35bn upfront and could pay a total of $6.9bn to jointly commercialize trastuzumab deruxtecan. The other big drug filing AstraZeneca is targeting for the second half of 2019 is roxadustat, a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) partnered with FibroGen Inc. The two partners are in a race to market with other drug manufacturers that have similar compounds, which could position roxadustat as the more likely recipient of the voucher.

The new class of drugs could displace erythropoietin-stimulating agents (ESAs) as the current standard of care. Roxadustat has been shown to increase red blood cell production while maintaining plasma erythropoietin levels in subgroups of CKD patients without the need for supplemental intravenous iron.

Other drugs advancing in late-stage development include Mitsubishi Tanabe Pharma Corp../Akebia Therapeutics Inc.'s vadadustat, Bayer AG's molidustat, GlaxoSmithKline PLC's daprodustat and Japan Tobacco Inc..'s enarodustat. GSK just filed daprodustat in Japan, but the global development is in Phase III.

Among the recent use of PRVs have been Novartis AG, which used vouchers both for Mayzent (siponimod) for multiple sclerosis and for brolucizumab for wet age-related macular degeneration (AMD), which is pending at the FDA. Novo Nordisk AS used a PRV for the regulatory filing of the oral GLP-1 agonist semaglutide earlier this year.

PRV MARKET VALUE CONTINUES TO FALL

The $95m selling price of the PRV is on the low end of the scale of recent PRV values, though not entirely out of line in what has been a declining value. Last year Spark Therapeutics Inc. sold a PRV to Jazz Pharmaceuticals PLC for $110m, while several PRV sales in 2017 ranged from $125m to $150m. The peak was set in 2015 when United Therapeutics Corp. sold a voucher to AbbVie Inc. for $350m.

The sale of the voucher by SOBI comes about one month after the company closed the acquisition of Gamifant and other assets owned by Novimmune SA for CHF515m ($519m). The deal included the PRV. The FDA's rare pediatric disease priority review voucher program has drawn some criticism for not meeting its intended purpose, which is to incentivize the development of drugs for rare pediatric diseases. A recent study found the program has not increased the number of drugs for rare pediatric diseases getting to the clinic.

Published online 22 August 2019

Bayer Says $7.6bn Farewell To Animal Health As It Sells Unit To Elanco

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Bayer AG is to sell its animal health unit to the Eli Lilly & Co. spin off, Elanco, in a cash and stock transaction to the tune of $7.6bn as the German conglomerate repositions itself towards life sciences.

The deal, announced on 20 August, will improve Bayer's ability to pay off some of the debt built up from the Monsanto acquisition. It is the largest transaction in the series of restructuring measures Bayer announced in November 2018 when its stated intention to pull out of the animal health business was seen as a sensible decision to help slim down the organization.

Analysts say Bayer has got a decent price for the division, which, as the fifth largest global animal health player, behind Zoetis, Boehringer Ingelheim GmbH, Merck & Co. Inc. and Elanco itself, was not that well positioned in the market.

Given Elanco's own debt position, the payment will not be all in cash. It will be made with $5.3bn in cash, and $2.3bn in Elanco stock. The divestment is expected to be concluded in mid-2020 subject to the satisfaction of customary closing conditions, including antitrust clearance. Bayer then intends to exit its stake in Elanco over time.

For Bayer chairman Werner Baumann, "This transaction enhances our focus as a global leader in life sciences." The company has already announced the divestiture of its consumer health brands Coppertone and Dr. Scholl's along with the sale of its 60% stake in German site services provider Currenta. "We are therefore delivering ahead of schedule on one of the key priorities for driving value creation that we communicated at our Capital Markets Day in December 2018," said Baumann.

Bayer's Animal Health business had sales of $1.8bn in fiscal 2018 for products for companion and farm animals.

But one potential blot on the landscape is the risk of anti-trust concerns stopping the deal. "By selling the animal health business to Elanco, the overlapping assets could become problematic for regulators concerned about too much control over the industry," said analysts at Morningstar in a 20 August reaction note. They point out that the top five animal healthcare companies control 70% of the market, as compared with the 30% of the human drug market that the top five human healthcare companies control – a concentration that has led to divestitures in past acquisitions in the animal health market.

"We expect divestitures are likely to be needed to gain approval from regulators for Bayer's animal healthcare sale to Elanco," the Morningstar analysts said. "From Elanco's perspective, we believe the company is willing to approve divestments to secure regulatory sign-off because scale in the animal healthcare business is important and difficult to replicate for other firms, outside the top five animal healthcare companies."

OTHER ISSUES

In pharma, Bayer needs to shore up its pipeline ahead of patent losses for major products, Xarelto (rivaroxaban) and Eylea (aflibercept) and in the wake of some R&D disappointments. Late last year it said it was looking to transact more deals like its tie up with Loxo Oncology Inc. (now part of Lilly) for the tumor agnostic anticancer, Vitrakvi (larotrectinib). This product is now facing competition from Roche's Rozlytrek (entrectinib) following its recent approval by the US Food and Drug Administration.

The major overhang, however, is the Roundup weedkiller lawsuits that still dog the firm. Bayer announced in June a new strategy to deal with US litigation and reassure investor and rumors (though denied) have circulated that it is willing to offer an $8bn settlement to draw a line under the matter. *(Also see "Anxious Investors Relieved At Bayer's Fresh Monsanto Litigation Strategy" - Scrip, 27 Jun, 2019.)*

Published online 23 August 2019

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In Search Of Goodwill, Several Pharmas Commit To New Corporate 'Statement Of Purpose'

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The leaders of the half dozen pharmaceutical manufacturers who are members of the US-based Business Roundtable signed on to the organization's updated principles on the "role of a corporation," announced 19 August.

The principles embrace a commitment to serving the concerns of consumers, employees, suppliers and communities over shareholders. That's a major reversal from previous versions issued since 1997, which have endorsed the idea that "corporations exist principally to serve shareholders," the roundtable noted in a release.

The Business Roundtable is a group of CEOs of major US corporations formed to promote pro-business public policy. The vast majority of the roundtable's members – 181 – endorsed the principles.

Drug company leaders include: Pfizer Inc. CEO Albert Bourla, Johnson & Johnson Consumer Inc. chairman and CEO Alex Gorsky, Bayer AG USA president Philip Blake, Bristol-Myers Squibb Co. chairman Giovanni Caforio, Allergan PLC chair, president and CEO Brent Saunders and Mallinckrodt president and CEO Mark Trudeau.

The move responds to increasing public discontent in some quarters with the way corporate America focuses on maximizing shareholders profits above all else.

Biopharma companies have been a particular target, with attacks over high pricing coming from all sides – the public, congress, the Trump Administration and now from Democrats on the presidential campaign trail. Industry has relied on high prices and price increases to sustain revenue growth and satisfy investors while it pursues innovative new treatments. Despite ongoing pressure from the administration and Congress there is little evidence that approach is changing. But clearly companies are looking to improve their standing with the public.

"Proud to join my fellow [Business Roundtable] CEOs in committing to lead our companies for the benefit of all stakeholders: customers, employees, suppliers, communities and stakeholders," Allergan's Saunders proclaimed in a same-day tweet.

All of the drug companies represented on the roundtable have felt public pressure over pricing tactics. But Allergan has been singled out because of its controversial patent licensing arrangement with the St. Regis Mohawk tribe to protect Restasis against competition. Mallinckrodt has also been on the hot seat over massive prices increases for its HP Acthar Gel.

J&J'S GORSKY COORDINATED UPDATE

JP Morgan Chase CEO Jamie Dimon, who heads the roundtable, led the charge on revising the principles. The updates were written under the direction of J&J's Gorsky, who is chair of the organization's governing committee.

"This new statement better reflects the way corporations can and should operate today," Gorsky said in a release. "It affirms the essential role corporations can play in improving our society when CEOs are truly committed to meeting the needs of all stakeholders."

The principles are broadly drawn. They espouse "delivering value to our customers" and promise to "further the tradition of American companies leading the way in meeting or exceeding customer expectations." But they do not address specifics like pricing practices.

The other principles include "investing in our employees," dealing "fairly and ethically with our suppliers" and "supporting the communities in which we work," including protecting the environment.

At the bottom of the list is "generating long-term value for shareholders, who provide the capital that allows companies to invest, grow and innovate."

The updated principles have generated favorable press coverage but it's unclear how they will translate into practice.

If nothing else, their focus on better serving American customers and workers may give pharma companies some leverage as they continue to engage with the Trump adminstration on policies like the International Pricing Index and with lawmakers on legislation that would impose price inflation rebates on drugs covered by Medicare Part D. Action on both initiatives may come in the near future.

Published online 20 August 2019

Lupin Rationalizes Japan Operations, Sheds Injectables Business

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Lupin Ltd. is divesting its injectables business in Japan to the Neopharma group as the Indian firm streamlines its operations there and hones its focus on a "hybrid" (brand/generics) pharma model.

The sell-off comes almost eight years after Lupin snapped up the Tokyo-based specialty injectables firm, I'rom Pharmaceutical Co. (since renamed Kyowa CritiCare Co. Ltd.) and is perhaps indicative of the challenging overall operating environment for pharma in Japan.

Lupin's Japanese arm Kyowa Pharmaceutical Industry Co. Ltd. will sell the injectables business and certain related as-

sets in Japan to Neo ALA Co. Ltd, a subsidiary of the Neopharma group, which is the United Arab Emirates' largest pharmaceutical manufacturer. Lupin's plant and associated facilities based out of Atsugi, Japan, which contract manufacture and sell injectable products, are part of the deal. Financial details of the transaction were not immediately disclosed.

All the issued and outstanding share capital in Kyowa Criticare will be divested to Neo ALA, Lupin said. The Indian firm also emphasized that the transaction does not involve or affect the other operations of Kyowa, namely research, manufacturing, marketing and distribution of oral solids and other dosage forms in Japan.

Neopharma said that the acquisition will strengthen its product offerings in Japan, which it dubbed as a "focus market" for driving the group's long-term sustainable growth by leveraging its global presence. Neopharma had earlier acquired Dr. Reddy's Laboratories Ltd.'s antibiotic manufacturing facility and related assets in Bristol, TN in the US and also certain manufacturing assets of the Hyderabad-based firm in India via another joint venture.

NEOPHARMA IS 'RIGHT PARTNER'

While specifics on the outlook for Kyowa Criticare could not immediately be ascertained, things had probably not shaped up to Lupin's expectations. The company's 2018-19 annual report notes that Kyowa Criticare reported a turnover of about INR3.64bn ($50.7m) and profit after taxation of INR140.7m, while Kyowa Pharmaceutical and Kyowa CritiCare together generated JPY33.9bn ($318m) in revenues, a decline of 4% over the previous year.

At the time of the acquisition of I'rom Pharma in 2011, Lupin had noted that injectable products enjoy significant usage in the DPC (Diagnostic Procedure Combination) hospital segment, and that generic injectable penetration was expected to grow significantly in the future.

There were over 1,400 DPC hospitals in Japan, covering more than 35% of all hospital beds nationwide, and a market size of $11bn, the Indian firm had noted at the time. For the fiscal year ended March 2011, I'rom Pharma reported sales revenues of JPY5.4bn. *(Also see "Lupin acquires injectables firm I'rom Pharmaceuticals in Japan" - Scrip, 25 Nov, 2011.)*

Lupin said that it believes Neopharma group is the right partner for Kyowa Criticare as they "appreciate the strategic importance of this business unit" and would be able to deliver value to business partners and customers, leveraging Kyowa Criticare's people who are "critical assets".

> Lupin's divestment in Japan is not entirely surprising.

JAPAN PRICING PRESSURE

Lupin's divestment in Japan is not entirely surprising. There had been past media reports suggesting that a review was underway at the Japanese operations and recent management commentary has consistently pointed to the tough pricing situation and other changing dynamics in Japan, even referring to the market as a "pain point" on one occasion.

Lupin's managing director Nilesh Gupta noted at the firm's annual investor meet in May this year that the generics segment in Japan was growing in volume but not value, and with annual price cuts anticipated, there was a "lot of pricing pressure". A company presentation at the time noted that the generics market in Japan was expected to grow at a slower pace than in past years. It stood at $7.2bn in 2016, $7.7bn in 2017 and $8.3bn in 2018, according to IQVIA moving annual total data presented by Lupin at the time.

In its 2018-19 annual report, Lupin also maintained that the Japan generics market is increasingly converging towards a substitution-oriented model. "We need to ensure that we develop products at the right cost, manufacture products more efficiently, and gain substantial market share. This is the time to optimise, improve efficiencies, and simultaneously build the specialty portfolio in Japan," the company stated in the report.

Several measures in that direction already appear to have been initiated. The company had earlier explained that it had "worked hard" to improve its margins in Japan through "back-ending products" into India, where it gets better end-to-end margins. It had also "right-sized" infrastructure in Japan based on current market needs.

Published online 23 August 2019

Amgen's US Biosimilar Launches Are Off To A Steady Start, With A Big Coverage Decision

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Amgen Inc. and Allergan PLC's two biosimilars Mvasi (bevacizumab-awwb) and Kanjinti (trastuzumab-anns) are the first to test the US commercial market for cancer biosimilars – and having won at least one important insurance coverage decision from UnitedHealthCare, the launches appear off to a steady start.

UnitedHealthCare announced it will cover the two biosimilars in a preferred position to Roche's reference drugs Avastin and Herceptin beginning on 1 October for new patient starts. For existing patients, Avastin and Herceptin will be allowed. Amgen launched the biosimilars in July at-risk as the first biosimilar versions of Roche's Avastin and Herceptin, respectively. In UnitedHealthCare's August Network Bulletin, the insurer also said Mvasi and Kanjinti will also be preferred over other biosmilar products, several of which could launch later this year.

The coverage decision is notable given that payers, including UnitedHealthCare,

haven't always paved such a clear market access path for biosimilars in the US. Market access has been one of the big hurdles for some early biosimilars in the US. For example, Pfizer Inc.'s Inflectra (infliximab-dyyb), a biosimilar of Johnson & Johnson's Remicade (infliximab), has struggled to gain traction in the US, in part because of J&J's successful defensive contracting strategy.

The US commercial dynamics are unique in that an innovator company can simply offer steeper discounts on the brand drug, often as part of an exclusive contract, and given the high volumes of those mature medicines the savings can be too significant for a payer to resist. The result has been some lackluster early biosimilar launches.

"We certainly are pleased to have coverage, and we want to have coverage not just at United but broadly," Amgen VP-oncology sales & marketing Susan Logan said in an interview. But she downplayed the decision as a signal of a broader trend.

"Each negotiation goes through a process and that bidding process is saving money for the system, and Amgen's products ended up in a preferred position in this case," she stressed. Amgen said the negotiations were competitive and that they did not involve any other portfolio products, as payer negotiations sometimes do.

The two biosimilar drugs launched at a 15% discount to the wholesale acquisition cost (WAC) of the two reference products, and Amgen confirmed it is negotiating additional discounts with payers.

United has drawn criticism for blocking biosimilars before, including versions of Amgen's neutropenia drug Neulasta (pegfilgrastim), by preferring the brand over biosimilars. As of 1 July, United's commercial and community plans covered Neulasta or Neulasta Onpro over two pegfilgrastim biosimilars on the market: Mylan NV/Biocon Ltd.'s Fulphila and Coherus BioSciences Inc.'s Udenyca. *(Also see "UnitedHealthcare Coverage Policy Undercutting Neulasta Biosimilars Draws Concerns" - Pink Sheet, 7 Jun, 2019.)* The August bulletin also includes a policy update on filgrastim, however, in which Sandoz International GMBH' Zarxio will be preferred over Amgen's branded Neupogen and other biosimilars.

The practice of blocking biosimilar market access has been widespread. Last year, then-US Food and Drug Administration commissioner Scott Gottlieb called out insurers for blocking biosimilars through rebating schemes. *(Also see "FDA's Gottlieb: 'Pricing And Reimbursement Mischief' Holding Back Biosimilar Market" - Scrip, 7 Mar, 2018.)* Pfizer filed a lawsuit against J&J in 2017, alleging that its exclusive contracts for Remicade are anti-competitive. *(Also see "Pfizer Sets The Stage For A Biosimilar Showdown Over Exclusive Contracts" - Scrip, 20 Sep, 2017.)*

Mvasi and Kanjinti could also be benefiting from Roche's focus on new versions of its products. The Swiss pharma's big defensive play has been mainly around product enhancements, like a new subcutaneous formulation of Herceptin that was approved by the FDA in February, for example, and the ongoing development of a new fixed-dose combination of Herceptin and Perjeta (pertuzumab) in a subcutaneous injection. The company does not appear to be as fixated on defensive rebating strategies to maintain market share as some competitors have been.

As Bernstein Research analyst Ronny Gal pointed out in a 15 August research note, "What Roche did not do was to attempt to obstruct competition against its first-generation products."

"This is a deliberate strategy (or at least conscious negligence)," Gal said. "In a chat with CEO [Severin] Schwan, he noted to us he is spending his effort ensuring access (at proper price) to innovation and while the country teams' job is to maximize current product revenue, they should not do so in a way that conflict with the ability of Roche to argue for paying for innovation (which we took as 'no strategies we can't morally justify')."

> "Physicians appreciate that these are biosimilars coming from Amgen." – Susan Logan

The vial products of Roche's three main franchises, Avastin, Herceptin and Rituxan (rituximab), are thus "largely facing market competition 'naked' – without incumbency-driven advantages," Gal said.

Amgen has the first-to-market advantage with the Avastin and Herceptin biosimilars for now, but more biosimilars are expected to launch later this year. Roche had signed patent settlement agreements with several manufacturers, paving the way for a launch in the second half of 2019. More launches could drive down prices lower.

"What is healthy for the system is that as you have increased competition, the system will benefit from increased cost savings," Logan said.

But Amgen believes one advantage it offers in the biosimilar field is the Amgen name recognition. "We fully expect that the biosimilar competitors will compete not just on price, but on a wide range of attributes, such as delivery devices, patient services and provider education," executive director-global value & access, biosimilars Chad Pettit said. "It is really the total package that the manufacturer brings to the table."

Amgen has already built a reputation with cancer providers and physicians through its branded supportive care medicines Neulasta and Neupogen, Logan said. At the same time, cancer physicians as have gained experience with biosimilars in the supportive care category, she said.

"Physicians appreciate that these are biosimilars coming from Amgen, and we have relationships with these physicians because we have been in the oncology space," Logan added. Having confidence in a reliable supply is an important factor, she said, particularly in a potentially curative setting like cancer.

Amgen is launching the biosimilars through its existing sales team.

Published online 20 August 2019

Can Dr Reddy's Carve Into Crowded Indian Avastin Biosimilar Market?

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Dr. Reddy's Laboratories Ltd. has introduced its biosimilar version of Roche's anticancer Avastin (bevacizumab) in India, trailing peers into a crowded segment which has recently seen price regulation.

Dr Reddy's biosimilar bevacizumab, marketed as Versavo, goes up against some formidable rivals, with over half a dozen firms including Mylan NV, Biocon Ltd., Intas Pharmaceuticals Ltd., Reliance Life Sciences, Hetero Drugs Ltd. and Zydus Cadila already selling other Avastin biosimilars on the Indian market. *(Also see "Biocon's Avastin Biosimilar To Put The Heat On Competition?" - Scrip, 23 Nov, 2017.)*

In addition, innovator Roche had previously struck a deal with Cipla Ltd. for a second brand of Avastin in India. *(Also see "Roche Primes New Push Via Cipla For Avastin, Actemra In India " - Scrip, 28 Feb, 2018.)(Also see "Asia Deal Watch: Boost For Esperion's Cholesterol Candidate As Daiichi Brought On Board" - Scrip, 8 Jan, 2019.)*

Many of the competitors have a significant head-start in the market and some of the relatively newer products such as Zydus Cadila's Bryxta, launched in January 2018, appear to have made gains in the recent past. Bryxta reported sales of INR260m ($3.6m), as per moving annual total (MAT) July 2019 data from the Indian market research agency AIOCD AWACS.

Dr Reddy's Launches Cut-Price Biosimilar Avastin In India

PRICE DIFFERENTIAL

Hyderabad-based Dr Reddy's appears to be banking on an interesting mixed pricing approach to claw its way into the market.

The 100mg injection formulation of Versavo, with a maximum retail price (MRP) of INR6,993 ($97.7m), appears to come at a sharp discount to competition, though it's not clear if trade bonuses and discounts could make the price differential less dramatic. On the other hand, Versavo 400mg has a MRP of INR41,994 and appears to be priced around the range of rival brands.

Dr Reddy's said that it expects Versavo to help improve access to high-quality therapy at an affordable cost, addressing the needs of patients with different cancers in India.

Competitor Intas' Bevatas 100mg injection has an MRP of INR9,500 and Hetero's Cizumab of the same strength an MRP of INR11,838. The 400mg versions of Bevatas and Cizumab have MRPs of INR36,061.64 and INR43,859 respectively, details on some online pharmacies indicate. Importantly, these figures reflect the price cuts effected for bevacizumab brands earlier this year, after the Indian government decided to clamp down on runaway trade margins on 400-plus anticancers.

Trade margins are essentially the difference between the price at which the manufacturer sells drugs to stockists/distributors (price to trade) and the final price to patients (the MRP).

Other initiatives for Versavo are also in the works. Dr Reddy's indicated to *Scrip* that it has plans in the pipeline which are "patient-centric" but provided no specifics. For the 12 months ended December 2018, Avastin and its biosimilars reported India sales of about INR2.23bn, according to data from the Ipsos India Tandem Oncology Monitor.

Meanwhile, Dr Reddy's is aiming to take its bevacizumab biosimilar to other emerging markets. "We are gearing up for filings in emerging markets for this product, leveraging our robust clinical data of 'normal healthy volunteer study and patient study' along with a strong analytical data package," the company told *Scrip*.

The Indian firm has six biosimilars commercialized in India and certain emerging markets and is developing a pipeline of biosimilars in the oncology and immunology space. Dr Reddy's had earlier identified six "spaces" – the US, India, Russia, China, global hospitals including biosimilars, and the global active pharmaceutical ingredients business – where it expects to strengthen its presence to drive the next level of growth.

It aims to attain self-sustainability for each of its businesses going forward.

Published online 22 August 2019

Big Pharma Nibbles As Turkey's Localization Policy Yields Limited Results

AHMET SEVINDIK

The Turkish government can claim some success for its controversial "localization" policy that urges foreign pharmaceutical producers to move their production to the country if they want their medicines to be eligible for reimbursement under the Turkish health system, with major firms including GlaxoSmithKline PLC, Gilead Sciences Inc., Chiesi Farmaceutici SPA and Sanofi making local investments.

Turkey has been pushing hard to increase local pharmaceutical production for the past three to four years, using carrot-and-stick policies to convince multinational pharmaceutical companies in favor of local production. The main "stick" is being thrown out of the reimbursement list, which in effect means to be out of the Turkish market (reimbursement accounts for 85-90% of the market). The "carrot" is fast licensing, swift access to the reimbursement list and, in some cases, purchasing guarantees. The aim of localization policy is to reduce Turkey's pharmaceutical imports, which reached $3.9bn last year.

The policy seems to be working to a certain extent, with a number of investments being announced in the past year.

GSK, for example, has announced an investment of $30m (TRY168m) in order to produce two of its asthma products at the facilities of Abdi Ibrahim, the largest local company. GSK will be transferring its nebuliser-related technology and the products are planned to be on the market in 2021.

Another investment was announced by Gilead Sciences. The company will produce Vemlidy (tenofovir alafenamide fumarate) for hepatitis B and Bictarvy, its single tablet antiretroviral regimen containing the HIV integrase inhibitor bictegravir (and emtricitabine and tenofovir alafenamide) through Pharmactive, a local company with a modern plant operating at GMP standards. The project is expected to be completed in five years and to cut pharmaceutical imports by $250m. Turkey has around 13,000 registered HIV patients, but experts say this figure could be much higher. The number of hepatitis B patients is estimated to be around 3.5 million. This investment is an exception as it includes new products under patent protection.

Turkey has been pushing hard to increase local pharmaceutical production for the past three to four years.

Gilead Sciences Turkey general manager Sebnem Girgin noted that Turkey would be the third country, after Canada and Ireland, where these medicines are produced and pointed out the potential for exporting these popular products. Gilead Sciences has been closely monitoring Turkey's efforts in hepatitis B and C for potential new collaborations, industry sources note.

Novartis, meanwhile, has started production of a drug for chronic myeloid leukemia [presumably imatinib – Ed] in Turkey at its own plant and it plans to start local production of two more oncology products this year. Chiesi has also joined the local production wave. It will be producing Rinoclenil (beclometasone) nasal steroid spray in Turkey. Its partner, once again, is Pharmactive, and production will take place at its plant.

Most recently, Sanofi signed a deal with local company, Birgi Mefar, involving the production of an antibiotic product. The only greenfield investment came from Iranian company CinnaGen, which invested $100m in a factory in Turkey to produce and export biosimilars.

The Turkish government has also managed to get commitments from other multinational companies for local production of some of their products. Many of them are small-scale facilities that companies do not feel the need to announce. The most recent statement about localization made by the Ministry of Health in October 2018 disclosed that 609 medicines were in the scope of localization. Most of the disclosed projects so far are for generic products; investments involving high-value products have been less popular.

This is mainly due to the poor investment environment. Getting new investments has become difficult in all sectors given the challenging economic and political environment and, under the presidential system, the need to seek approval by President Tayyip Erdogan. But the most important negative factor for the pharmaceutical industry is the fixed euro rate applied by the government to the pharmaceutical industry. The rate for this year is TRY3.40, compared with the market rate of TRY6.22, leading to shortages in the market as companies periodically slow down or stop the import of high-value products.

Multinational CEOs may talk about the value they give to Turkey and how ready they are to serve Turkish healthcare system and invest in Turkey, but these pronouncements are not followed by concrete actions. Analysts do not expect big scale investments as long as the pricing policy continues with unrealistic fixed euro rate. The Government is currently working on a new package to increase incentives and support local producers by providing them with funds, expertise and networks.

Published online 21 August 2019

Lilly's Taltz Approved For AS As New Guidelines Keep TNF Inhibitors In Front Line

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The US Food and Drug Administration approval of a third indication for Eli Lilly & Co.'s interleukin-17 (IL-17) inhibitor Taltz (ixekizumab) in radiographic ankylosing spondylitis (AS) brings the label in line with Novartis AG's Cosentyx (secukinumab) in the same drug class, just days after new AS treatment guidelines recommended IL-17 agents after TNF inhibitors.

Taltz was approved on 26 August for adults with active AS, also known as radiographic axial spondyloarthritis (r-axSpA), which affects the pelvic joints and spine leading to chronic inflammatory back pain, stiffness, and impaired function and mobility in an estimated 1.6m people in the US. The biologic also has generated positive Phase III results in non-radiographic axSpA (nr-axSpA), an indication for which Lilly plans to seek US FDA approval in 2019. *(Also see "Taltz Results In Spondyloarthritis Add To Lilly Franchise Hopes" - Scrip, 23 Apr, 2019.)*

The axial spondyloarthritis market is about half AS and half nr-axSpA, but the company told *Scrip* that patients with both diseases are underserved and those two markets have the potential to double in size.

Taltz has been competing with Cosentyx for US market share since the Lilly drug won FDA approval to treat moderate-to-severe plaque psoriasis in 2016 and gained an indication for active psoriatic arthritis in 2017. Cosentyx was approved for psoriasis in 2015 and won US indications for psoriatic arthritis and AS in 2016, but it also is expected to seek FDA approval in nr-axSpA this year.

Taltz's new indication in AS was for monotherapy or in combination with a conventional disease-modifying anti-rheumatic drug (DMARD), such as sulfasalazine, corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) and/or analgesics.

Rebecca Morison, vice president in Lilly's US immunology commercial business, said the company is looking forward to talking with physicians who treat AS about data from the Phase III clinical trials that evaluated Taltz versus placebo in 657 AS patients. The COAST-V trial enrolled patients who were biologic DMARD-naïve, while COAST-W included patients who had an inadequate response to or could not tolerate TNF inhibitors.

The primary efficacy endpoint in both studies was the proportion of patients at 16 weeks who achieved Assessment of Spondyloarthritis International Society 40 (ASAS40) responses, which means at least a 40% improvement in pain, function and inflammation. Phase III trials for Cosentyx in AS had ASAS20 as their primary endpoints.

Morison said Lilly sees ASAS40 as "a high bar in the sense of setting the expectation for efficacy."

"This [was] a good opportunity for us in the way we were running the trial to sort of push the standard of care up in the community, which I think you've seen happen in psoriasis as well with the IL-17 class," she added.

Morison noted that the addition of AS to the Taltz label gives the company more of an opportunity to talk about the benefits across indications with rheumatologists and with payers.

"The way that we look at it, in addition to being able to serve another patient population, which is important given the mission that we have with Taltz to try and reach as many patients that we can, it's also important for payers as they look at and consider payer choices when they're looking at different agents," she said.

"And then, for us in terms of the Taltz brand, it's another set of data that continue to show the impact of Taltz and the ability for it to deliver quick onset of action, and for it to maintain and deliver efficacy over time," she said. "It builds on the same type of data in terms of powerful consistency for psoriatic arthritis and psoriasis."

LITTLE CHANGE EXPECTED BASED ON NEW AS GUIDELINES

Given the growing number of choices for treating AS, the American College of Rheumatology (ACR) in partnership with the Spondylitis Association of America (SAA) and the Spondyloarthritis Research and Treatment Network (SPARTAN) issued new treatment guidelines for AS on 22 August. After NSAIDs, the guidelines recommend TNF inhibitors as first-line biologic therapies and IL-17 inhibitors for patients who don't respond to or can't tolerate anti-TNF agents.

"I'm not sure it changes much," Morison said, relative to how physicians and payers already are sequencing AS treatments and how patients are being required to step through therapy with more well-known therapies before they are treated with an IL-17 inhibitor.

"The Lilly perspective on algorithms that have a lot of step therapy is that it's not always in the best interest of patients," she said, "especially when you're requiring step-through therapy through older medications. But certainly, the addition of another newer agent – like Taltz, another IL-17 – that can offer AS patients an alternative, we hope will create some more momentum to reduce step therapy."

She said that after years of seeking treatment and finally getting an AS diagnosis, both patients and doctors can be frustrated by being required to try oral therapies or other older drugs before pursuing more novel treatments.

"When you look at overall numbers of patients, it's estimated that 1.6m patients suffer from AS and 80% of those are likely drug-treated, but only 15% are treated by biologics, so I think there's quite a bit of space and time between that 80% and 15%," Morison said.

The ACR, SAA and SPARTAN guidelines recommend NSAIDs as the first treatment option for patients with active AS, but sulfasalazine, methotrexate or Pfizer Inc.'s oral JAK inhibitor Xeljanz (tofacitinib) are recommended for patients who have active disease despite treatment with an NSAID. However, TNF and IL-17

inhibitors are recommended before use of Taltz, because Xeljanz isn't approved for AS and only Phase II data are available for the Pfizer drug in AS to date.

While TNF inhibitors, such as AbbVie Inc.'s Humira (adalimumab) and Amgen Inc.'s Enbrel (etanercept), are the favored biologic class in the ACR, SAA and SPARTAN recommendations, the guidelines do not favor one anti-TNF agent over another. However, they recommend that doctors don't switch an AS patient who is adequately treated with a brand-name TNF inhibitor to a biosimilar for that product.

The guidelines say that TNF inhibitors should be used before anti-IL-17 agents based on greater familiarity and longer-term use of TNF-targeting biologics. If AS patients don't respond to TNF inhibitors, the guidelines recommend that they should be treated with Cosentyx or Taltz. But if AS patients initially respond to a TNF inhibitor, then stop responding after six months or more, the guidelines say that doctors should prescribe a second anti-TNF biologic before switching to an IL-17 inhibitor.

However, the guidelines note that Xeljanz is a better option than IL-17 inhibitors for AS patients with inflammatory bowel disease (IBD), since the drug has been studied in Phase III and approved for ulcerative colitis (UC). *(Also see "Pfizer's Xeljanz Pushed By New Tailwind From Approval In Ulcerative Colitis" - Scrip, 30 May, 2018.)* Several TNF inhibitors are approved to treat IBD – either UC or Crohn's disease or both – including Humira, Johnson & Johnson's Remicade (infliximab) and its biosimilars, J&J's Simponi (golimumab) and, as of March, UCB SA 's Cimzia (certolizumab pegol). *(Also see "Keeping Track: Approvals For Mayzent, Mavenclad, Duaklir, Jatenzo And Cimzia" - Pink Sheet, 31 Mar, 2019.)*

COMPETITION IS COMING, INCLUDING NEW CLASSES

Xeljanz is being tested in AS in a single Phase III trial with data expected in the second half of 2020, but the JAK inhibitor class is facing questions about cardiovascular safety.

AbbVie's JAK1 inhibitor Rinvoq (upadacitinib), recently approved in the US for rheumatoid arthritis, is in Phase II/III for AS, but the study's primary completion date is in November 2020. *(Also see "AbbVie's Post-Humira Strategy Continues Taking Shape With Rinvoq Approval" - Scrip, 16 Aug, 2019.)*

Gilead Sciences Inc. and Galapagos NV also are running a Phase II study in AS for their JAK inhibitor filgotinib, but the partners also will seek their first US indication this year in rheumatoid arthritis. *(Also see "Gilead To File Filgotinib For RA in 2019, Earlier Than Forecast " - Scrip, 2 Jul, 2019.)*

UCB recently reported positive Phase IIb results for its IL-17 inhibitor bimekizumab – targeting IL-17A and IL-17F, while Taltz and Cosentyx target only IL-17A – and has moved the candidate into Phase III for AS.

Meanwhile, like Lilly with Taltz, Novartis continues to promote long-term responses observed in clinical trials among patients treated with Cosentyx in AS and the product's other indications. *(Also see "Five-Year Data Consolidate Cosentyx Benefits" - Scrip, 26 Oct, 2018.)*

Cosentyx is the clear leader across indications in terms of sales with $2.8bn in 2018, which was up 36% from the prior year, while Lilly reported a 68% jump in sales to $937.5m in 2018.

"Even though we do compete in the space, I would say it's a good thing that there are as many agents as there are, and there are many agents continuing to do studies in some of these areas, like ankylosing spondylitis and others, where maybe there wasn't as big a focus as before," Morison said.

"The other side of me says, yeah, it is hard out there, and because there are good agents coming forward, it makes the market feel crowded," she continued. "What we hope is that we can continue to raise the standard of care [for] symptom relief, because … when patients expect more and when physicians expect more, we think Taltz will be able to shine. The lower the standard of care, the more of the competing agents that can meet that expectation. We want the expectations to go up, both because Taltz can perform well there and then also because it's great for patients."

Published online 26 August 2019

Nabriva Faces Skepticism After Years Of Preparing For Novel Antibiotic Xenleta's Launch

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Nabriva Therapeutics PLC has been preparing for two years to launch Xenleta (lefamulin), which the US Food and Drug Administration approved as an intravenous and oral treatment for community-acquired bacterial pneumonia (CABP) on 19 August. The company believes that it has laid the groundwork for a successful launch at a time when reimbursement for antibiotics finally may be moving in a positive direction, though there still is some skepticism about commercial prospects. Nabriva's 60 sales representatives initially will target about 900 hospital and health care system accounts where physicians are looking to send CABP patients treated in the emergency department home with an oral antibiotic, treat patients with co-morbidities who have limited antibiotic options, and shorten hospital stays for patients receiving IV treatment.

Xenleta will be available through specialty distributors starting in mid-September with a list price of $205 per day for IV treatment and $275 per day for the oral version. Nabriva expects 70-80% of sales to come from oral prescriptions with 20-30% from IV use, chief commercial officer Francesco Maria Lavino explained during a 19 August call to discuss Xenleta's approval in the US.

Lavino said the company's sales team will keep its focus on the hospital setting, but will look for creative ways to market the drug in the community setting. The same sales reps will promote the IV anti-

biotic Contepo (fosfomycin), assuming it is approved in 2020, for complicated urinary tract infections. The US FDA issued a complete response letter rejecting Contepo due to manufacturing concerns, but Nabriva intends to refile the drug early in the fourth quarter of 2019. *(Also see "Keeping Track: US FDA Approves Sanofi's Dengvaxia, But Heron's HTX-011 And Nabriva's Contepo Fall Short" - Pink Sheet, 5 May, 2019.)*

CEO Ted Schroeder and Lavino noted during Nabriva's call that most CABP patients treated in hospitals and emergency departments are older patients covered by Medicare and Medicaid. They noted that recent policy changes at the Centers For Medicare and Medicaid Services (CMS) improve reimbursement for novel antibiotics, and Lavino said Medicare and commercial payers have been supportive of Xenleta's use in appropriate CABP patients.

CMS recently approved a policy increasing new technology add-on payments (NTAPs) that boost the amount of money Medicare and Medicaid will pay to reimburse the costs of antibiotics. The NTAP for drugs used in hospital settings in 2020 will be 65% of the amount of the cost that exceeds bundled payments for specific medical services or 65% of the cost of the drug, whichever is lower. But for anti-infectives with qualified infectious disease product (QIDP) designations from the US FDA, like Xenleta, the NTAP percentage is 75%.

Also, CMS adopted a new diagnosis-related group (DRG) code for treatments that may play a role in reducing antimicrobial resistance (AMR), which may result in higher payment for new antibiotics starting on 1 October. *(Also see "Commercial, Reimbursement Hurdles Need To Be Addressed By Antimicrobial Resistance Efforts" - Scrip, 15 Feb, 2019.)*

In addition, Schroeder said congressional support for the DISARM Act is growing. The legislation would carve out antibiotic reimbursement from the DRG system for inpatient hospital costs.

Despite the news of Xenleta's approval and Nabriva management's optimistic outlook, investors were skeptical given the difficulty other companies have had turning new antibiotics into successful products. Achaogen Inc. went out of business following approval and minimal use of Zemdri (plazomicin) and Tetraphase Pharmaceuticals Inc. recently reorganized to focus entirely on the launch of its first commercial antibiotic, Xerava (eravacycline). *(Also see "Finance Watch: Tetraphase Reorganization Follows Troubled Antibiotic Commercialization Path" - Scrip, 14 Jun, 2019.)*

> "We see Xenleta as eventually making inroads into the elderly CABP population." – David Lebowitz

Nabriva's stock price rose in after-hours trading on 19 August following the Xenleta approval announcement, but held steady on 20 August, closing up just two cents (0.9%) at $2.23 per share.

"We see Xenleta as eventually making inroads into the elderly CABP population, a market in which drug resistance is high and a new antibiotic class is highly desired," Morgan Stanley analyst David Lebowitz said in a 20 August note. "While the approval is a clear positive, some investors would be keen to point out that the antibiotic market is challenging, with many generic therapies available that can make it difficult for new therapies. As such, we expect some investors might want to see a track record of growing revenue before warming up."

NOVEL PLEUROMUTILIN MAY FILL UNMET NEEDS

Xenleta is a first-in-class, semi-synthetic pleuromutilin antibiotic that Nabriva is positioning as a first-line monotherapy based on its novel mechanism of action, targeted spectrum of activity, low risk of antimicrobial resistance and relative safety compared to generic fluoroquinolone antibiotics, and the availability of both IV and oral formulations. Nabriva noted that its drug is the first novel oral and IV antibiotic approved in almost two decades for CABP.

Lavino said doctors have been demanding new antibiotics for CABP, particularly with novel mechanisms of action rather than new versions of well-known antibiotic classes. The most recently approved drug for CABP prior to Xenleta in the US was Paratek Pharmaceuticals Inc.'s Nuzyra (omadacycline), a broad-spectrum IV and oral tetracycline administered for seven to 14 days versus the five- to seven-day course of treatment for Nabriva's drug. *(Also see "Paratek's Antibiotic Nuzyra Survived 20 Years – Now For The US Launch" - Scrip, 3 Oct, 2018.)*

Current first-line CABP treatments including the IV beta-lactam antibiotics ceftriaxone, which requires admission to the hospital and a switch to a macrolide antibiotic for discharge, since there's no oral version of ceftriaxone. Also, beta-lactams have a high risk for *Clostridium difficile* (C. diff.) infections, macrolides are resistant to certain *Pneumoniae* bacteria and beta-lactam/macrolide combinations provide no methicillin-resistant *Staphylococcus aureus* (MRSA) coverage.

Fluoroquinolones also are used in the front line for CABP, but they also have a high risk for C. diff. infections and their use is being discouraged due to increasing safety and antibiotic resistance concerns. *(Also see "EMA Acts On Patient Concerns Over Fluoroquinolone Antibiotics" - Pink Sheet, 8 Oct, 2018.)* and

"Emergency departments across the country treat hundreds of thousands of patients with CABP each year. Many of these patients, especially elderly patients with comorbidities, are admitted solely because of the lack of an effective and well-tolerated oral treatment option" Philip Giordano, vice chairman of emergency medicine at Orlando Regional Medical Center, said in Nabriva's statement about Xenleta's approval.

"With a new oral antibiotic option that has been shown to be as effective as a respiratory fluoroquinolone, possessing a favorable side effect profile, we can consider sending more patients home directly from the emergency department and avoid costly hospitalizations, which is

good for both patient care and the health system," Giordano said.

Xenleta met the criteria for non-inferiority versus moxifloxacin in Phase III clinical trials generally viewed as positive, though Nabriva's drug caused higher rates of gastrointestinal side effects. The risk of C. diff has been characterized as low with only one patient in the Phase III program developing a C. diff infection. *(Also see "Nabriva On Pace For Lefamulin NDA; Stock Tumbles Despite Trial Success" - Scrip, 21 May, 2018.)*

The most common adverse events in clinical trials were diarrhea, nausea, injection site reactions, elevated liver enzymes and vomiting. Xenleta may cause prolonged QT interval in ECG readings, so patients with prolonged QT interval or irregular heart rhythms (arrhythmias) and patients taking drugs for those conditions should not be treated with the antibiotic. Xenleta is contraindicated for patients taking CYP3A4 substrates that prolong the QT interval.

NABRIVA LAUNCH STRATEGY TOOK ROOT TWO YEARS AGO

With clinical need and market demand seemingly in its favor, Lavino said Nabriva invested in the Xenleta commercial strategy early to support a differentiated antibiotic launch strategy.

"The launch team has been working in the field since late 2017 preparing the market for Xenleta," he said. "Our highly experienced eight regional business directors have been working on market development over the last couple of years by profiling more than 600 accounts and these represent more than two-thirds of our target accounts at launch. Thanks to this hard work, we have a deep understanding of the medical needs at each account for the management of CABP."

For example, Nabriva identified which hospitals are under CMS scrutiny to lower the cost of CABP treatment, which facilities are trying to limit the use of fluoroquinolones and which ones are implementing strategies to send CABP patients home from the hospital sooner with an oral drug.

"These unique profiles will allow us to target at launch those accounts with the greatest unmet needs and at the same time those with the highest readiness for Xenleta, where we can expect a quicker uptake," Lavino said.

He noted that Nabriva is working with Medicare and commercial plans to make sure there are low hurdles to obtaining reimbursement for Xenleta in the outpatient setting. The company's market access team has met with payers representing about 95% of the CABP patient lives.

"We have initiated already the contracting process with the majority of key payers and some contracts have been already finalized, including a contract with a large integrated health system," Lavino said. "We are very encouraged by our conversations with customers to date and in particular we are pleased that very large health systems have indicated they will be placing Xenleta on their formulary – a reflection of the value that Xenleta brings to patients and the medical community."

Nabriva noted that US hospital stays for pneumonia typically are about three to four days, driving direct costs for pneumonia treatment of about $17bn annually. The company said pneumonia is the number one cause of infectious death, number three cause of hospital readmissions and number five cause of total hospitalizations in the US, and the mortality rate is 15% in the hospital and 25-30% in the intensive care unit.

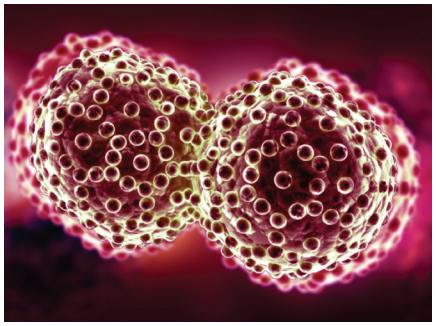
Wedbush analysts predict that at its peak, Xenleta will be used to treat about 10% of the 900,000 patients treated for CABP in US emergency departments annually and 10% of the 2.4m CABP patients admitted to the hospital for IV treatment and discharged with oral antibiotics. Driscoll said Wedbush hasn't forecast sales yet for the inpatient hospital or outpatient community settings, but those settings see 3.8m patients and 2.3m patients, respectively, every year.

Published online 21 August 2019

AstraZeneca's Imfinzi-Treme Checkpoint Inhibitor Combination Fails Again In NSCLC

AstraZeneca PLC's Imfinzi-tremelimumab combination has failed to improve overall survival in metastatic non-small cell lung cancer (NSCLC) patients, dealing another blow to the company's push to establish its anti-CTLA4 antibody as part of the immuno-oncology treatment toolkit.

The analysis of the NEPTUNE trial centered on first-line patients with a high tumor mutational burden (TMB), defined by AstraZeneca for this study as 20 or more mutations per megabase. AstraZeneca, like Bristol-Myers Squibb Co. before it, focused on TMB-high patients in the belief the larger numbers of neoantigens associated with their cancer cells could fuel a stronger antitumor immune response.



AstraZeneca's NEPTUNE results raise further doubts about that theory. The top-line finding is that the combination of anti-PD-L1 antibody Imfinzi and anti-CTLA4 antibody tremelimumab failed to better the overall survival achieved by chemotherapy. Observers were braced for the failure.

"Expectations for first-line NSCLC are low after the MYSTIC failure. We are cautious on Imfinzi+treme combo arms in Phase III NEPTUNE and POSEIDON given prior setbacks," analysts at Jefferies wrote in a note to investors last month. The high bar set by Merck's checkpoint inhibitor Keytruda in NSCLC means even a moderate clinical success may have mattered little commercially.

TURN TO PAGE 18

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CONTINUED FROM PAGE 16

Researchers at AstraZeneca are still analyzing the clinical and biomarker data generated in the trial with a view to presenting the full results at an upcoming medical meeting. The lack of data available publicly today make a deep analysis of the trial and its implications for AstraZeneca impossible, but the top-line findings and their concurrence with other studies provide some pointers.

As the Jefferies analysts referenced last month, the Imfinzi-tremelimumab combination has been tarnished by earlier clinical failures. Tremelimumab failed its first Phase III back in 2008, three years before AstraZeneca picked up rights to the CTLA-4 drug from Pfizer, and has been involved in a series of weak clinical readouts over the past two years.

AstraZeneca's MYSTIC, the company's big hope of making up lost ground in immuno-oncology, found the Imfinzi-tremelimumab combination failed to improve progression-free survival in first-line NSCLC in 2017. The following year, AstraZeneca reported the trial also failed to improve overall survival.

In between those readouts, AstraZeneca identified TMB-high patients as a subpopulation that could increase the likelihood of NEPTUNE generating better results than MYSTIC. A subsequent post hoc analysis of MYSTIC data showed overall survival was longer in TMB-high patients, in that case defined as above 16 mutations per megabase. By then, AstraZeneca had already expanded NEPTUNE to gain the option to look at TMB-high patients.

BMS, an early mover in TMB, has also faced setbacks in its efforts to turn the idea into a commercial opportunity. BMS filed for FDA approval of its checkpoint inhibitor combination – anti-PD-1 antibody Opdivo and anti-CTLA-4 antibody Yervoy – in advanced NSCLC patients with TMBs above 10 mutations per megabase last year, only to withdraw the filing in January.

BMS withdrew the filing after talks with the FDA led it to conclude it would need "further evidence on the relationship between TMB and PD-L1" to show the impact of its combination. As the required data was not available at that time, it pulled the submission. The comany has since reported that its combination improved overall survival in first-line NSCLC.

Analysts asked AstraZeneca last month about the potential readthrough from the BMS's data for NEPTUNE's prospects but management declined to offer an opinion.

"What we're learning is that these immuno-oncology studies have a degree of inconsistency," José Baselga, head of oncology R&D at AstraZeneca, said on the quarterly results conference call.

The failure of NEPTUNE leaves AstraZeneca reliant on the ongoing POSEIDON trial for evidence of the efficacy of its immuno-oncology combination in NSCLC. That Phase III trial is also looking at Imfinzi in combination with chemotherapy. POSEIDON is due to readout by the end of the year.

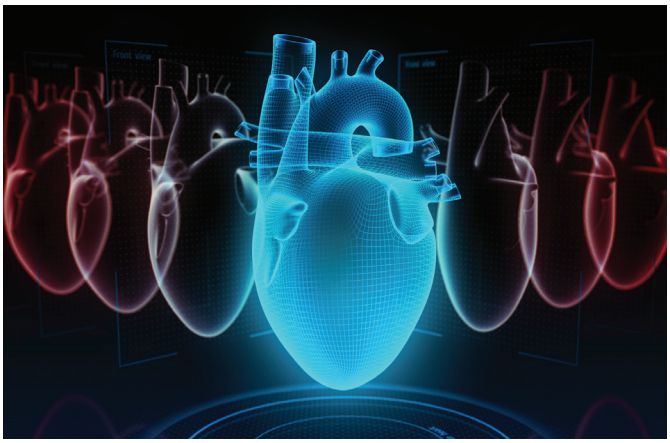
Published online 21 August 2019

AZ's Dapagliflozin Impresses In Topline Phase III Heart Failure Study

JOHN DAVIS john.davis@informa.com

AstraZeneca PLC's Farxiga/Forxiga (dapagliflozin) has become the first SGLT2 inhibitor to show a reduction in the risk of cardiovascular death or worsening of heart failure in patients with reduced ejection fraction heart failure (HFrEF), with or without type 2 diabetes, when added to the standard of care.

The positive results, from the DAPA-HF study, should give a boost to dapagliflozin, whose sales grew by 14% to reach $737m in the first half of 2019 in the highly competitive SGLT2 inhibitor sector.



In DAPA-HF, dapagliflozin met the primary composite endpoint with a significant and clinically meaningful reduction of cardiovascular death or worsening of heart failure (defined as hospitalization or an urgent heart failure visit), AstraZeneca announced on 20 August. Side effects were consistent with the drug's established safety profile, and the big pharma says it will discuss the results with regulators.

Further details were not given and are expected to be presented at a forthcoming scientific meeting, although according to John McMurray, of the University of Glasgow's Institute of Cardiovascular and Medical Sciences, the benefits of dapagliflozin were "very impressive, with a substantial reduction in the primary composite outcome of cardiovascular death or hospital admission."

An effective therapy for HFrEF is sorely needed: "Half of heart failure patients will die within five years of diagnosis, and it remains one of the leading causes of hospitalization," commented AstraZeneca's Mene Pangalos, executive vice president of BioPharmaceuticals R&D.

Analysts at Informa Intelligence's Datamonitor Healthcare recently noted that the "high co-occurrence of diabetes with chronic heart failure means that the cardiovascular benefits of SGLT2 inhibitors could facilitate substantial uptake of the class in type 2 diabetic patients at risk of heart failure. Further studies are look-

ing into use in non-diabetics, and this could significantly expand the class's target population, if the drugs are shown to be effective in reducing hospitalizations and/or mortality in the broader non-diabetic CHF population."

Companies have been active in evaluating CV outcomes in diabetic patients before narrowing down their focus to chronic heart failure. Earlier this month, dapagliflozin had its EU label updated to include positive cardiovascular outcomes and renal data from the DECLARE-TIMI 58 trial, in type 2 diabetics with no existing cardiovascular disease.

Sector leader, Boehringer Ingelheim GmbH/Eli Lilly & Co.'s Jardiance (empagliflozin), had its label updated several years ago based on improved CV outcomes in the EMPA-REG study, and initial results are expected shortly from its clinical trial program in patients with chronic heart failure.

Marketed drugs in other product classes, such as Novartis AG's Entresto (sacubutril/valsartan), are already approved to treat patients with HFrEF, although Entresto recently missed the primary endpoint point in the Phase III PARAGON study in heart failure patients with preserved ejection faction (HFpEF).

In DAPA-HF, dapagliflozin 10mg once daily or placebo was administered to patients with a left ventricular ejection fraction of less than 40%, to patients with and without type 2 diabetes, whose treatment included drugs such as ACE inhibitors, ARBs, beta-blockers, mineralocorticoid receptor antagonists and neprilysin inhibitors. Dapagliflozin is also being studied in patients with heart failure in the DELIVER (HFpEF) and DETERMINE (HFrEF and HFpEF) studies, and in patients with chronic kidney disease in the DAPA-CKD trial.

Published online 20 August 2019

DREAMM-2 Put GSK's BCMA Drug In Pole Position

GlaxoSmithKline PLC's anti-B-cell maturation antigen (BCMA) therapy has improved outcomes in a pivotal multiple myeloma trial, setting the company up to file for approval by the end of the year.

The asset, belantamab mafodotin, is an anti-BCMA antibody-drug conjugate (ADC) that uses a linker technology licensed from Seattle Genetics Inc.. As the transmembrane glycoprotein BCMA is expressed at elevated levels by multiple myeloma cells, but not the vast majority of noncancerous cells, GSK and a number of other drug developers have identified the target as a way to better treat the disease.

GSK now has more evidence to support that belief. In the trial of 223 relapsed/refractory multiple myeloma patients, belantamab mafodotin was associated with an overall response rate sufficient for the study to hit its primary endpoint. GSK is yet to share data from the trial but called the rate "clinically meaningful" in a statement, adding that it will use the results as the basis for a regulatory filing later this year.

GlaxoSmithKline PLC has six new drug and indication expansion filings planned in the second half of 2019, the company said during its second quarter financial call on 23 July. Three of those filings are in oncology, including two new oncology drugs.

An earlier study of belantamab mafodotin, also known as GSK2857916, provides a pointer to the level of efficacy GSK may have seen in the pivotal trial. In the second part of its early phase DREAMM-1 trial, GSK reported an overall response rate of 60.0% and a complete response rate of 15%. Progression-free survival came in at 12 months.

Belantamab mafodotin achieved that efficacy in heavily pretreated patients. Two-fifths of people in the study had received five or more lines of therapy before starting on belantamab mafodotin.

There are reasons to think the patients enrolled in the pivotal trial would be even harder to treat. In the previous study, just 13 of the 35 patients had been treated with Johnson & Johnson's Darzalex (daratumumab) prior to enrollment. Among that subpopulation, the response rate was 38.5%, compared with 71.4% in people who had never been treated with J&J's blockbuster anti-CD38 antibody.

As the DREAMM-2 trial only enrolled people previously treated with an anti-CD38 antibody, the 38.5% response rate achieved in the Darzalex subgroup may be more indicative of the new efficacy data. The eligibility criteria for the pivotal trial also required subjects to have tried an immunomodulatory drug, such as Celgene's thalidomide, and a proteasome inhibitor, such as Takeda Pharmaceutical's Velcade.

The level of efficacy achieved in DREAMM-2 will matter as, while the targeted patient population currently has limited options, developers of other BCMA drugs are working to serve the same people as GSK.

BCMA is among the most fought over targets in drug development. Johnson & Johnson, Poseida Therapeutics Inc. and a Celgene Corp./bluebird bio Inc. alliance all have anti-BCMA CAR-T therapies in advanced trials; AstraZeneca PLC has an anti-BCMA ADC that is trailing belantamab mafodotin in the clinic; and companies including Amgen Inc., Regeneron Pharmaceuticals Inc. and Pfizer Inc. are testing bispecific antibodies against the target in humans.

GSK is near the front of the BCMA pack but will need to move quickly to capitalize on that advantage. Recognizing that, Hal Barron, chief scientific officer at GSK, has made belantamab mafodotin the poster child for a new model of R&D at GSK. Under Barron, GSK singled out belantamab mafodotin as a particularly promising candidate and committed to a broad clinical trial strategy designed to get the ADC to market and then quickly expand its label.

"It is a good example of our cultural progress in terms of improving our focus and investing behind the most promising effort," Barron said on a quarterly results conference call with investors late last month.

In practice, that means Barron's team is putting belantamab mafodotin through a number of clinical tests simultaneously. The current strategy calls for GSK to start four pivotal trials over the next year, with a fifth to follow in 2021. The goal is to expand use beyond the fourth-line setting in which GSK hopes to win approval next year by showing the drug works in patients who have received between zero and two lines of therapy.

Published online 23 August 2019

What Else Analysts Want To Know About TMC's Inclisiran

JOSEPH HAAS joseph.haas@informa.com

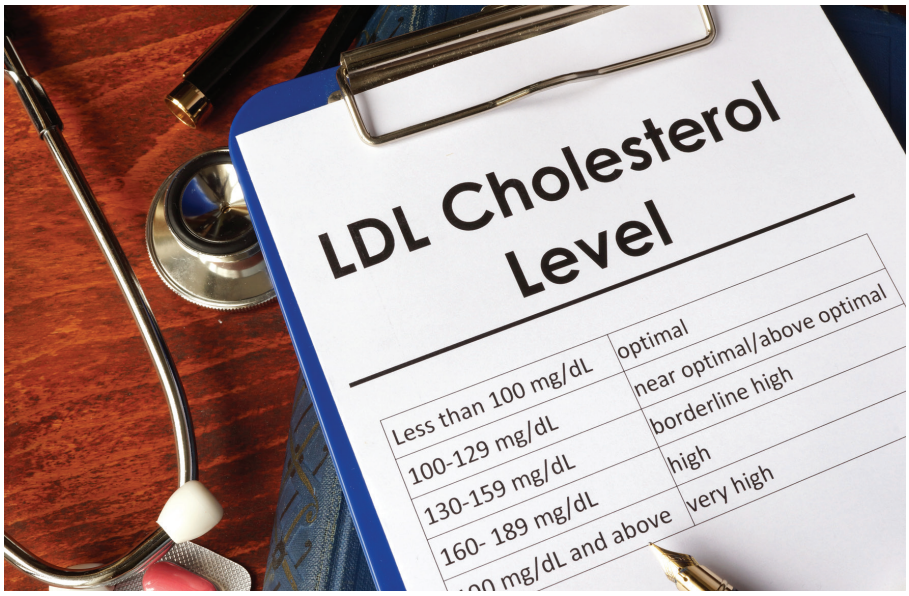
Top among the things analysts want to see when additional data for The Medicines Co.'s inclisiran are presented next week are the magnitude of the efficacy results for the RNA-interference therapy and a clear understanding of the safety profile, especially liver toxicity.

The Medicines Co. released topline Phase III results from the ORION-11 study, the first in a three-trial program, on 26 August – just ahead of the presentation of more detailed data from the study at European Society of Cardiology's 2019 Congress in Paris on 2 September.

The drug's potential as a twice-annual subcutaneous therapy to reduce LDL cholesterol levels is clear-cut. The company reported that inclisiran, an oligonucleotide that silences the production of the PCSK9 enzyme, met all primary and secondary efficacy endpoints in the 1,617-patient ORION-11 study while offering a safety profile at least as good as seen in Phase II studies. *(Also see "Medicines Company Gets Aggressive With Inclisiran Phase III Plans" - Scrip, 31 Aug, 2017.)*

In a same-day note, J.P. Morgan analyst Jessica Fye said TMC told her its statement of "at least as favorable" safety as seen in earlier studies means that every aspect of inclisiran's safety profile is looking clean – including liver enzyme levels, renal function and platelets. As a short-interfering RNA (siRNA) therapy to be dosed twice-annually, inclisiran would be positioned to compete with antibody PCSK9 inhibitors, such as Amgen Inc.'s Repatha (evolocumab) and Sanofi/Regeneron Pharmaceuticals Inc.'s Praluent (alirocumab), which are given once or twice a month. *(Also see "The Medicines Co. CEO Timney On Selling Inclisiran And Why Big Pharma Is Still Interested In CV Disease " - Scrip, 29 Apr, 2019.)*

TMC anticipates reporting out data from three Phase III studies of inclisiran before the end of the third quarter, including ORION-9 in heterozygous familial hypercholesterolemia. ORION-10 and ORION-11 are testing the therapy in atherosclerotic cardiovascular disease (ASCVD) and its risk equivalents. ORION-11 enrolled patients with ASCVD or risk-equivalent disease with elevated LDL-C despite receiving the maximum tolerated dose of statin therapy, with or without Merck & Co. Inc.'s Zetia (ezetimibe).



TMC hopes inclisiran can reduce LDL-C levels with twice-annual dosin

In the double-blind, placebo-controlled ORION-11, a 300mg dose of inclisiran was given to patients at days one and 90 and then every six months afterward. Without providing numerical details, TMC said on 26 August that the drug met the primary endpoints of percentage change in LDL-C from baseline to 17 months (day 510) and time-adjusted percentage change in LDL-C from baseline after 90 days and up to 18 months (540 days). The study also met secondary endpoints of mean absolute change at 510 days and average absolute reduction from day 90 through day 540 of treatment.

Patients from ORION-11 and the two other ongoing Phase III studies of inclisiran are eligible to roll over to the ORION-8 open-label, long-term extension study, which will provide the drug for three years to ascertain long-term efficacy, safety and tolerability. TMC hopes to file inclisiran for US approval during the fourth quarter of 2019 and then in Europe during the first quarter of 2020.

JPM analyst Fye said investors are focused on safety details going forward, so the fuller report to be given at ESC will be watched closely, especially for signs that will de-risk the drug for liver safety.

One safety aspect that will be evaluated over the longer-term will be the full impact of blocking PSCK9 synthesis, as opposed to the safety of PCSK9 inhibitors, which clear up the enzyme after it has been produced. When TMC outlined its Phase III plans at ESC 2017, researcher Philip Barter of Australia's University of New South Wales pointed out that the effects of inhibiting PCSK9 beyond the LDL receptor, as a gene-silencing therapy would do, are unknown.

On safety, Biomedtracker echoed the viewpoint that the details will prove key. "For Phase II, it was noteworthy that there were no drug-related increases in liver function tests in the ORION-3 extension and a similar rate as placebo in ORION-1," it noted in a 26 August analysis. "There should be more details on other safety parameters of interest at ESC, such as renal function, though there were apparently no concerns raised in the ORION-7 renal impairment study."

KEEPING AN EYE ON EFFICACY

Biomedtracker's analysis also emphasizes that the magnitude of inclisiran's LDL-C-lowering effect will be critical. In a

Jefferies note issued on 15 August looking ahead to data from the three ORION pivotal studies, analyst Biren Amin said at least replicating the 51% reduction of LDL-C from baseline seen in Phase II will be critical for inclisiran's prospects. TMC has guided that a 54% reduction from baseline should be seen across the trio of Phase III studies.

The ongoing Phase II ORION-3 open-label extension study includes a comparator arm in which some patients receive Repatha, Biomedtracker pointed out, but TMC has said it won't release the comparator data until they are necessary and relevant; the study is slated to run into 2022. "Even if inclisiran were not quite as strong as current PCSK9 inhibitors, though, its infrequent dosing may be quite compelling for patients," Biomedtracker's analysts added.

JPM's Fye had an overall positive take on the news. "We came away from this encouraging top-line release with even stronger conviction in the safety profile of inclisiran and believe this coupled with rational pricing and greatly improved dosing convenience/compliance will lead to a substantial market opportunity," she wrote.

> "Inclisiran's infrequent dosing may be quite compelling for patients." – Biomedtracker

When Mark Timney was named TMC's new CEO, succeeding the longstanding top exec Clive Meanwell in late 2018, he outlined a strategy of developing inclisiran as a game-changing potential blockbuster, but a product that his company would look to sell off, believing ultimately it would fare better in the hands of a deeper-pocketed large pharma company. *(Also see "The Medicines Co. Names Mark Timney As CEO In A Shakeup" - Scrip, 11 Dec, 2018.)* In unveiling the top-line data from ORION-11, TMC said it perceives an addressable population of as many as 12.7m patients for the therapy in the US.

TMC's drug, which was licensed from RNAi pioneer Alnylam Pharmaceuticals Inc. in 2013, is not the first gene-silencing candidate advanced for lipid-lowering therapy – Akcea Therapeutics Inc.'s Waylivra (volanesorsen) for familial chylomicronemia syndrome received a complete response letter from the US Food and Drug Administration in August 2018, following a close vote at an FDA advisory committee. Waylivra obtained EU approval this past May; Akcea said it plans to launch the therapy in Germany this year and in other EU markets in 2020. *(Also see "New EU Approvals" - Pink Sheet, 9 May, 2019.)*

Published online 26 August 2019

Retrophin's Focus Shifts After Phase III PKAN Failure

JOSEPH HAAS joseph.haas@informa.com

Retrophin Inc. will shelve its most advanced pipeline asset and place its R&D focus on sparsentan in focal segmental glomerulosclerosis (FSGS) and IgA nephropathy (IgAN), after announcing on 22 August that fosmetpantotenate (fosmet) failed an 84-patient Phase III trial in the rare central nervous system disorder pantothenate kinase-associated neurodegeneration (PKAN).

PKAN, which has no approved drug therapy, is caused by a mutation in the PANK2 gene, resulting in metabolic pathway disruption that reduces levels of coenzyme A (CoA), which is essential to regulating critical processes, including energy metabolism and membrane integrity. Thought to affect roughly 5,000 patients worldwide, PKAN is characterized by progressively debilitating symptoms that begin in childhood, including dystonia, rigidity and dysphasia.

While not detailing the data from the Phase III FORT study, Retrophin told an investor call that fosmet failed to show a difference from placebo on a primary endpoint of PKAN-ADL (activities of daily living scale) at 24 weeks of treatment. It also failed a secondary endpoint – a clinician-scored monitored motor evaluation of the Unified Parkinson's disease rating scale (UPDRS-part III). Retrophin developed PKAN-ADL, a patient-reported outcome, based on the UPDRS tool. Executives said during the call that they have not completed a full review of the FORT data, but admitted they see no subpopulation statistics that could illustrate a path for further development of fosmet in PKAN. They plan to present the full dataset at a future medical conference.

CEO Eric Dube noted that the FORT study went forward on the evidence obtained from a small number of investigator-sponsored studies. "We were encouraged by the clinically meaningful improvement reported in a small number of individual case reports from physician-initiated treatment with fosmetpantotenate over the last several years," he said. "Unfortunately, we did not see a consistent outcome with FORT. And we are surprised that fosmetpantotenate did not demonstrate an effect in a broader population of patients with PKAN."

The US Food and Drug Administration told Retrophin in 2014 that it could not file an investigational new drug (IND) application for fosmet in PKAN based on investigator-sponsored trials, so it initiated its own IND-enabling studies. Dube told the 22 August call that he was confident that FORT was soundly structured and well conducted. It should at least provide the PKAN patient community with "one of the most comprehensive datasets to date in this patient population," he added.

The only other ongoing effort to develop a drug for PKAN, according to Biomedtracker, is PZ-2891, a preclinical, oral pantothenate kinase activator developed by CoA Therapeutics, a portfolio company of rare disease-focused BridgeBio Pharma Inc.. CoA hopes to bring the allosteric modulator discovered by and licensed from St. Jude Children's Research Hospital into Phase I during the first quarter of 2020.

TURN TO PAGE 23

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

PIPELINE WATCH, 16–22 AUGUST 2019

PHASE II

Event Stage	Lead Company/Partner	Drug Name	Indication	Comments	Change To LOA (%)	LOA (%)
Phase II Updated Results	Kalytera Therapeutics, Inc.	cannabidiol (Kalytera)	Graft vs. Host Disease	KAL-05; Encouraging Results	0	20
Phase IIa Top-Line Results	Oxurion NV	THR-137	Diabetic Macular Edema	w/ranibizumab; Mixed Results	-	-
Phase Ib/IIa Top-Line Results	Synlogic, Inc.	SYNB1020	Hepatic Encephalopathy	Lack Of Efficacy, Discontinued	-24	0
Phase IIb Trial Initiation	Fulcrum Therapeutics, Inc.	losmapimod	Muscular Dystrophy, Facioscapulohumeral	ReDUX4; A p38alpha/beta MAPK Inhibitor	24	24
Phase IIb Trial Initiation	Aimmune Therapeutics, Inc.	AR201 (dried egg white protein)	Allergy To Eggs	Oral Immunotherapy Desensitization	24	24
Phase II Trial Initiation	Landos Biopharma Inc.	BT-11	ulcerative colitis, mild to moderate	At 60 Sites In US And Europe	-	-
Phase II Trial Initiation	Knopp Biosciences	dexpramipexole	Asthma, Eosinophilic	AS201; Dose-Ranging Study	18	18
Phase II Trial Initiation	Rocket Pharmaceuticals Inc.	RP-L102	Fanconi Anemia	FANCOLEN-II; In Spain In Children	0	30
Phase II Trial Initiation	Novartis AG	CMK389	Pulmonary Sarcoidosis	In 66 Subjects	-	20
Phase II Trial Initiation	Scancell Holdings PLC	SCIB1	Melanoma	w/Keytruda; In The UK	0	10
Phase IIb Trial Announcement	MedPacto Inc.	vactosertib	Bladder Cancer	With durvalumab; Single-Arm Study	-	10

PHASE III

Event Stage	Lead Company/Partner	Drug Name	Indication	Comments	Change To LOA (%)	LOA (%)
Phase III Published Results	Teva Pharma	Ajovy (fremanezumab)	Migraine Prevention	FOCUS; The Lancet, 16 Aug, 2019	0	100
Phase III Published Results	Bristol-Myers Squibb	Opdivo (nivolumab)	Renal Cell Carcinoma	The Lancet Oncology, 16 Aug, 2019	0	100
Phase III Published Results	Heron Therapeutics	HTX-011	Pain Relief In Hernia Surgery	EPOCH2; Hernia online, 19 Aug, 2019	0	97

Source: Biomedtracker | Informa, 2019

CONTINUED FROM PAGE 21

Retrophin chief medical officer Noah Rosenberg said 84 patients were enrolled in the FORT study, balanced between adult and pediatric patients, and were randomized on a 1:1 basis to study drug or placebo. Seventy-eight patients completed the 24-week treatment cycle – a low dropout rate – and all control-arm patients who finished 24 weeks opted to participate in an open-label extension with fosmet.

"Unfortunately, the FORT Study did not meet the primary endpoint as there was no difference demonstrated between treatment groups after 24 weeks," the exec said. "The study also did not meet its secondary endpoint. In the analyses we have seen thus far, there is nothing that would suggest that treating patients for a longer period would result in any difference in response. We have also done an initial analysis of the PK profile, and that showed an exposure that was consistent with the range in our Phase I work. The mean placebo effect seen in the study was also within our expectations."

Biomedtracker called the FORT data "resoundingly negative" and indicated agreement with Retrophin's assessment that there likely is a not a path forward for fosmet.

"While there is heterogeneity in the disease, [Retrophin] officials said they have so far looked at age and onset of disease, without finding a subgroup where the drug worked better, and they do not expect to find any other specific subpopulations that may benefit, though will still be doing additional analyses, including patients with differing mutations," Biomedtracker's analysis states. "They do not yet know the timeline of those analyses however, or when the data will be presented. Preclinical data did suggest the drug gets into the brain, but that is not something they will be able to tell from the clinical study, as testing CSF (cerebrospinal fluid) would have been burdensome."

Retrophin will discontinue development of fosmet and work with the trial investigators to determine "appropriate next steps" for patients in the open-label extension, Rosenberg added. The shuttering of fosmet closes another chapter in the rocky tenure of former Retrophin CEO Martin Shkreli, who was listed among the drug's inventors on patent documents. Shkreli currently is serving a seven-year federal prison sentence for securities fraud.

Retrophin's share price declined 22% to close at $13.56 on 22 August, even though analysts said virtually unanimously that the trial failure was not a surprise. Liisa Bayko of JMP Securities called the study "a long shot" and had given FORT a 20% likelihood of success, she said in a same-day note.

However, the investment firm maintained a "market outperform" rating for Retrophin based on its optimism for sparsentan in FSGS and IgAN. Bayko assigns sparsentan, a dual blocker of angiotensin II receptor 1 and endothelin type-A receptor, a 70% likelihood of approval in FGFS and 40% in IgAN.

Retrophin's confidence in sparsentan stems from the Phase II DUET study, in which it demonstrated statistically significant, clinically meaningful reductions in proteinuria. "We see positive read from the DUET results and continued updates from the open-label safety study as de-risking the Phase III DUPLEX study [in FSGS], which is expected to read out in the first half of 2021," William Blair & Co. analyst Tim Lugo said.

Published online 22 August 2019

APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
Simon King	Daiichi Sankyo Inc	Chief People Officer	Bristol-Myers Squibb	Global Head, Talent and Workforce Innovation	12-Aug-19
Maya Martinez-Davis	GlaxoSmithKline plc	President, US Pharmaceuticals	EMD Serono	Senior Vice President, Global Oncology	15-Sep-19
Shahin Fesharaki	Hikma Pharmaceuticals plc	Chief Scientific Officer and Global Head, Research and Development	Actavis	Chief Operating Officer, Global Research and Development	5-Aug-19
Hilary McElwaine-Johnn	Karus Therapeutics Ltd	Chief Medical Officer	PsiOxus	Chief Medical Officer	17-Jul-19
Fred Grossman	Mesoblast Ltd	Chief Medical Officer	Glenmark	Chief Medical Officer	12-Aug-19
Lars Nieba	Nordic Nanovector ASA	Chief Technology Officer	Bayer AG	Vice President and Strategic Product Lead	1-Dec-19
Noah Nasser	Serimmune Inc	Chief Executive Officer	Human Longevity Inc	Chief Commercial Officer	6-Aug-19

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Source: Medtrack | Informa, 2019

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