



Inclisiran's Safety Data Suggest Game-Changing Potential In PCSK9 Market

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The Medicines Co. followed up its 26 August top-line readout for the Phase III ORION-11 trial of inclisiran with a full dataset that shows the short-interfering RNA (siRNA) therapy can offer LDL cholesterol-lowering capability similar to on-market PCSK9 inhibitors with twice-yearly dosing and a safety and tolerability profile similar to placebo.

Presenting the data at the European Society of Cardiology meeting on 2 September, The Medicines Co. asserted that inclisiran can be a market-disrupting LDL-C therapy that will address needs for therapeutic adherence and convenience.

The data "increase our confidence and excitement in the substantial possibility for inclisiran to fundamentally reshape the landscape of cardiovascular care like never before," CEO Mark Timney said. "It's the first and only LDL-C therapy that would be administered by a health care professional twice yearly. We believe that inclisiran is a game-changer that solves two critical unmet needs – additional LDL-C lowering and poor adherence – which will get many more patients to goal."

On 26 August, the New Jersey company announced inclisiran met all primary and secondary endpoints in ORION-11, which was the first of three pivotal studies ex-

pected to read out during this quarter, but observers wanted more detail on the magnitude of its LDL-lowering effect and its safety profile.

The Medicines Co. hopes to position inclisiran, which silences production of the PCSK9 enzyme, as a more-convenient alternative to approved PCSK9 inhibitors.

Amgen Inc.'s Repatha (evolocumab) and Sanofi/Regeneron Pharmaceuticals Inc.'s Praluent (alirocumab) are given once or twice a month versus inclisiran's twice-yearly administration. (Also see "The Medicines Co. CEO Timney On Selling Inclisiran And Why Big Pharma Is Still Interested In CV Disease" - Scrip, 29 Apr, 2019.)

SVB Leerink analyst Joseph Schwartz called the ORION-11 data "better than expected" in a 2 September note and said they partially de-risk the upcoming Phase III ORION-9 and ORION-10 studies. ORION-9 tests the candidate in heterozygous familial hypercholesterolemia, while ORION-10 and ORION-11 are in the atherosclerotic cardiovascular disease (ASCVD) setting.

EFFICACY RESULTS MATCH PHASE II, SIMILAR TO PCSK9 INHIBITORS

In a 1,617-patient study that randomized patients to 4mg, 8mg or 12mg of inclisiran twice-yearly or placebo, the 12mg dose yielded a placebo-adjusted mean reduction in LDL-C of 54% from baseline ($p < 0.0001$) at 17 months (510 days) and a time-averaged placebo-adjusted LDL reduction of 51% from days 90 through 540 of treatment ($p < 0.0001$). The study was designed to dose patients on day one and day 90 and then every six months after that.

Analysts previously said the drug would need to at least replicate the 51% LDL reduction seen in Phase II to stand a strong

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from the editor

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RNA interference drug inclisiran is showing signs that it could be a thorn in the side of Amgen, Regeneron Pharmaceuticals and Sanofi in the market for PCSK9 inhibitors to reduce cholesterol (see cover story). If trials continue to report favorably, there will be room for developer The Medicines Co. to price it in a way that is meaningful to both its own bottom line and that of payers. Its twice-yearly dosing schedule is much more convenient than that of the monoclonal antibody PCSK9 inhibitors Repatha (evolocumab - Amgen) and Praluent (alirocumab - Sanofi/Regeneron), which are dosed every two or four weeks.

Nevertheless, inclisiran, should it make it to approval, will be competing in a space that has not delivered anything like the returns that those front runners had once

been expected to generate. Repatha sales were \$550m in 2018; Praluent generated \$307m. These drugs have been on the market for more than four years now, and their manufacturers have already had to drop prices significantly since launch to secure any kind of market at all. At one point they were predicted to have peak sales upwards of \$3bn each.

With a lower annual cost for inclisiran versus Repatha and Praluent, The Medicines Co. may be able to grow the market to target more of the patients that could benefit from PCSK9 inhibition if only it weren't so expensive and inconvenient. That will erode the existing market for the incumbents. It will be interesting to see how much it is also able to grow the size of the market in terms of overall revenues.

Scrip

Informa Pharma Intelligence

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Finance Watch: Here Come The IPOs Again As Bellus Raises \$70m And Vir Joins The Queue

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Canada's Bellus Health Inc. launched an initial public offering in the US on 5 September, raising \$70m in the first US IPO by a biopharmaceutical company since 17 July.

Even while biopharma IPOs came to a standstill in the latter half of the summer, companies continued to file paperwork with the US Securities and Exchange Commission (SEC) in support of future offerings. The latest drug developer to join the queue is Vir Biotechnology Inc., the infectious disease-focused firm led by former Biogen CEO George Scangos, with plans to raise up to \$100m in a forthcoming IPO.

Bellus's stock already trades on the Toronto Stock Exchange in Canada, but the company acted quickly during the first few days of September to access US investors. Laval, Quebec-based Bellus said in SEC filings on 3 and 4 September that it had \$32.4m in cash as of 30 June and planned to raise up to \$60m in a US offering. The company then launched its IPO on 5 September with 9.86m shares priced at \$7.10 each to gross \$70m before the potential sale of additional shares to meet overallotments.

Published online 6 September 2019

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chance competing against Repatha and Praluent. Jefferies analyst Biren Amin pointed out in a 2 September note that those antibody therapies posted 56% and 47% LDL-lowering efficacy in their Phase III programs, respectively.

“With unrivaled convenience, clean safety and comparable efficacy to approved PCSK9 antibodies, ORION-11 data reinforces inclisiran as a potential front-runner in the PCSK9 space, in our view,” wrote Leerink’s Schwartz.

On safety, inclisiran was numerically superior on several measures compared to placebo. Serious treatment-emergent adverse events occurred in 22.5% of control-arm subjects and 22.3% of patients receiving study drug. Rates of death (1.9% versus 1.7%) and malignancies (2.5% versus 2%) also were higher among those who received placebo. Liver and renal function tests favored inclisiran over placebo as well.

ORION-11 tried to give an early indication of cardiovascular outcomes, although The Medicines Co. conceded that significantly more data would be needed before inclusion in labeling would be possible. The company noted

that 87% of trial subjects had established cardiovascular disease, and the rest were high-risk patients for whom prevention was being sought. Ninety-five percent of patients were on high-intensity statin therapy, and the baseline LDL level was more than 100mg/dL.

The rate of fatal and non-fatal heart attack was lower in patients who received inclisiran (1.2%) than placebo (2.7%), as was the rate of fatal and non-fatal strokes (0.2% for treated patients, 1% for control).

Kausik Ray of Imperial College London, lead clinical investigator for the ORION-11 study, told a 2 September investor call that those are the primary endpoints being investigated in the 15,000-patient ORION-4 cardiovascular outcomes study of inclisiran, expected to yield data in 2022.

“Although not powered for statistics, we believe this early peek at outcomes data is encouraging for long-term trial ORION-4 and may improve physician uptake ahead of full outcomes results,” Schwartz said. Jefferies’ Amin called the cardiovascular data “encouraging,” suggesting success for ORION-4, which is enrolling patients with similar characteristics to ORION-11.

One notable safety and tolerability difference between the study drug and pla-

cebo was injection-site reactions, seen in 4.7% of those who received inclisiran, but just 0.5% of control-arm subjects. However, “the majority were mild, none were severe and none were persistent,” Ray told the call.

Amin said the use of a 22-gauge needle and the volume of drug administered may be the cause for the injection-site reactions, and may lead to more in-office administration of inclisiran. “Typically, 22-gauge needles are associated with intramuscular injections or subcutaneous vaccine shots, and we think doctors and patients will prefer in-office use,” he said.

A potential benefit here is that since doctors administer the medicine, they can be assured of therapeutic adherence. Morgan Stanley analyst David Leibowitz noted on 3 September that The Medicines Co. believes roughly two-thirds of patients receiving first-line LDL-reducing therapy are not adherent after one year.

Ray emphasized the vast difference for patients between taking 365 tablets a year or getting up to 26 injections, compared to twice-annual injections that would coincide neatly with scheduled doctor visits. 🌟

Published online 3 September 2019

Vertex Buys Semma, Gaining Cell Therapy-Based Type 1 Diabetes Treatments

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Vertex Pharmaceuticals Inc. is building out its early pipeline beyond cystic fibrosis with the \$950m acquisition of Semma Therapeutics Inc., a privately-held cell therapy company working in type 1 diabetes. Semma is pioneering a novel and potentially curative approach to treating type 1 diabetes based on the development of insulin-producing beta cells grown from stem cells that can restore insulin secretion.

Semma’s technology is early stage, having only been tested in animal models, but two lead programs have demonstrated preclinical proof-of-concept, including the ability to end hypoglycemia in animal

models. The company has also developed a device to encapsulate and protect the cells from the immune system to allow for durable implantation without the need for immunosuppressive therapy.

The acquisition is part of Vertex’s strategy to build out the company’s pipeline for the long term, beyond its current emphasis in cystic fibrosis. The company’s near-term growth driver is expected to be a triple combination for cystic fibrosis to be filed with the US Food and Drug Administration in the third quarter, made up of the CFTR corrector elexacaftor with the currently marketed double therapy Symdeko (tezacaftor/ivacaftor). (Also see “Vertex



Selects VX-445 For CF Triple Therapy Due To Safety/Tolerability” - Scrip, 30 May, 2019.)

But Vertex has also been focused on expanding the early pipeline to develop the next-generation of products. The company announced two deals in June to strengthen its gene-editing capabilities, including the acquisition of Exonics Therapeutics Inc. for \$245m upfront, bringing Vertex into the area of Duchenne muscular dystrophy, and the expansion of an existing collaboration with CRISPR Therapeutics AG into DMD. (Also see “Deal Watch: Vertex Expands Gene-Editing Efforts With A Pair Of Deals” - Scrip, 10 Jun, 2019.)

“Rather than wait on their laurels, Vertex is nicely laying the groundwork by getting companies early and preparing well in advance,” Jefferies analyst Michael Yee said.

“Many large-caps suffer because they can’t find new growth or drugs beyond their first blockbuster within a few years, but Vertex is nicely building a wealth of interesting pipeline programs right now – all in late preclinical or Phase I/II that will provide the growth in 2025 and beyond,” Yee added.

Vertex CEO Jeffrey Leiden said the acquisition aligned with the company’s strategy of investing in treatments for serious diseases in specialty markets.

Cambridge, MA-based Semma launched in 2015 with a \$44m Series A round, backed by venture investors like ARCH Ventures, MPM Capital and Fidelity Biosciences. A Series B round in 2017 brought in \$114m. Semma’s science is based on the work of Harvard University’s Douglas Melton, one of the founders of Semma.

CLINICAL DEVELOPMENT TIMELINE TBD

The company is pursuing the development of both the direct intra-hepatic transplantation of the islet cells and an islet cell-filled device in an immune-protection strategy. Semma recently said it was on track to initiate a two-part clinical trial program in the first half of 2020, the first being a clinical trial in patients with difficult to treat diabetes and hypoglycemia unawareness, when someone doesn’t experience the typical symptoms associated with hypoglycemia. A second trial in the second half of 2020 would be for the broader adult type 1 diabetes population using the cells encapsulated in the immunoprotective device without immunosuppression.

Vertex said it is too early to confirm the timing for the initiation of the first clinical trials, but it did say it would move forward with a phased approach. An initial trial will evaluate the cells alone, implanted intrahepatically in type 1 diabetes patients, in-

cluding those who have received an organ transplant and are already on immunosuppressive therapy. A second trial would evaluate the cell/device combination in patients without immunosuppression.

Semma will become a separate operating subsidiary of Vertex, led by Semma CEO Bastiano Sanna, who will join Vertex as Semma president. Melton will continue in his role as chair of Semma’s Scientific Advisory Board, providing oversight and guidance on the development of the programs. The transaction is expected to close in the fourth quarter. The company employs about 85 people.

Vertex won’t be the only one working in the space. One of the world’s global leaders in diabetes, Eli Lilly & Co., is working with partner

Sigilon Therapeutics Inc. to develop encapsulated cell therapies for the treatment of type 1 diabetes. The companies signed a global collaboration in 2018 with Lilly offering Sigilon \$63m upfront. ✨

Published online 3 September 2019

\$3bn Roivant Deal To Fill Holes At Dainippon

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Sumitomo Dainippon Pharma Co. Ltd. (SDP) has entered into a memorandum of understanding to acquire multiple Roivant Sciences GmbH assets, including ownership interests in up to 11 “vant” companies and other platform technologies, in a planned deal worth \$3bn (around JPY320bn).

The move will give the mid-size Japanese pharma firm’s pipeline a major boost as it faces the first loss of exclusivity for its top product Latuda (lurasidone) in the US in early 2023. The atypical antipsychotic had sales in North America of \$1.66bn in the fiscal year ended 31 March and is the company’s top product globally.

SDP had already intimated that it would seek mergers and acquisitions as part of its current mid-term plan, which calls for the Osaka-based company to become a “global specialized player” by 2033 in its core areas of psychiatry and neurology.

To this end, it is setting aside JPY300-600bn over the next five years for M&A and to fill what it sees as pipeline gaps; the group is targeting total revenues of JPY600bn by April 2023.

RECENT FAILURES

It has also faced several late-stage failures in the recent past, including of the novel agent napabucasin - which came through the \$2.63bn acquisition of Boston Biomedical Inc. in 2012 - at Phase III for pancreatic cancer. (Also see “Dainippon’s Lead Boston Asset Hits Wall In Pancreatic Cancer” - *Scrip*, 4 Jul, 2019.)

Before that, DSP shares were hit hard in January after Japanese bioventure partner SanBio Co. Ltd. unveiled disappointing results

for a novel cell therapy in ischemic stroke. (Also see “Surprising SanBio/Sumitomo Stroke Stumble Slams Stocks” - *Scrip*, 31 Jan, 2019.)

The Roivant deal has yet to be finalized and is subject to due diligence, but a legally binding definitive agreement is expected to be signed by the end of October, once terms have been set. In the meantime, neither company will be allowed to negotiate with third parties.

“Roivant will continue to launch other innovative Vants in the future.” – Vivek Ramaswamy

SDP said it aims to achieve mid- to long-term growth through the transaction, and “to acquire a rich pipeline with multiple development compounds that are expected to be launched by FY2022, including potential blockbusters.” The deal is also expected to enhance R&D productivity and accelerate digital transformation.

DEAL BREAKDOWN

If any final deal follows the non-binding MoU, it would have several components. SDP would initially acquire privately held Roivant’s ownership interests in five subsidiaries, which are expected

to receive multiple product approvals in the US over the FY2019-22 period. These include listed firms Myovant Sciences Ltd. (NYSE), which specializes in women's health and prostate cancer, and Urovant Sciences Ltd. (Nasdaq), which focuses on urinary disorders.

The other major companies are Enzyvant Sciences Ltd. with a presence in pediatric rare diseases, and Altavant Sciences (respiratory rare diseases), both of which are privately held by Roivant.

The Japanese firm will also have options (exercisable by the second half of FY2024) to acquire Roivant's interests in up to six additional "vant" companies, which together would give it access to more than 25 innovative clinical programs.

On top of this, SDP will acquire Roivant's proprietary DrugOme data analytics platform, which can accelerate clinical development using data from all aspects of the process to identify promising assets. Its Digital Innovation technology uses data analysis to optimize business operations, along with related employees, and Roivant would continue to access these under contract.

Roivant's Datavant operation, which handles external health data, and its Alyvant arm, which uses big data to improve sales and marketing effectiveness, will both remain subsidiaries but will provide services under contract to DSP.

Roivant CEO Vivek Ramaswamy, who founded the company in 2014, noted that his firm would still "continue to launch other innovative Vants in the future."

The final component of the deal is a still to be decided stock holding (of at least 10%) by SDP in Roivant itself.

KEY PIPELINE ASSETS

The major clinical stage assets that would come to DSP through a finalized deal include Myovant's oral GnRH receptor antagonist relugolix, which has completed Phase III trials for uterine fibroids and is scheduled for US NDA submission by the end of fiscal 2019 (next April). (Also see "Myovant Plans Q4 Uterine Fibroid Drug Filing In A Showdown With AbbVie" - Scrip, 23 Jul, 2019.)

This is also in Phase III for advanced prostate cancer, with top line results expected

in the same timescale, and in Phase III for endometriosis.

Urovant's lead program is vibegron, an oral beta-3 adrenergic receptor agonist that has completed Phase III in overactive bladder (OAB) and is also due for a US NDA by next April. This is also in Phase III for men with OAB and benign prostatic hypertrophy, and in Phase II for pain associated with irritable bowel syndrome.

The regenerative cell therapy RVT-802 is Enzyvant's lead asset, for which a US BLA has been filed for pediatric congenital athymia and for which a US commercial launch may happen sometime in fiscal 2019.

At Altavant, the tryptophan hydroxylase inhibitor rodatristat ethyl is in Phase II for pulmonary arterial hypertension and, idiopathic pulmonary fibrosis and sarcoidosis.

While the shape of the post-deal management structure remains to be finalized, the companies said this would include "the continued involvement of Roivant's senior leaders."

Published online 6 September 2019

Vascepa Included In European Dyslipidemia Guidelines Ahead Of Approval

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Amarin Corp. PLC hasn't even sought European Medicines Agency (EMA) approval for its purified fish oil therapy Vascepa (icosapent ethyl) to treat hypertriglyceridemia, but already the drug has won an endorsement from the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) in new dyslipidemia treatment guidelines presented on 2 September at the ESC Congress in Paris.

The ESC/EAS guidelines now state that doctors should consider prescribing Vascepa for patients who have high triglyceride levels despite treatments with statins and who are at high or very high risk for cardiovascular events. The cardiology groups cited Amarin's REDUCE-IT cardiovascular outcomes trial (CVOT), which found that Vascepa on top of statins cut the risk of cardiovas-

cular (CV) events by 25%, including CV death, in patients with baseline triglyceride levels between 135 mg/dL and 499 mg/dL. (Also see "That's Huge, Folks': Amarin's Vascepa Cuts CV Risk By 25% On Top Of Statins" - Scrip, 24 Sep, 2018.)

Vascepa is approved in the US to treat adults with severe hypertriglyceridemia, or triglyceride levels of 500 mg/dL or higher, but a supplemental new drug application (sNDA) under review at the US Food and Drug Administration would expand the product's label to reflect the reduction of cardiovascular events observed in patients with triglyceride levels from 135 mg/dL to 499 mg/dL in REDUCE-IT. Amarin intends to submit a marketing authorization application (MAA) to the EMA before the end of 2019 seeking an EU label similar to Vascepa's potentially expanded US label.

The company stunned investors in August with the announcement that the US FDA would convene an advisory committee meeting to review the application. (Also see "An AdComm After All: Amarin's Vascepa Labeling Update Now Delayed By FDA" - Scrip, 8 Aug, 2019.) Vascepa has a tentative meeting date of 14 November, but the FDA hasn't adjusted the sNDA's action date of 28 September, which leads Amarin to believe the agency will make a decision on the application soon after the committee review, CEO John Thero told Scrip in an interview.

"We're looking forward to that AdComm. We would've been ready for it if it would have been in August; we'll be even more ready for it in November," Thero said. "The PDUFA date has not been changed. We are assuming, as we've stated previously, that the FDA will act on the

approval of Vascepa promptly following that AdComm and hopefully before the end of this year.”

ESC/EAS NOT THE FIRST TO ADD VASCEPA TO GUIDELINES

In the meantime, Amarin continues to talk to doctors in the US and EU about the REDUCE-IT data at major cardiology meetings and win endorsements for Vascepa in treatment guidelines. Prior to the ESC/EAS guideline update, the American Diabetes Association (ADA) recommended that doctors prescribe Vascepa for patients with type 2 diabetes and high triglycerides.

The REDUCE-IT results were not released in time for an update to American Heart Association (AHA)/American College of Cardiology (ACC) treatment guidelines. However, the AHA noted in a scientific advisory issued in August that prescription-strength omega-3 fatty acid products – including both Vascepa and GlaxoSmithKline PLC’s now-generic Lovaza (omega-3 ethyl esters capsules) – can effectively reduce triglyceride levels.

Lovaza contains both the eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) forms of omega-3, while Vascepa is a proprietary EHA-only product. (*Also see “Teva generic fish oil pill win ruffles Amarin investors” - Scrip, 9 Apr, 2014.*) And, unlike Vascepa, Lovaza (Omacor in Europe) has not shown a benefit in terms of the reduction of cardiovascular events.

The ESC/EAS guidelines note that DHA-containing omega-3 therapies have not shown a CV risk reduction benefit. The European guidelines do not tell doctors to consider prescribing those products; instead they specifically note that physicians should consider Vascepa.

Thero said Vascepa’s inclusion in the ESC/EAS guidelines is “part of a growing chorus of recognized large unmet need and advocating for more preventative care in these patients.”

He noted that while Amarin’s product is not yet approved in Europe, “physicians who are seeing these patients on a regular basis appreciate the need for this care and it’s great to see this early advocacy coming from Europe, which sort of piggybacks on what we’ve seen from the American Diabetes Association and American Heart Association and from many individual physicians.”

PCSK9 Inhibitors Also Benefit From Updated ESC/EAS Guidelines

The updated ESC/EAS dyslipidemia guidelines also weighed in on PCSK9 inhibitors, recommending use for very high-risk patients whose LDL does not reach desired levels with statins and now-generic Zetia (ezetimibe) and for patients who are statin-intolerant. Previously the guidelines said doctors should consider prescribing PCSK9-targeting therapies – an endorsement based on a lower level of supporting evidence, which was issued before outcomes data were available for the two approved therapies in this class.

The guidelines also recommend more intensive reduction of LDL levels with revised treatment goals, meaning more aggressive pharmaceutical interventions – like PCSK9 inhibitors – may be needed to bring patients in line with desired LDL levels. Guidelines released in 2016 set an LDL goal of 70 mg/dL or a 50% reduction from baseline for very high-risk patients with a goal of 100 mg/dL or a 50% reduction for high-risk individuals, but now the goals are LDL reductions of at least 50% and 55 mg/dL for very high-risk and 70 mg/dL for high-risk patients.

This is good news for the PCSK9 inhibitor manufacturers – Amgen Inc. with Repatha (evolocumab) and Sanofi/Regeneron Pharmaceuticals Inc. with Praluent (alirocumab) – and for The Medicines Co., which presented its first set of positive Phase III data for inclisiran at the ESC Congress. Inclisiran could have an advantage over its predecessors given its comparable efficacy with twice-yearly dosing instead of once- or twice-monthly injections for Repatha and Praluent.

Sanofi/Regeneron recently won a reprieve from Amgen’s attempt to block sales of Praluent in the US in an ongoing intellectual property dispute. But Amgen has had greater success with its patent challenges in the EU, where it has blocked Praluent in Germany.

REDUCE-IT was conducted in 11 countries with the largest number of patients coming from the US, followed by sites in Europe, particularly in the Netherlands.

“We know we have some strong supporters there and we think that that showed up in these guidelines, so I should think that these guidelines would help both our submission in Europe as well as reimbursement for our product in Europe once it’s approved,” Thero said.

EU LAUNCH WILL REQUIRE A PARTNER, AS IN OTHER EX-US MARKETS

The Amarin CEO explained that the company intentionally waited to pursue approval and a product launch in Europe based on the REDUCE-IT results rather than for the “niche indication” that Vascepa has in the US with its current indication for patients with baseline triglycerides of at least 500 mg/dL.

First, Thero said Amarin didn’t have the financial resources to bring Vascepa to

market in Europe sooner. Second, he said the EU market for hypertriglyceridemia therapies is confused by Omacor.

“The Omacor side has been sorted out with them having failed multiple outcomes studies and EMA no longer recommending use of Omacor for cardiovascular risk,” Thero said.

Jefferies analyst Michael Yee pointed out in a 3 September note that “the EMA issued a memo earlier in March 2019 confirming (other) omega-3 fish oils were not effective in treating CV disease and should not be used in EU. At that time, Amarin traded up because it was seen as cleaning up the EU market and getting rid of any other generic fish oils that might have competed, i.e. clearing the way for future Vascepa.”

The company’s stock initially traded up to \$15.25 per share on 3 September, but ended the day down 1.6% at \$14.75 following Amarin’s ESC/EAS guideline announcement.

“Also, by waiting [to launch in the EU], we preserved the 10 years of regulatory

exclusivity that's available in Europe," he added. "Our plan is to hold off on a commercialization partner for Europe until we have progressed further our regulatory submission. We think we will get a better deal by doing that. There's been expressions of interest from a number of companies seeking to help us promote Vascepa in Europe, but we still think it's a bit too early to enter into such an arrangement."

Thero noted that "the European opportunity is large and roughly about 60% of the opportunity in the United States," where Amarin said about 15m people match the criteria of triglyceride levels of 135 mg/dL or higher despite statin therapy.

Yee predicted that Vascepa could achieve peak annual sales of \$3bn globally with about \$1bn coming from the EU.

In other ex-US markets, Amarin is partnered with HLS Therapeutics Inc. in Canada, where Health Canada is considering Vascepa approval under a priority review with a decision expected before the end of this year. Also, partner Eddingpharm International Holdings Ltd. has a clinical trial ongoing in China in anticipation of bringing the first prescription omega-3 product to market there.

And in the Middle East, Amarin's partner has won approvals for Vascepa in Lebanon and the United Arab Emirates to date.

"We continue to evaluate the opportunities with other partners in other geographies, but first and foremost our priority is the US, followed by Europe," Thero said.

Amarin markets Vascepa in the US on its own and is working on doubling the size of its sales team. The company's CEO said the drug has strong reimbursement in the US ahead of the sNDA approval, with most prescriptions being approved and only some payers restricting coverage to patients that fall within the current Vascepa label.

"For those plans where Vascepa has restrictions, we would look forward to those being addressed by health plans relatively quickly after approval," Thero said. "The overall approval rate of Vascepa prescriptions today is about 80%. That's high for any drug and that's comparable to the approval rate for generic Lovaza, so we're getting very good approval rates already and that's with a drug where a considerable amount of its use is prescribed off label." 🌟

Published online 3 September 2019

Interview: AstraZeneca's Pangalos on Landmark DAPA-HF Results

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Mene Pangalos, AstraZeneca
EVP Biopharmaceuticals R&D

Source: AstraZeneca

The stand-out session at this year's European Society of Cardiology Congress in Paris, France was the presentation of results from AstraZeneca PLC's DAPA-HF Phase III study of Forxiga/Farxiga (dapagliflozin) in heart failure with reduced ejection fraction. The study paves the way for the SGLT-2 inhibitor's approval – likely in the first half of 2020 – to treat heart failure in both diabetic and non-diabetic patients.

Already approved to treat type 2 diabetes, with a label expansion for cardio-

vascular outcomes expected imminently, Forxiga can expect a sizable sales boost from an approval in heart failure. The product is also in ongoing trials for heart failure for preserved ejection fraction, in additional studies looking at other measures in heart failure, and in chronic kidney disease. Fellow SGLT-2 inhibitor Jardiance (empagliflozin) from Eli Lilly & Co. and Boehringer Ingelheim GmbH has been ahead of AstraZeneca as a preventive for cardiovascular outcomes, but is trailing in the heart failure indication.

Nevertheless, Jardiance is being put through similar paces in its ongoing clinical trial program and is likely to provide robust competition across the board.

Boehringer reported net sales of Jardiance of about €1bn in the first half of 2019, with Lilly reporting its 50% share of the gross margin on Jardiance at \$436m, while Forxiga's first-half sales were \$726m.

Mene Pangalos, executive vice-president of biopharmaceuticals R&D at AstraZeneca, spoke to *Scrip* about the findings.

SCRIP: I'd like to start with DAPA-HF, which studied dapagliflozin in a mixed population of diabetics and non-diabetics. I hear there were standing ovations during the presentation.

MENE PANGALOS: It was fun. You don't go to conferences very often and get a response like that. You get it once in your career if you're lucky, a few times if you're really lucky. It was really nice, actually.

S: What can you say about that fact that there didn't seem to be a difference between diabetics and non-diabetics?

MP: There wasn't a difference, and that's the really exciting piece for us. This is now moving beyond being a diabetes medicine. It's the first outcome study with an SGLT-2 inhibitor looking at patients with and without diabetes – and that was obviously a question mark – and the data I think are very compelling that there is absolutely no difference in effect size whether you are diabetic or not diabetic in terms of the benefit on heart failure risk and heart failure progression.

S: What does that mean for the way we think about SGLT-2 inhibitors? We have thought about them as diabetes drugs primarily, but it sounds like there's more to them.

MP: Well we haven't been thinking about them as a diabetes drug, we've been thinking about them as a class of drug that has got very broad and significant potential. If you look at the studies that we have ongoing, obviously DAPA-HF has read out now, but behind that we have the trial that's ongoing in heart failure with preserved ejection fraction as well as reduced ejection fraction and that's going to read out in the next year or so, and that's also in diabetic and non-diabetic patients. We also have a trial running in chronic kidney disease which should be reading out in the next 12 months or so as well, and that is also in patients with and without diabetes. So we look at this molecule not just as a diabetes medicine but as a medicine that's going to be useful for patients with cardiovascular disease and heart failure but also for patients with chronic kidney disease as well.

S: And that fact that there isn't anything at the moment for heart failure with preserved ejection fraction (HF-pEF) – what hope do you have that dapagliflozin might change that?

MP: I think we are very encouraged by the data we have seen so far, both in terms of the data we've seen from our DECLARE study, which was in diabetics but included patients with preserved ejection fraction, but also from the data that we've seen and the scientific hypothesis we feel we've got a good chance of hit-

ting the HFpEF population as well in a positive way, but obviously the data need to read out before we can be confident.

S: What is it about the scientific hypothesis that means there is more hope for this?

MP: It's an interesting question and I don't want to get into too much detail because we're still trying to get to the bottom of understanding fully the mechanism of action, there are a number of different hypotheses, but when you look at the impact that this has on not just glucose but sodium and overall volume, the impact it has on the metabolic state of cells in terms of being able to create a starvation-like phenotype in cells that actually then stimulates pathways that are important in regeneration: I think there's some interesting biology here that we're digging into which takes it beyond just being something that enables you to excrete glucose in the urine.

S: The other interesting thing was that even when patients were on Entresto [Novartis AG's approved angiotensin receptor-neprilysin inhibitor sacubitril/valsartan] already, there was a benefit. What does that mean for the drug?

MP: To be clear what we've showed was that in the 500 or so patients in the trial that were on Entresto, the efficacy of dapagliflozin was the same in terms of benefit whether you were on or not on Entresto. Mechanistically there's no reason to think anything other than these two drugs would be complementary to one another. So we view this as being additive: if a patient is on Entresto you can put Forxiga on top of that, and it's a very easy drug to use, it's a once a day, and if you're not on Entresto that's also fine. I think it's a nice simple option for physicians to use in patients with heart failure with reduced ejection fraction.

S: But what would that mean for uptake and pricing given that neither drug is all that cheap?

MP: I don't really want to comment on the pricing or on the uptake – given the data we have, and that this is re-

imbursed for diabetes today, I don't think being reimbursed for heart failure should be a challenge.

S: How about differentiation over other SGLT-2 inhibitors or indeed other products in development for heart failure that work in different ways?

MP: Yes, obviously I think this is very likely to be a class effect. I think what is very good about the data is that we have it in hand, it was very compelling, and we've got a very clean safety profile, which I think is really pleasing. We have no imbalances on things like lower limb amputations, gangrene, all of the things we have in terms of safety profile are very clean. Major hypoglycemic events is the same in both treatment groups, renal adverse events is the same, volume depletion is the same, so this is going to be a relatively simple drug for physicians to use. Obviously other companies will have to get their data readouts and look at their data – we can concentrate on ours and we have a head start. But I would not be surprised if ultimately we see good data with other SGLT-2 inhibitors as well. But I'm very happy to have our data in hand and ready to go, and have our conversation with the regulators and get this hopefully approved as fast as possible.

S: How quick do you think that could be?

MP: Filing second half this year, there's not that much of the second half of this year left, and hopefully approved in the first half of next year.

S: Have you already started having conversations with insurers, or reimbursement authorities?

MP: No. People are acutely aware of the data now given that it's been presented, and Forxiga is already on many formularies around the world, so this is really about expanding its label. Nothing is straightforward in the commercial world and I'm an R&D person, so I'm the last person that should be talking about it, but the fact that this is a well-established brand, mechanism of action, used widely in diabetes around

the world, what we're saying now is that we can expand it into the cardiology population.

S: What was the reaction amongst that cardiology physician population – because these people are going to have to get used to prescribing something that is not in their normal armamentarium?

MP: I think they're thrilled actually – they're thrilled because the data were highly compelling, and however we cut the data it was highly significant in terms of the benefit, and it's a very simple once-a-day drug to use with a relatively benign side-effect profile, so I think the cardiologists in the room – there was a reason why we were getting spontaneous applause for the data set, and why it's on the front page of the Congress News today, because it's being viewed as a landmark study and a breakthrough therapy for these patients.

S: So – again, you're in R&D, but what does this mean for the additive sales potential of the drug?

MP: This should increase our forecast for Forxiga considerably in terms of the heart failure population. There are 64 million people globally with heart failure and I would say about half of them have HFrEF. So this is a very big opportunity.

S: Can you comment on how it squares up against Jardiance?

MP: No, I would say we have the data and they don't! I think this puts us in a really good spot now in terms of cardiology and heart failure. They've had for some time the advantage with their data because we haven't had our CV outcomes data in our label, which we should have before the end of the year, we both have studies running in HFrEF and HFpEF, we both have studies running in kidney disease, this is a large opportunity, it's good to grow the class. I think the other big opportunity for us is to start to displace much more dramatically the DPP-IVs [dipeptidyl peptidase-IV inhibitors Januvia (sitagliptin), Gal-

vus (vildagliptin), Onglyza (saxagliptin) and Tradjenta/Trajenta (linagliptin)], because given the data we have now, the DPP-IVs should be moving backwards in terms of proportion of patients being prescribed those for diabetes relative to SGLT-2. I think there's a lot of opportunity for both of us to do well here, with a very important drug class now for both diabetes and non-diabetic patients.

KEY DAPAGLIFLOZIN TRIALS IN CARDIOVASCULAR AND RENAL INDICATIONS

- DAPA-HF: type 2 diabetics and non diabetics with heart failure: time to death or worsening heart failure event. Estimated filing 2019.
- DELIVER: dapagliflozin in patients with HFpEF: worsening HF or CV death. Estimated filing 2020+.
- DETERMINE: dapagliflozin's effect on exercise capacity in patients with HFpEF or HFrEF. Estimated filing: US H2 2020.
- DAPA-CKD: renal outcomes and cardiovascular mortality in patients with chronic kidney disease. Estimated filing 2020+.
- DECLARE-TIMI examined cardiovascular outcomes (hospitalization for heart failure or cardiovascular death vs placebo) in patients with type 2 diabetes. MACE didn't meet significance. Label updated in EU in August 2019, pending in US.

KEY EMPAGLIFLOZIN TRIALS IN CARDIOVASCULAR AND RENAL INDICATIONS

- EMERALD: heart failure symptoms and exercise ability in patients with HFrEF and HFpEF, regardless of whether they have diabetes. Top-line results expected 2019.
 - EMPEROR: time to first event of cardiovascular death or heart failure hospitalization in patients with HFrEF and HFpEF. Estimated completion 2020.
 - EMPA-KIDNEY: cardiorenal outcomes in type 2 diabetes patients with chronic kidney disease. Top-line results expected 2022.
 - EMPA-REG OUTCOME: cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease. Approved in this population to reduce cardiovascular death risk in 2016. 🌟
- Published online 4 September 2019*

Boehringer Ingelheim Snaps Up Lupin's MEK Inhibitor For Difficult-To-Treat Cancers

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In its second major out-licensing R&D deal of the past 12 months, Lupin Ltd. has signed a pact with Boehringer Ingelheim GmbH. The German group is to collaborate on the development of Lupin's clinical-stage MEK inhibitor, LNP3794, for the treatment of difficult-to-treat KRAS-driven cancers.

The licensing, development and commercialization agreement, under which Lupin will receive an upfront of \$20m,

potential total milestones of \$700m, and sales royalties, will involve the two companies evaluating LNP3794 in combination with Boehringer Ingelheim's investigational KRAS inhibitors for the treatment of gastrointestinal and lung cancers with oncogenic KRAS mutations.

KRAS-mutated cancers have no targeted treatments and monotherapy has been tried but, to date, has not been successful.

"We've actually seen synergy using combinations in the relevant models, and our compound has shown efficacy in a small number of patients in a UK trial, and now combining with their (BI's) agent will enhance the probability [of success]," said Raj Kamboj, president of Lupin's novel drug discovery and development (NDDD) unit, speaking at a press briefing in India.

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4 December 2019 | London Hilton on Park Lane, London

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The KRAS gene is the most frequently mutated cancer-causing gene, with mutation rates of more than 90% in pancreatic cancers, more than 40% in colorectal cancers and more than 30% in lung adenocarcinomas. KRAS mutations occur in one in seven of all human metastatic cancers.

Lupin believes LNP3794 can be effectively combined with chemotherapy and other targeted agents, such as RAF, PI3K, KRAS, BTK and EGFR inhibitors, for the treatment of BRAF and RAS mutant cancers. "Combining LNP3794 with other targeted agents is expected to provide high response rates," the company said.

Boehringer Ingelheim and Lupin reported on 4 September that preclinical studies show a combination of a KRAS inhibitor with a MEK inhibitor can keep KRAS-driven tumors in check. They target different parts of the intracellular signaling KRAS-RAF-MEK-ERK pathway. In early clinical studies, Lupin's MEK inhibitors have already shown benefits in a small subset of patients, and MEK inhibitors such as Novartis AG's Mekinist (trametinib) and Pierre Fabre Group's Mekto-

vi (binimetinib) are already marketed for the treatment of melanoma containing the BRAF V600 mutation.

Lupin reckons LNP3794 stacks up favorably with existing MEK inhibitors and may have significant advantages over other MEK agents in terms of both efficacy and safety. With regard to potential competitors in development, another KRAS inhibitor, Amgen Inc's AMG-510, has a different target, KRAS G12C mutations, Kamboj told *Scrip*.

Lupin is transitioning from a pure-play generics company – it is the third largest pharmaceutical company in the US in terms of the volume of prescriptions – to having a more diversified business strategy involving generics, complex generics, biosimilars, manufacturing and drug discovery. At the end of 2018, the Mumbai-headquartered company out-licensed its MALT1 (mucosa-associated lymphoid tissue lymphoma translocation protein 1) inhibitor program to AbbVie Inc. for a \$30m upfront and more than \$900m in potential milestone payments, significant amounts for a preclinical asset.

Other companies, including Novartis AG and Galapagos NV, are interested in

developing MALT1 inhibitors, for inflammatory and oncological diseases.

For Boehringer Ingelheim, the development of inhibitors to the KRAS oncogene is part of a concerted research and business development effort into new anti-cancer medicines, particularly those targeting lung and gastrointestinal cancers with novel modes of action. Two months ago, it acquired the Swiss biotech Amal Therapeutics SA whose candidate therapeutic cancer vaccine ATP128 is being evaluated in stage IV colorectal cancer.

A potential first-in-class myeloid checkpoint inhibitor, BI 765063, entered Phase I in June at Boehringer Ingelheim, in its partnership with the French biotech OSE Immunotherapeutics SA. BI 765063 is also being combined with Boehringer Ingelheim's T-lymphocyte checkpoint inhibitor BI 754091.

The German multinational already has some experience in the oncology field, as a marketer of Giotrif (afatinib) for non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutations, and Vargatef (nintedanib) for NSCLC combination therapy. 🌟

Published online 4 September 2019

BioNTech Gets Gates Foundation Funding For HIV, TB Drug Discovery

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The Bill & Melinda Gates Foundation has given a loud vote of confidence to German mRNA-focused biotech BioNTech AG's ambitions to branch out from its initial immuno-oncology focus to explore the potential of its platforms in infectious diseases, notably HIV and tuberculosis.

The clinical-stage biotechnology company announced on 4 September that it has signed an agreement with the Gates Foundation to develop HIV and tuberculosis programs, further expanding BioNTech's infectious disease portfolio.

This partnership includes an initial equity investment of \$55m, which is expected to close within the next week.

The funds will be used to develop preclinical vaccine and immunotherapy



"Targeting severe infectious diseases such as tuberculosis and HIV infection is in line with our mission."
– Ugur Sahin

candidates to prevent HIV and tuberculosis infection as well as to lead to durable antiretroviral therapy-free remission of HIV disease.

The privately held biotech, founded in 2008 and based in Mainz, Germany-based said total funding under its latest collaboration could reach \$100m through potential future grant funding from the Gates Foundation that would be used to underwrite the evaluation of these candidates in the clinic and support the initiation of new infectious disease projects.

BioNTech's pipeline to date includes individualized mRNA-based product candidates, innovative chimeric antigen receptor T cells, novel checkpoint immunomodulators, targeted cancer antibodies and small molecules.

The biotech says its product development approach has already been validated by existing collaborations with big pharma players. Since 2016, Roche has been working with the privately-held group to develop novel messenger RNA cancer vaccines tailored to individual patients based on the particular neoantigens on their tumor cells.

In January this year BioNTech added Sanofi as a strategic investor as the French pharma giant took an €80m equity stake and agreed to extend a 2015 research collaboration between the two companies. (Also see “Sanofi Takes €80M BioNTech Stake & Extends 2015 Deal” - *Scrip*, 4 Jan, 2019.)

The biotech also has collaborations with Pfizer Inc., Eli Lilly & Co., Genmab AS and Bayer Animal and so far boasts a development pipeline of more than 20 product candidates. It clearly hopes to expand that with the Gates Foundation alliance.

“We are thrilled about the partnership with the Gates Foundation and the outstanding network of infectious disease spe-

cialists that it has built,” Ugur Sahin, the CEO of BioNTech said in a statement.

“Targeting severe infectious diseases such as tuberculosis and HIV infection is in line with our mission to leverage our immunotherapy capabilities not only for cancer but also beyond, in disease areas of high medical need.”

The Gates Foundation said it had high hopes for the collaboration with BioNTech.

“BioNTech’s innovative mRNA-based approach and in-depth understanding of the immune system offer exciting pathways to develop effective new immune-based therapies that could dramatically reduce the global incidence of HIV and tuberculosis. We believe this partnership will add to our portfolio of innovative tools and could make a significant impact,” said Lynda Stuart, deputy director of vaccines and human immunobiology, discovery and translational sciences at the Gates Foundation. ✨

Published online 5 September 2019

Gyroscope Targeting ‘Huge’ Population With Dry AMD Gene Therapy

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Gyroscope Therapeutics has raised £50.4m (\$60.3m) in a series B fundraising which will fuel the ongoing development of its lead gene therapies and surgical delivery systems for retinal diseases.

The company’s lead investigational candidate is GT005, a gene therapy for dry age-related macular degeneration (dry-AMD).

The new funding from long-term backers Syncona and Cambridge Innovation Capital (CIC) will not only fund a Phase I/II clinical trial of the product but also use of a first-of-its-kind subretinal delivery system (SDS) to administer the gene therapy to the eye.

The company’s backers believe that Gyroscope could be the first gene therapy company to achieve approval for a “mass market” therapy.

Dry AMD is the number one cause of permanent vision impairment for people aged 65 and over, and affects more than 35 million people in the western world alone. That means any gene therapy which proves successful in treating such a common disease would be a potential multi-billion dollar seller.

The first gene therapies reaching the market are for rare genetic conditions affecting no more than a few thousand



patients worldwide. The most notable example is Spark Therapeutics’ Luxturna, which became the first ever FDA-approved gene therapy in December 2017, but which isn’t expected to exceed peak annual sales of \$500m.

By contrast, a gene therapy which proved safe and effective in treating even just a fraction of the 11 million patients worldwide who experience serious vision loss or blindness with dry AMD would clearly have blockbuster potential.

That dream is still some way off, though, as GT005 only began its Phase I/II clinical trial, (the FOCUS study) earlier this year, with the study expected to conclude in February 2021.

Chris Hollowood, chief investment officer of Syncona and chairman of Gyroscope, declined to put a figure on the market size of the dry AMD population the company is targeting: “There is a lot of talk about how many patients might be eligible, but whatever the exact figure is, it’s huge.”

Hollowood said the company’s trials would first target a cohort of likely high-responding patients (number undisclosed) and then the larger eligible population.

Gyroscope is unusual in having both a gene therapy platform and a proprietary delivery system, a combination achieved through its merger with another Syncona-backed company, Orbit Biomedical in April this year.

The Stevenage, UK-based company is one of a stable of cell and gene therapy companies being funded by venture capital fund Syncona, which has provided the lion’s share (£48m) of the series B financing, with Cambridge Innovation Capital (CIC) contributing the additional £2.4m.

The therapy is also unusual in that rather than targeting a single gene defect, it acts to restore balance to the complement system, the part of the body’s immune system implicated in AMD pathogenesis, by increasing production of a human complement factor.

The company says the goal of its clinical trials is to demonstrate the treatment can slow, or possibly stop the progression of dry-AMD. Just how effective and how durable the therapy is will be crucial for its commercial success.

The Phase I/II FOCUS open-label study will look at safety and dose response and efficacy of the therapy, which will be given to patients in a single dose through an injection below their retina.

This proprietary and minimally-invasive surgical delivery method, the Orbit Subretinal Delivery System (Orbit SDS), could be a competitive advantage for the company. It is designed to allow surgeons to access the eye's "subretinal space" without needing to remove the vitreous (the gel-like substance that fills the eye) or make a hole in the retina.

Hollowood was also chairman of Nightstar Therapeutics, another Syncona-backed gene therapy company, but which targeted monogenic eye diseases. Night-

star was acquired by Biogen earlier this year for \$800m.

He says Gyroscope's Orbit SDS represents a leap forward compared to the highly invasive surgical techniques used by Spark and Nightstar Therapeutics to deliver their viral vectors, which require a general anesthetic and leave patients with a hole in their retina. The Orbit SDS instead uses a canula inserted under the side of the eye, with the gene therapy brought directly to the subretinal space. This allows the therapy to be administered under local anesthetic, and also eliminates the risk of an inflammatory response in the vitreous humour.

Hollowood says Gyroscope's surgical technique 'fundamentally reinvents' the administration of gene therapy to the eye.

He says it creates a much more routine and uniform procedure which could be carried out by local retinal surgeons rather than specialist centers, which will be necessary to reach the full eligible population.

Hollowood rejected any suggestion that the gene therapy space had become overheated and overcrowded in the past 12 months, but said M&A valuations had clearly been based on gene therapy companies providing a "launchpad" out of smaller monogenic diseases and into diseases with much bigger populations – something that Gyroscope has had from the outset.

Gyroscope says it aims to raise further revenues by partnering and licensing the Orbit SDS technology to other gene and cell therapy companies.

Following its merger, company also gained a new CEO, Khurem Farooq. He has extensive experience in the field, including 11 years as SVP of Immunology and Ophthalmology at Roche's Genentech division where he led the launch and commercialization of a number of medicines, including the company's blockbuster wet AMD treatment Lucentis (ranibizumab). 🌟

Published online 3 September 2019

Global Blood Therapeutics' Voxelotor On Track For 2020 Sickle Cell Shakeup

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Global Blood Therapeutics Inc. will be poised to launch voxelotor, a new treatment for sickle cell disease, in early 2020 if its US Food and Drug Administration review goes smoothly, setting up a tight race with Novartis AG to bring new treatments to market for sickle cell disease, an area of high unmet medical need with limited treatment options.

GBT's new drug application (NDA) for voxelotor was accepted by the FDA with a priority review and a target action date of 26 February, the company announced on 5 September. Its stock price jumped 10.8% over its closing one day earlier to close the day at \$52.66.

Novartis filed its monoclonal antibody crizanlizumab in the US and EU in July for the prevention of vaso-occlusive crisis (VOC) in sickle cell patients. The FDA also granted the biologics license application (BLA) a priority review, positioning the drug for approval in January. (*Also see "Keeping Track: Recarbrio Approval Highlights Two-Week Roundup" - Pink Sheet, 19 Jul, 2019.*)

The two drugs work differently and could have important clinical differences. Voxelotor is an oral once-daily therapy that works by increasing hemoglobin's affinity for oxygen, blocking polymerization and the resulting sickling of red blood cells. By improving hemolytic anemia and oxygen delivery, GBT believes voxelotor could reduce strokes and modify the course of the disease, an inherited blood disorder

marked by episodes of severe pain, long-term organ damage and shortened lifespan.

DIFFERENT ENDPOINTS

Crizanlizumab is a monthly injection, an antibody that binds to P-selectin in blood vessels, one of the drivers of the vaso-occlusive process. GBT tested voxelotor for increase in hemoglobin, while Novartis tested crizanlizumab for the prevention of VOCs in patients with sickle cell disease.

If approved by the FDA, both drugs' approvals would be based on early data, so longer-term trials will be needed to understand the long-term impacts on sickle cell disease, including endpoints like organ damage and risk of death.

The voxelotor filing is based on data from the Phase III HOPE trial, which enrolled 274 patients who received 1,500mg of voxelotor, 900mg of voxelotor or placebo, with the primary endpoint being improvement in hemoglobin, which the company believes can reduce strokes in sickle cell patients. The FDA agreed to the endpoint for accelerated review, but will require a confirmatory study using transcranial doppler flow velocity as a primary endpoint to demonstrate stroke risk reduction. (*Also see "Global Blood Therapeutics Leaves ASH With Momentum Behind Voxelotor In Sickle Cell Disease" - Pink Sheet, 4 Dec, 2018.*)

The hemoglobin improvement endpoint is a novel one for sickle cell disease, an area where development has typically focused on the common clinical manifestation of VOCs and pain episodes as a primary endpoint, but that research has not yet resulted in much success. Voxelotor has not shown a significant reduction in VOC episodes in clinical trials, though it has shown numerical improvements. The company said it anticipates a broad label for the treatment of sickle cell disease.

Novartis's BLA filing for crizanlizumab is based on the Phase II SUSTAIN study, which enrolled 198 patients and showed that the median rate of crises per year was significantly lower with crizanlizumab versus placebo.

Meanwhile, Pfizer Inc. and partner GlycoMimetics Inc. were among the latest to announce a Phase III failure in sickle cell disease, using VOC-based endpoints. The partners' pan-selectin antagonist rivipansel failed to show a significant benefit on the primary endpoint: time to readiness-for-discharge from hospitalization and secondary endpoints around opioid consumption. (Also see "Sickle Blow For Pfizer's Rivipansel At Phase III RESETs Expectations" - *Scrip*, 5 Aug, 2019.)

Interestingly, GBT said the FDA has indicated in the NDA filing acceptance notification letter for voxelotor that it does not currently plan to hold an advisory committee meeting to discuss the application.

EMMAUS LAYING SOME GROUNDWORK

The agency has granted the GBT and Novartis drugs breakthrough therapy designations given the high unmet need. There are limited options for patients with sickle cell disease, including the old chemotherapeutic hydroxyurea, antibiotics, blood transfusions and pain medications. The first new drug to launch in nearly 20 years debuted last year from Emmaus Life Sciences Inc. called Endari (L-glutamine).

The drug, which was approved by the FDA in 2017 to reduce acute complications associated with sickle cell disease, is a prescription grade version of the widely available amino acid supplement L-glutamine. (Also see "Emmaus Plans Modest Pricing In 4Q Rollout Of Sickle Cell Drug Endari" - *Scrip*, 9 Jul, 2017.)

Sales have been off to a slow start, with Emmaus reporting second quarter revenues of \$5.9m. In the clinical trial supporting approval, patients treated with Endari experienced fewer hospital visits for pain treated with a parenterally administered narcotic on average compared to those on placebo, fewer hospitalizations for sickle cell pain and fewer days in the hospital.

In an interview, CEO Yutaka Niihara said the company is making substantial progress on the drug's commercialization. "Physicians, providers and patients are very happy with Endari," he said. "We hear stories like, 'Now I can go to school, now I can stay at work, I don't have to go to the hospital anymore.'"

Nonetheless, the European Medicines Agency recently said it did not believe there was enough efficacy data to support approval of Endari in Europe. Niihara called the decision a misunderstanding of the clinical data and said the company will appeal the decision.

In the US, it seems increasingly likely Endari will be facing more competition in early 2020. 🌟

Published online 5 September 2019

Concert Looks To Phase III In Alopecia Areata, Ahead Of Pfizer's JAK Inhibitor

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With a full dataset now illustrating success for a deuterated formulation of ruxolitinib in alopecia areata, Concert Pharmaceuticals Inc. continues to believe its selective JAK1/2 inhibitor is on pace to get to market first in the unmet medical need, ahead of Pfizer Inc.'s competing Phase II candidate, selective JAK3 inhibitor PF-06651600.

Many patients consider alopecia areata "life changing."

Concert unveiled new data from its Phase II dose-ranging study of CTP-543 on 3 September, showing that a 12mg twice-daily dose met statistical significance compared to placebo by achieving a 50% or greater change from baseline at 24 weeks on the Severity of Alopecia Tool (SALT). In March, it reported that an 8mg twice-daily dose met statistical significance on this endpoint, while a 4mg twice-daily dose did not. (Also see "Concert Says Phase II Alopecia Drug Could Beat Pfizer's Candidate To Market" - *Scrip*, 4 Mar, 2019.)

The specialty firm plans to meet with the US Food and Drug Administration in early 2020 to plan out a Phase III program.

Fifty-eight percent of patients in the Phase II study who received the 12mg dose met the SALT score endpoint, a clinician-reported measure, compared to 9% in the control group ($p < 0.001$). For the 8mg dose, 47% of patients hit the SALT endpoint ($p < 0.001$). A total of 149 patients were randomized in the study to receive either a 4mg, 8mg or 12mg study dose or placebo.

The Lexington, MA-based firm also noted that CTP-543 met statistical significance on a patient-reported secondary endpoint for both the 8mg and 12mg doses compared to placebo. Seventy-eight percent in the 12mg cohort rated their disease state as "much" or "very much" improved, along with 58% of those who received the 8mg dose, compared to 21% of control group participants. Concert CEO Roger Tung told *Scrip* that more than 90% of the patients who received the 12mg dose also crossed over into an open-label extension after the 24-week study treatment period ended.

"We're thrilled that as we've continued the study and now have the full dataset, the 12mg dose has continued [a dose-related efficacy] trend and has put us into what we think is the pole position with the most robust data that have been reported in a controlled trial of alopecia areata," Tung said in an interview.

The company plans to take both the 8mg and 12mg twice-daily doses into Phase III, but still has a pair of studies ongoing testing a 16mg daily dose versus 8mg twice-daily and a 24mg daily versus 12mg twice-daily. Tung said data for the 16mg

daily dose should be available before year-end and, along with a partial data-set cut from the 24mg daily dose study, will be part of the package Concert will take into the end-of-Phase II meeting with the FDA. The data from the 24mg study will be part of the safety database for the new drug application (NDA) filing for CTP-543.

WORKING ON PHASE III DESIGN

Tung expects the pivotal studies will use the two twice-daily doses but is open to the possibility that 16mg daily will be included as well. It is possible more than one dose will be included in the NDA, he added.

"At this point, we see good efficacy that's still rising at the 24-week time-point, we see good tolerability that hasn't really significantly differentiated between the two arms, and we want to be in a position to do a robust comparison of the two doses in pivotal evaluation to really get a sense of whether there's one or two doses that might be commercially viable," he said.

Safety and tolerability will be crucial since alopecia areata is not a life-threatening condition, but Tung noted that Concert learned much about how the patients view the disease during a pa-

tient-focused drug development meeting on alopecia areata that the FDA conducted in September 2017. That many patients consider alopecia areata "life changing" and that more than 90% in the 12mg twice-daily arm of the Phase II study elected to enter the open-label extension makes Tung suspect that the drug's safety and tolerability profile will be sufficient for approval.

The most common side effects – occurring in 10% or greater of patients – in the Phase II study's 12mg cohort were headache, nasopharyngitis, upper respiratory tract infections and acne. There were no thromboembolic events reported during the study.

Tung said Concert expects that SALT will be the primary endpoint for the pivotal trials, although the company is still considering whether a treatment period longer than 24 weeks might be optimal since therapeutic response appeared to be increasing at 24 weeks in Phase II. He was uncertain whether a patient-reported measure also will be included in Phase III.

PATENT DISPUTE

CTP-543 is a deuterated formulation of ruxolitinib, the active pharmaceutical ingredient in Incyte Corp. and Novartis AG's

myelofibrosis therapy Jakafi. Incyte has pursued a patent suit claiming ownership of intellectual property for the deuterated formulation, but Tung said nothing will be resolved with that claim until CTP-543 is nearing approval.

"With respect to their ownership of deuterated ruxolitinib, this is something where we have no standing to have interaction with them while we're in development," the exec said. "At this time, we are in a protected stage of development under the Hatch-Waxman regulations; they can around the time of our filing for approval choose to assert their IP and make the case that we're infringing on their IP, but that's something that we'll deal with at that time. We strongly dispute that view and we believe we have very strong arguments for that perspective, but that won't really come into play until the time that we're nearing approval."

Pfizer's PF-06651600 is in Phase II for alopecia areata – data from that trial are expected during the second half of 2021. (Also see "Pfizer Eyes First-To-Market Opportunity In Alopecia" - *Scrip*, 18 Sep, 2018.) The drug also is a Phase II candidate for ulcerative colitis, rheumatoid arthritis and Crohn's disease. ✨

Published online 3 September 2019

After AR-105 VAP Failure, Aridis Looks To AR-301 For Value Justification

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Aridis Pharmaceuticals Inc. put on a brave face after its experimental drug AR-105 failed in a Phase II trial for the treatment of ventilator-associated pneumonia (VAP), saying it will not invest further in the mAb and will instead focus on remaining more promising pipeline assets, in particular AR-301 which targets Gram-positive *Staphylococcus aureus* alpha-toxin and which is currently in Phase III global clinical development for the treatment of VAP.

Shares in Aridis slid heavily on 3 September after the company reported that AR-105, a fully human IgG1 monoclonal antibody, had failed to meet its primary

endpoint in a Phase II trial evaluating it as a treatment for VAP caused by Gram-negative *Pseudomonas aeruginosa*.

Ventilator-associated pneumonia is a type of lung infection that occurs in people who are on mechanical ventilation breathing machines in hospitals. VAP typically affects critically ill persons that are in an intensive care unit and is consequently a major source of increased illness and death.

The US-based biotech also said there that at day 21 of the trial there was a significant imbalance seen in all-cause mortality and serious adverse event (SAE) rates between treatment groups that favored

placebo. But no SAE or mortality in the study was deemed to be drug related by the study investigators or the study's data monitoring committee, Aridis added.

"Our team is analyzing the full data set to better understand these top-line results and report the final analysis as soon as possible," Aridis's chief medical officer Wolfgang Dummer said.

The San Jose, CA-based company said that as a result it "will no longer allocate further development resources to AR-105," at least for the time being.

Aridis aims to discover and develop anti-infectives for use as add-on treatments to standard-of-care antibiotics



AR-105 missed endpoints in a Phase II ventilator-associated pneumonia trial

using its proprietary MablGx technology platform to rapidly identify rare, potent antibody-producing B-cells from patients who have successfully overcome an infection.

FOCUS ON AR-310

Analysts at Laidlaw & Company said Aridis's decision to no longer fund development of AR-105 was "a wise decision" and added: "We had always viewed AR-105 as a higher risk call due to lack of data and difficulty of patient population.

"While we have slightly increased our risk associated with the MablGx platform, we don't see much read-through to their upcoming Phase III trial readout for AR-301 that targets Gram (+) *S aureus* for VAP," the analysts said in a reaction note to investors dated 4 September, retaining their

buy recommendation on the stock.

The AR-301 Phase III trial, initiated in the first quarter of 2019, is actively enrolling in approximately 240 clinical centers in 20 countries. Participating centers in all countries are following a single stringent clinical protocol and standard of care procedures for critically ill VAP patients.

The trial represents the first ever Phase III superiority clinical study evaluating immunotherapy with a fully human monoclonal antibody for the treatment of acute pneumonia in the intensive care unit (ICU) setting.

Aridis expects an interim Phase III readout on the AR-301 trial to come in the first-half of 2020, with subsequent topline data released in late 2020.

The biotech noted that AR-301's anti-toxin target and mode of action are dif-

ferent from AR-105's cell surface carbohydrate target and mode of action and is independent of the antibiotic resistance profile of *S aureus*.

It noted that additional external validation of targeting *S aureus* alpha-toxin has also been obtained from AstraZeneca PLC's MEDI-4893, another monoclonal antibody against this epitope, which is in development for the prophylaxis of *S aureus* VAP.

Analysts at Laidlaw & Company said Aridis in July won valuable 'breathing room' when it entered into an equity purchase and option agreement with the Serum International BV (SIBV), an affiliate of Serum Institute of India, which is the world's largest vaccine manufacturer measured by dose units.

The pact, announced on 30 July, gave SIBV the option to license multiple programs from Aridis as well as access their MablGx platform. (Also see "Deals Shaping The Medical Industry, August 2019" - *In Vivo*, 12 Aug, 2019.)

In return, SIBV made an equity investment of \$10m and committed to pay Aridis an upfront cash payment of \$5m and an additional \$10m upon execution of the license agreement. Aridis will also receive future milestone payments for achieving product development and commercial objectives, along with royalties on net sales.

"We view this agreement as a testament to the MablGx platform and a significant positive in-terms of capital runway," Laidlaw & Company said. 🌟

Published online 4 September 2019

Genfit Addresses Multiple Transition Issues With CEO Change

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As Genfit SA prepares to shift from a clinical- to a commercial-stage company, Pascal Prigent was named the firm's new CEO on 2 September because he brings the right skill set to make the transition.

Prigent was recruited for the French biotech in May 2018, as executive VP of marketing and commercial development. His prior experience in marketing, sales and management at GlaxoSmithKline PLC and before that at Eli Lilly & Co. was seen as ideal for shepherding the firm from an R&D enterprise into the commercial sector. Prigent takes over as CEO on 16 September.



Genfit is expecting Phase III data for its non-alcoholic steatohepatitis (NASH) candidate elafibranor before the end of 2019, which if positive keeps it in position to potentially be the second firm to market with a NASH therapy, behind Intercept Pharmaceuticals Inc.

Co-founder and current CEO Jean-Francois Mouney, who will remain as chairman of the board, stressed that the transition is being made at his request. No external candidate search was conducted.

In a video presentation posted to Genfit's website, Mouney said that at Prigent's urging he will remain present and active in supporting executive management's efforts. The board also will add

three new members over the next year to enhance the company's expertise in activities related to US drug launches. While seeing Genfit through the expected filing of elafibranor for approval in the US and Europe in 2020, Prigent also is charged with managing the firm's transformation from a French biotech into an international company with a strong foothold in the US, Mouney said.

Perhaps to reflect that transition, Prigent spoke in both French and English on the video, saying Genfit is going to stay on its present course with the teams it has in place. He emphasized that, along with Intercept, Genfit is one of two companies poised to bring a NASH drug therapy to market in the near-term and asserted that its investigational fibrosis diagnostic, NIS4, could have a game-changing impact in NASH.

Also participating in the video was co-founder and chief scientific officer Dean Hum, who recently took on the chief operating officer role as well. Hum, in charge of development and regulatory activities, will be second in command to Prigent, Mouney noted. Hum's promotion came in tandem with Genfit's \$135.1m US initial public offering in March, which was intended partially to increase the company's presence in the US. (Also see "Finance Watch: Genfit Launches IPO To Expand US Presence Ahead Of Phase III NASH Results" - *Scrip*, 28

Mar, 2019.) Genfit divides its 180 employees between Lille, France, and Boston.

AT THE FRONT OF THE NASH PACK

Genfit expects to report data from its 72-week, Phase III RESOLVE-IT study of elafibranor in NASH before year's end, hoping the dual PPAR agonist will demonstrate an ability to resolve NASH without worsening of fibrosis. Intercept's obeticholic acid (OCA) – branded as Ocaliva for primary biliary cholangitis – demonstrated the ability to reduce NASH patients' fibrosis scores by one stage or greater in the Phase III REGENERATE study. (Also see "Intercept Retakes The Lead In NASH" - *Scrip*, 19 Feb, 2019.)

With its FXR agonist, Intercept became the first company to produce successful Phase III efficacy data in NASH and is on track to file a new drug application (NDA) at the US Food and Drug Administration for OCA in NASH fibrosis before the end of the third quarter. Intercept said during its second quarter earnings call on 7 August that it also is working toward applying to treat NASH cirrhosis with the 900-patient Phase III REVERSE study, expected to yield data in 2021.

FINDING THE RIGHT LEADERSHIP

SVB Leerink analyst Pasha Sarraf called Mouney's decision to "pass the baton" at

Genfit to Prigent "a tremendous act of leadership to free the company to grow and execute with the experience it needs to manage the new obstacles it will face," in a note issued on 3 September.

Sarraf also pointed to Prigent's varied background in terms of geographic and therapeutic area expertise, with specialization in product launch, market access, business turnaround and growth strategies. As head of GSK's US vaccines business and before that as a Lilly executive, Prigent held "various country and divisional roles, across marketing, sales and general management experience in Europe, the US and Latin America and in diverse therapeutic settings, including cardiovascular, diabetes, neuroscience and respiratory," the analyst wrote.

The Leerink analyst also credited Mouney as being a visionary in recognizing and addressing the need for non-invasive diagnosis of NASH, where the current standard is liver biopsy. "Mouney quickly saw the value of a blood-based diagnostic in simplifying the approach in access for patients and directed Genfit's resources to identify, build and test a practical algorithm for diagnosing patients with inflammatory disease, currently largely identifiable via biopsy," Sarraf said.

Genfit inked a partnership around the experimental NIS4 diagnostic, which is incorporated into its Phase III program, with LabCorp in January. 🌟

Published online 4 September 2019

Phase III Win In Kidney Disease For Ardelyx's Tenapanor

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A week before a decision is due from the US Food and Drug Administration on tenapanor for irritable bowel syndrome, Ardelyx Inc. has seen its shares jump following more positive Phase III results for the first-in-class NH3E inhibitor as a treatment for hyperphosphatemia in patients with end-stage renal disease.

The California-headquartered biotech has presented data from the AMPLIFY trial evaluating tenapanor in combination with phosphate binders in patients with chronic kidney disease on dialysis whose hyperphosphatemia was not previously controlled with binders alone. The results showed that twice as many patients on

tenapanor achieved the established treatment goal of reducing serum phosphate to less than 5.5mg/dL compared with placebo (49.1% versus 23.5%) after four weeks, the primary endpoint of the trial.

On a conference call, Ardelyx CEO Michael Raab emphasized that tenapanor also achieved a 22%-24% reduction within the four-week treatment period in levels of FGF23, a biomarker "clearly associated with an increased risk of major cardiovascular events." He added that the AMPLIFY data "further our conviction that tenapanor has the potential to be a game changer for patients [and] provides irrefutable clinical evidence of the benefit

that tenapanor may be able to provide difficult to treat patients when used in combination with phosphate binders."

The AMPLIFY data follows an earlier Phase III study which demonstrated the efficacy of tenapanor as a monotherapy "that could displace binders and relieve many patients from the burdens of intensive dosing regimen associated with binders," Raab said. Ardelyx chief development officer David Rosenbaum added, "With phosphate binders as the only approved treatment for hyperphosphatemia, the high pill burden, the size of the pills and the dosing frequency associated with this treatment, patients are frustrated

and doctors are challenged by the lack of compliance. We believe tenapanor will be a paradigm shift.”

Rosenbaum also said that there were no serious adverse events related to tenapanor, which is one small pill taken twice daily, and only one adverse event with a placebo-adjusted rate greater than 3%, which was loose stools or diarrhea at 36%. “This speaks to the consistent, very favorable tolerability profile of tenapanor across all of our clinical trials,” he added, noting that only three of 116 people in the tenapanor arm discontinued treatment due to loose stools.

Raab said that given the positive data published thus far and with the impending results from the long-term Phase III PHREEDOM study, Ardelyx plans to submit a new drug application next year for both monotherapy and combination use.

The AMPLIFY data went down well with analysts. Jefferies issued a note on 3 September claiming that as only 35% of patients are able to achieve serum phosphate levels below 5.5mg/dL with existing binders, “tenapanor could potentially fill this unmet medical need.” The broker added that “we think the appeal of tenapanor could be as add-on therapy to current phosphate binders in patients who do not reach goal and remain uncontrolled” and forecast peak US sales of \$250m.

“AMPLIFY furthers our conviction that tenapanor has the potential to be a game changer for patients.” – Michael Raab

Ami Fadia at SVB Leerink wrote that the AMPLIFY results “are a positive for the commercial potential of tenapanor in hyperphosphatemia,” saying that the data should not only broaden its use to patients already on binders rather than monotherapy alone “but could also support a nice ramp despite competition from generic binders.” She also noted that Ardelyx’s management commented that it was known binders could cause constipation, which may offset the loose stools caused by tenapanor, leading to a more

moderate loose stools/diarrhea profile.

“The company’s market research even suggests that physicians and patients may appreciate the improvement of constipation with the combination therapy,” Fadia said in a flash note on 3 September. She is currently modelling a 30% peak penetration for tenapanor in the CKD population, primarily attributed to monotherapy use.

In the near term, Ardelyx’s focus will be on 12 September, the prescription drug user fee date for tenapanor for irritable bowel syndrome with constipation (IBS-C). Raab said the data package submitted by the company demonstrating the ability of the therapy to have a durable effect on reducing the constipation and abdominal pain that IBS-C patients with irritable bowel experience, adding that the favorable safety profile of tenapanor, “which has been demonstrated across all trials,” was further supported by a completed long term safety study.

Rabb added that “the highly burdensome and difficult to treat condition” affected more than 11 million people in the US. “Assuming a positive outcome on our PDUFA date, we look forward to establishing a commercial collaboration with a partner that has the capability to drive the successful launch and marketing of tenapanor in the large and under-served IBS-C population,” he concluded. 🌟

Published online 4 September 2019

AstraZeneca Aiming To Extend Brilinta Use In PCI patients

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The THEMIS trial of Brilinta/Brilique (ticagrelor) in combination with aspirin in patients with coronary artery disease (CAD) and type 2 diabetes with no prior heart attack or stroke will give a modest boost to sales but is unlikely to prevent the product being overtaken by Farxiga in AstraZeneca PLC’s CV portfolio.



THEMIS was one of two positive Phase III studies unveiled on Sunday at the European Society of Cardiology (ESC) annual congress in Paris, France, but was overshadowed by the DAPA-HF trial of Farxiga (dapagliflozin). DAPA-HF suggests the SGLT2 inhibitor could make a big impact in heart failure, setting up an expanded label and boosting the product’s standing in this competitive class I.

THEMIS showed the Brilinta/aspirin combination reduced the relative risk of a composite endpoint event (cardiovascular (CV) death, heart attack, or stroke) by 10% compared with aspirin alone.

But a subgroup of patients with previous percutaneous coronary intervention (PCI) saw a better than average response, with a 15% reduction on the endpoint.

Mene Pangalos, AZ’s executive vice president, biopharmaceuticals R&D told *Scrip* that this PCI subgroup would be the focus for the company’s discussions with regulators about a possible label change. The study also showed that patients taking the combination had a higher bleeding risk than those just taking aspirin (2.2%

vs. 1.0%), but the company said that this bleeding profile was very similar to that seen previously with Brilinta, and that the additional benefit seen in the PCI population made it the most appropriate population for a label extension.

Gabriel Steg, THEMIS co-chair and professor at Université de Paris, said: "Patients with type 2 diabetes who had undergone a percutaneous coronary intervention, face a similar risk of a cardiovascular event as those who have had a heart attack.

"The PCI population is a sizeable and easily identifiable group of patients where we saw a more favorable net clinical benefit, that we hope in the future will be con-

sidered for long-term therapy with Brilinta and aspirin."

Although, the THEMIS results were significant and will help consolidate the drug's position in the anti-platelet market, analysts at Bryan, Garnier & Co. were underwhelmed. They said in a 2 September research note that the results were only a "nice-to-have" to strengthen Brilinta's label, and would not be as transformative as Farxiga's DAPA-HF read-out. They also expect no significant impact on its market share.

Brilinta enjoyed strong growth in the first half of 2019, rising 21% to reach \$737m in the first half of 2019.

Farxiga trails just behind in terms of revenues, earning \$726m over the same period thanks to 19% growth over the six months, suggesting that the strength of its DAPA-HF results could help it overtake its stablemate as the company's biggest cardiovascular brand.

AZ has two further Brilinta programs in its late-stage pipeline: the THALES study in acute ischemic stroke or transient ischemic attack, which it expects to file before the end of this year, and HESTIA, for prevention of vaso-occlusive crises in pediatric patients with sickle cell disease, which it expects to file after 2020. 🌟

Published online 2 September 2019

Second Launch For Rozlytrek, In Japan, But Sales Prospects Limited

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Japan has become the second market globally after the US to see the launch of Roche/Chugai Pharmaceutical Co. Ltd.'s tumor-agnostic cancer drug Rozlytrek (entrectinib). But while the step provides a new option to patients with a rare mutation, it looks likely to have limited commercial significance.

The oral selective inhibitor of ROS1 and neurotrophic tyrosine receptor kinase is both the first tumor-agnostic and NTRK-targeting therapy to be made available in the country, and is indicated initially for NTRK fusion-positive advanced or recurrent solid tumors.

The product was filed in mid-December and approved on 18 June - its first marketing nod worldwide - following an expedited review under orphan status and Japan's "sakigake" scheme for pioneering drugs. Read the full article here

Unlike in the US, where Rozlytrek had its first launch worldwide (through Roche's Genentech Inc. arm) following its 15 August approval there, the product has not yet been approved for ROS1-positive, metastatic non-small cell lung cancer in Japan.

A filing for ROS1-positive locally advanced or metastatic disease was submitted this March, and given standard review periods might be approved for this use in Japan by the end of the year.

Rozlytrek is being marketed in Japan by Chugai, Roche's licensee and majority-owned Japanese affiliate, following a 4 September reimbursement price listing, which allows nationwide launch under the country's national health insurance scheme.

PRICING

The 100mg and 200mg capsule formulations are reimbursed at JPY5,214.20 (\$48.90) and JPY9,889.90 respectively, with a normal adult dosage of 600mg once-daily and 300mg/m²

body surface area once daily to a maximum of 600mg/day for pediatric patients.

At the adult dose, the equivalent monthly cost of JPY890,091 (\$8,348) compares with a stated monthly cost of \$17,050 in the US for adults, although Genentech is running an Access Solutions program to help eligible patients. US pricing for pediatric patients is based on dose.

The specific (non-NSCLC) indication in the US is for adults and children over 12 with NTRK fusions and tumors without a known acquired resistance mutation, and who are metastatic and have tumors for which resection is likely to cause severe morbidity, or who have progressed after initial therapy or have no satisfactory alternative therapy. (*Also see "Roche/Genentech Set Lower Rozlytrek Price To Catch Up With Bayer's Vitrakvi" - Scrip, 15 Aug, 2019.*)

LIMITED JAPAN SALES POTENTIAL?

Only 1-2% of all solid tumor patients carry any form of NTRK fusion, and some research has suggested the incidence may be even lower in Japan - just 0.04% according to one study. The very specific population means that the commercial opportunity for Rozlytrek in the country is limited.

As part of the reimbursement price-setting process, the Ministry of Health, Labour and Welfare's advisory body Chuiyō (the Central Social Insurance Medical Council) forecast peak annual sales of just JPY1.17bn for the drug in the tumor agnostic NTRK setting.

In NSCLC, only 1-2% of all NSCLC cases in Japan are ROS1-positive (the fusion is particularly expressed in adenocarcinoma), so approval in this indication also appears unlikely to add substantially to the commercial prospects.

The use of Rozlytrek will be determined through a companion diagnostic, CDx Cancer Genomic Profile, which tests for NTRK

gene fusions among multiple other mutations. This received separate regulatory approval in late June.

Given the very limited number of patients in the clinical trials supporting the Japanese approval, Chugai has drawn up a risk management plan for the product and will be required to conduct all-patient postmarketing surveillance until the regulatory authorities are satisfied of efficacy and safety.

While Rozlytrek is the trailblazer for tumor-agnostic drugs in Japan, in the US it is the third after Bayer AG's Vitakvi (larotrectinib) for NTRK gene fusion-positive tumors and Merck & Co. Inc.'s Keytruda (pembrolizumab) for microsatellite instability-high or mismatch repair deficient tumors.

TECENTRIQ NOD FOR SCLC

Chugai also received Japanese approval late last month for Tecentriq (atezolizumab) for the additional indication of extensive-stage small cell lung cancer (SCLC), making it the first immunotherapy for this use in the country and the first new treatment option in the indication in 17 years.

The standard adult dose in the new setting is 1,200mg in combination with carboplatin and etoposide, intravenously infused over 60 minutes once every three weeks.

JAPANESE MARKET SIZE

The Roche anti-PD-L1 antibody was already approved in Japan for unresectable advanced or recurrent NSCLC and untreated unresectable advanced or recurrent non-squamous NSCLC, and is also awaiting local approval for breast cancer.

Chugai notes that SCLC accounts for 10-15% of the roughly 125,100 new cases of lung cancer annually in Japan, and has generally high and broad metastatic potential.

The new approval was supported by the IMpower133 study, which met its co-primary overall survival and progression-free survival endpoints, showing statistically significant improvements in both versus chemotherapy alone. (Also see "More Data Backs Tecentriq As IMpower133 Combo Meets Primary SCLC Endpoints" - *Scrip*, 25 Jun, 2018.)

Published online 5 September 2019

Achilles Advances Armed With £100m

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At a time when UK biotechs have struggled to access funds, Achilles Therapeutics Ltd. has bucked the trend, raising an impressive £100m to advance its personalized cancer immunotherapies targeting clonal neoantigens into the clinic.

New investor RA Capital led the series B round which included founding backer Syncona additional new investors Forbion Capital Partners, Invus, Perceptive Advisors and Redmile Group. The firm was spun out from the Francis Crick Institute and University College London with £13.2m in 2016 and "a fantastic scientific concept and we've spent the last two and a half, three years building that into the basis for a clinical company," CEO Iraj Ali told *Scrip*.

Ali joined Achilles in January 2018 as interim CEO, whilst also serving as a partner of Syncona but took on the role full time in December last year and enlisted former Ablynx NV CEO Edwin Moses to join the board as chairman. He had already started to assemble a strong leadership team, with Michael Giordano joining the board, having served as head of immuno-oncology at Bristol-Myers Squibb Co. and in February this year Markus Dangel joined from Medigene AG as chief scientific officer.



'We aren't interested in treating ten patients, we're interested in treating thousands of patients' – Iraj Ali

Having put such an experienced team together, Ali said, "We could go out and raise the money that we needed to take the company into the next phase which has culminated in this landmark raise." The round was heavily oversubscribed and Derek DiRocco, principal of RA Capital and Rogier Rooswinkel, a partner at Forbion, are joining the board.

The cash will be used to fund proof-of-concept trials using what the firm says is a unique personalized T-cell therapy approach targeting clonal neoantigens in non-small-cell lung cancer and melanoma. Ali said the studies, which are about to start, will have an 18-24 months' timeline to fully read out and "we'll look to treat around 60 patients across both indications."

He added that Achilles's strategy of targeting clonal neoantigens which are unique to the individual and present on all cancer cells but completely absent from healthy tissue represented "a unique capability and unique approach in the field." The funds will also be used to build out the firm's manufacturing capability, a vital area, Ali stressed.

He told *Scrip* that "if you were to define the challenge of the advanced therapies, it is to get manufacturing right so from

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, 30 AUGUST – 5 SEPTEMBER 2019

| Event Stage | Lead Company/Partner | Drug Name | Indication | Comments | Change To LOA (%) | LOA (%) |
|----------------------------|-------------------------------|------------------------------------|---|--|-------------------|---------|
| Phase III Updated Results | The Medicines Company/Alnylam | inclisiran, twice-yearly | Hyperlipidemia | ORION-11; Met All Endpoints | 2 | 60 |
| Phase III Updated Results | AstraZeneca PLC | Brilinta (ticagrelor) Plus aspirin | Coronary Artery Disease and Diabetes | THEMIS; Mixed Results | -7 | 45 |
| Phase III Top-Line Results | Novartis AG/Genmab | ofatumumab | Multiple Sclerosis | ASCLEPIOS I, II; Met Primary Endpoints | 4 | 58 |
| Phase III Top-Line Results | Ardelyx Inc. | tenapanor | Hyperphosphatemia In Dialysis | AMPLIFY; Met Primary Endpoint | 4 | 69 |
| Phase III Top-Line Results | Bristol-Myers Squibb Company | Opdivo (nivolumab) | MGMT-Methylated Glioblastoma | CheckMate-548; Missed PFS, Study Continues | -4 | 24 |
| Phase III Trial Initiation | Apellis Pharmaceuticals, Inc. | pegcetacoplan (APL-2) | Paroxysmal Nocturnal Hemoglobinuria | PRINCE; A Complement C3 Inhibitor | 0 | 59 |
| Phase III Trial Initiation | Applied Therapeutics Inc. | AT-001 | Diabetic Cardiomyopathy | ARISE-HF; An Aldose Reductase Inhibitor | | 47 |
| Phase III Trial Initiation | Mapi Pharma | glatiramer acetate Depot | Multiple Sclerosis, Relapsing Remitting | Encouraging Results | 35 | 52 |

Source: Biomedtracker | Informa, 2019

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CONTINUED FROM PAGE 21

day one, when I was involved in setting up a company with the with the scientific founders, it was key that we understood the path to commercial-scale manufacturing. We aren't interested in treating ten patients, we're interested in treating thousands of patients and so your manufacturing process has to be designed from the very first day to do that."

MANUFACTURING

Ali went on to say that "since we designed the company and the manufacturing process, everything, every single experiment is under our control. We didn't inherit any academic data, we created everything towards a commercial process to treat thousands of patients and you will see over the next phase of the company that we will really build space between us and other cell therapy companies because of that differentiation."

The product will be manufactured at the GMP-approved cell and gene therapy facility at the Royal Free Hospital in London, about 30 miles from Achilles's headquarters in Stevenage. Ali noted that the firm had secured capacity there

for the next five years, saying that "we want to build a manufacturing process that is robust and is not going to let people down."

The CEO also commented on the firm's relationship with regulators as it has been preparing the trials, saying that "we've had very positive interactions. The field in general, has taken a big step forward over the last five years, as we come into the realm of gene and cell therapy, and the regulators have been very open to therapies that can bring transformational impact and address patient groups that have been recalcitrant to current therapies and modalities, whether a small or large molecule – what they're here to do is help us balance risk/benefit."

As for the future, he said that "we can absolutely go all the way and I don't say that flippantly but with careful consideration." He added that there was a clear opportunity to explore the potential for partnerships. "That's something all biotech companies of all sizes and stage should be thinking about [and] given where we are in the technology space, we're a technology leader, we will be looking to identify and evaluate part-

nerships that could create value for the shareholders in the business and allow us to do more in parallel."

Ali said that in the first two years of the company, "I don't think anyone had really heard about us, we were in stealth mode and what we were doing is just with 100% focus figuring out the cell therapy." He added that in the immunotherapy field, "there has been a myriad of approaches, across vaccines and all sorts of different modalities from RNA proteins and different delivery technologies, which could have very easily been a distraction and there was certainly a lot of people that wanted to work with us. As tempting as it was, we wanted to just focus on the cell therapy and make sure that we can develop a robust process and deliver product to patients reliably."

He concluded by saying that like all private companies, "we will consider our financing options beyond the series B but step one is that we've got to run a really ambitious and exciting clinical trial and validate our excitement behind the technology and it's critical that we execute on that trial." 🌟

Published online 3 September 2019

APPOINTMENTS

| Executive | To Company | New Role | From Company | Previous Role | Effective Date |
|-------------------------|-----------------------------|---|-------------------------|---|----------------|
| Shakti Narayan | Accent Therapeutics Inc | Chief Executive Officer and Director | Tango Therapeutics | Chief Business Officer | 3-Sep-19 |
| Jens Schneider-Mergener | Adrenomed AG | Chief Executive Officer | Jerini AG | Chief Executive Officer | 1-Aug-19 |
| Marianne De Backer | Bayer AG | Head, Business Development and Licensing and Executive Committee Member | Johnson & Johnson | Head, Business Development | 3-Sep-19 |
| David Garrett | Dynacure SAS | Chief Financial Officer | Nabriva Therapeutics | Vice President, Corporate Controller and Head, Investor Relations | 3-Sep-19 |
| Soren Bregenholt | Macrophage Pharma | Chief Executive Officer | Medicon Valley Alliance | Chairman | 3-Sep-19 |
| Robert Weiskopf | Stealth BioTherapeutics Inc | Chief Financial Officer | ArQule | Chief Financial Officer and Treasurer | 3-Sep-19 |

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