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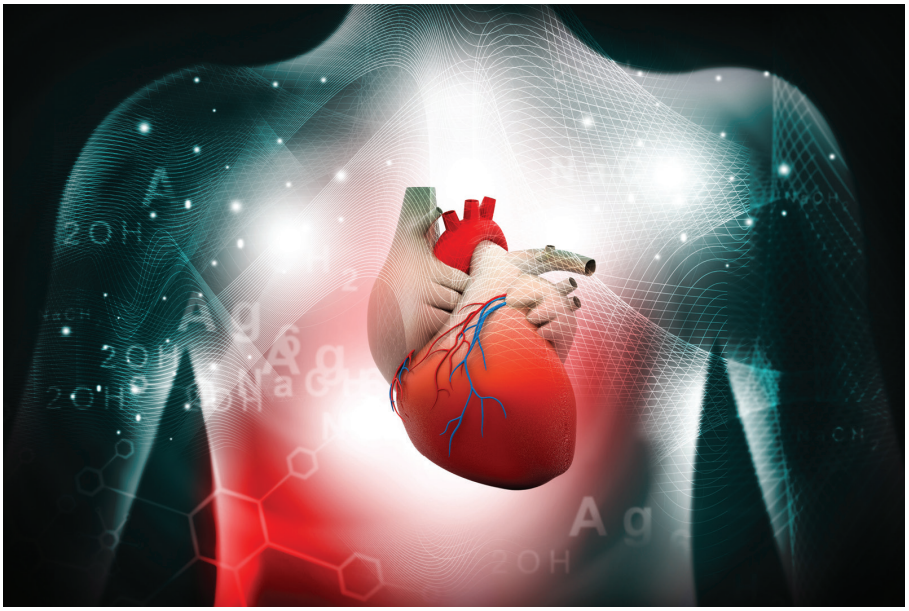

Farxiga Data Change Heart Failure Treatment Outlook

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Diabetes drug Farxiga/Forxiga (dapagliflozin) looks set to become a new standard of care in the treatment of heart failure based on the results of the DAPA-HF Phase III trial presented at the European Society of Cardiology Congress in Paris, France on 1 September. The product reduced the composite endpoint of cardiovascular death or worsening heart failure by 26% when given on top of standard of care and the benefits were seen in both diabetic and non-diabetic patients.

The sodium glucose cotransporter-2 (SGLT-2) inhibitor has stolen a march on rivals in its class with regulatory filings slated by the end of this year, and approvals expected in the first half of 2020, to treat patients with heart failure with reduced ejection fraction regardless of whether they have type 2 diabetes. But as AstraZeneca PLC's executive vice-president biopharmaceuticals R&D Mene Pangalos acknowledges, there is likely to be a class effect with SGLT-2 inhibitors. Boehringer Ingelheim GmbH/Eli Lilly & Co.'s Jardiance (empagliflozin) is also being studied in the indication.

> "The results likely mark a new standard of care for heart failure patients."

Nevertheless, being first to market is a boon, and the size of the opportunity is large.

Describing the results of DAPA-HF as "game-changing for Farxiga", Bryan, Garnier & Co analyst Eric Le Berrigaud wrote in a 2 September note that the results were "unequivocally positive across the board with a benefit similar in magnitude to what Entresto [Novartis AG's approved sacubitril/valsartan] provided in PARADIGM-HF, on top of background therapy." Deutsche Bank analysts described the results as "exceptionally impressive," adding that they "likely mark a new standard of care for heart failure patients both with and without diabetes."

They forecast that the SGLT-2 inhibitor class stands to exploit an additional $1-4bn market opportunity in heart failure patients without diabetes. "We expect the results to put upward pressure on Farxiga consensus sales of $2.5bn [annually] by 2024," they added, suggesting that Farxiga itself stands to gain at least a $1bn opportunity in heart failure without diabetes "based on the trajectory of Novartis' Entresto." Farxiga's first-half 2019 sales were $726m.

Pangalos told *Scrip* that he expected cardiologists to be "thrilled" to have the opportunity to prescribe the once-a-day pill with its relatively clean side-effect profile. Entresto requires patients to be titrated and monitored for renal function, and some patients cannot tolerate it.

Notably, 11% of patients in the 4,744-patient DAPA-HF trial were on Entresto; there was no difference in the benefit seen in those patients compared with those in the rest of the trial, prompting study investigator John McMurray to note that the two products work in a complementary way. "What is less clear at this stage is whether the effects are

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from the editor

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There was much excitement at the European Society of Cardiology Congress in Paris when the first Phase III data on an SGLT-2 inhibitor for heart failure in both diabetics and non-diabetics were presented (see cover story). Prompting enthusiastic applause, the magnitude of the benefit and its consistency across subgroups pave the way for a large new market for AstraZeneca's Farxiga beyond the diabetic population.

Farxiga looks set to leapfrog fellow SGLT-2 inhibitor Boehringer Ingelheim/Eli Lilly's Jardiance, which had previously taken an early advantage with the first cardiovascular outcomes label. In the longer run, Farxiga is unlikely to be be the only SGLT-2 approved for heart failure. And with the class also advancing in kidney disease studies, there are further opportunities to serve significant new markets. For an interview on DAPA-HF with AstraZeneca's R&D chief Mene Pangalos, click here or visit www.scripnews.com.

DAPA-HF studied patients with reduced ejection fraction (HFrEF). Also at ESC there was a valiant pitch for Novartis's already approved HFrEF drug Entresto, which recently narrowly missed its primary composite endpoint in the pivotal PARAGON-HF trial in the tricky population of heart failure with preserved ejection fraction (HFpEF), an indication with no approved therapy. When a company talks about "the totality of the data" it is often grasping at straws. But Novartis executives are hopeful that given the benefit seen in certain prespecified subgroups and the seriousness of the need, regulators will decide the totality of the data make Entresto approvable for HFpEF at least in women and/or those with an ejection fraction at the lower end of preserved.

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Synthorx Throws THOR-707 Into Competitive IL-2 Space With HAMMER, Its First-Ever Clinical Trial

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Synthorx Inc. is putting its Expanded Genetic Alphabet platform to test in the company's first-ever clinical trial, evaluating the recombinant interleukin-2 (IL-2) THOR-707 in patients with advanced or metastatic solid tumors in the Phase I/II HAMMER study, to see if its technology can deliver on a promise of highly specific, more effective and safer biologics for cancer and autoimmune diseases.

THOR-707 is the first candidate to enter the clinic for San Diego-based Synthorx based on technology developed by scientific founder Floyd Romesberg, formerly of The Scripps Research Institute and currently a member of the company's board of directors. This first development program reflects Synthorx's initial focus on creating optimized cytokines, starting with IL-2 in solid tumors and moving on to a separate IL-2 candidate for autoimmune diseases, then IL-10 and IL-15 in cancer.

"We have some undisclosed cytokines as well that look to be very promising," CEO Laura Shawver told *Scrip*.

Romesberg created new DNA base pairs, known as XY, that expands the genetic alphabet to develop better biologics called Synthorins, which are proteins with novel amino acids encoded by the new DNA base pairs to allow for site-specific modifications that enhance the protein's pharmacological properties. Transcription is enabled by a semi-synthetic *Escherichia coli* (*E coli*) strain that contains the novel DNA base pairs.

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

inside:

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cumulative and in terms of daily practice whether Entresto and Farxiga will largely be used in combination from now on," commented Le Berrigaud.

DAPA-HF DETAILS

The trial enrolled 4,744 patients, 42% of whom had prior diagnosis of type 2 diabetes and 45% of whom had any baseline type 2 diabetes (ie, including previously undiagnosed patients). 2,373 received 10mg daily dapagliflozin on top of background treatment, and 2,371 received matching placebo pills on top of background treatment.

93-94% of patients in both groups were treated with diuretics, with 56% receiving an ACE inhibitor, 27-28% receiving an angiotensin receptor blocker, 11% receiving the angiotensin receptor neprilysin inhibitor sacubitril/valsartan and 96% on beta-blockers. 71% received a mineralocorticoid receptor antagonist, 26% had an implantable cardioverter defibrillator and 7-8% a cardiac resynchronization therapy heart device.

The primary composite outcome of cardiovascular death, first episode of worsening heart failure (defined as heart failure hospitalization or urgent heart failure visit) occurred in 16.3% of the treatment arm and 21.2% in the placebo arm (HR: 0.74; 95% CI 0.65-0.85). This translated to a 26% reduction in the composite endpoint ($p<0.0001$), a 30% reduction in worsening heart failure events ($P<0.0001$) and an 18% decrease ($p=0.0294$) in the risk of dying from cardiovascular causes.

The trial showed Farxiga was as effective in treating heart failure patients with diabetes as those without, with the effect on the primary composite endpoint generally consistent across key subgroups examined. It also showed a nominally significant reduction in all-cause mortality by 17%.

Published online 2 September 2019

Zogenix To Pay $250m Upfront To Buy Modis For Ultra-Orphan Drug

Zogenix Inc. has struck a deal to buy Modis Therapeutics Inc. for $250m upfront, giving it control of another late-phase rare disease drug to complement its lead product, Fintepla.

The planned takeover centers on MT1621, a deoxynucleoside substrate enhancement therapy that Modis is developing as a treatment for an inherited mitochondrial DNA depletion disorder. Zogenix sees MT1621 as a good fit for its efforts to expand beyond its existing rare disease asset, Fintepla (ZX008, low-dose fenfluramine hydrochloride), which in April was slapped with a refusal to file letter by the US Food and Drug Administration.

"Our business strategy beyond Fintepla is to seek out and acquire similarly potentially transformative rare disease therapeutic opportunities to complement our lead program. We believe we have found such an opportunity in the acquisition of Modis Therapeutics," Zogenix CEO Stephen Farr said on a conference call with investors to discuss the deal on 27 August.

Zogenix has been on the hunt for some time for a development-stage drug with breakthrough therapeutic potential in a serious rare disease.

Zogenix has been on the hunt for some time for a development-stage drug with breakthrough therapeutic potential in a serious rare disease that has limited or ineffective treatment options. The belief that MT1621 fits the bill rests on the data generated to date and the nature of the disease it targets, thymidine kinase 2 deficiency (TK2d).

TK2d presents, sometimes as early as the first year of life, as a progressive, severe muscle weakness that impairs movement, breathing and eating. Most cases develop during infancy or childhood and end in death from respiratory failure. There are no treatments beyond supportive care. Zogenix thinks TK2d affects 650 to 2,500 people in the US, although, as the disease is often misdiagnosed as spinal muscular atrophy, it is possible that more patients will become available.

Modis assessed the efficacy of MT1621 in TK2d by treating 38 subjects with the drug and comparing their outcomes with a matched natural history cohort of 68 patients. The comparison linked MT1621 to a significant improvement in the probability of survival, plus improvements in functional abilities.

Zogenix plans to meet with regulators in the US and Europe to discuss the path to approval in the first quarter of next year. As it stands, Zogenix expects to need to generate additional safety data and plans to start doing so by treating people in the natural history cohort with MT1621.

The discussions and work related to MT1621 add to an already busy schedule at Zogenix, which is still recovering from the refuse-to-file notice issued by the FDA in response to a request for approval of Fintepla in the treatment of seizures associated with Dravet syndrome. Zogenix expects to refile for approval in the third quarter and deliver top-line Phase III data on Fintepla in a second indication, Lennox-Gastaut syndrome, in the first quarter of next year.

Farr downplayed concerns that the takeover would distract Zogenix from these activities, noting that the 15-person team at Modis will shoulder much of the near-term burden of advancing MT1621.

"We're acquiring a company here that has people who have done a really great job in advancing the program. We really hope and expect that that same team will continue with this program moving forward," Farr said.

In the longer term, Farr foresees leveraging some of the same resources for MT1621 and Fintepla. However, by acquiring a candidate that is outside of its existing focus on the central nervous system, Zogenix has limited its ability to use exactly the same infrastructure for both therapies.

"There are definitely synergies we can leverage on the commercial side, particularly around market access, pricing [and] reimbursement discussions, our medical science liaison team that helps support product in the field. The field sales force is likely to be different but that's ok because these will be relatively small and efficient teams," Farr said. Farr expects the sales team to have 10 to 20 people.

For Modis and its investors, the deal represents a big, quick return. Modis raised a $30m series A financing round led by F-Prime Capital Partners and OrbiMed in October. Ten months later, Zogenix is set to pay $250m upfront and commit to $150m in regulatory approval milestones to buy the company.

Zogenix has reduced the cash outlay by paying $75m of the upfront fee in stock. The remaining $175m will come out of the $460m Zogenix had in cash and marketable securities as of the end of June. Despite eating into its savings, Zogenix thinks it has enough money to support the anticipated launches of Fintepla in the US and Europe. The deal is due to close in September.

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Despite BMS Bid, Celgene Pays $75m Upfront For Immatics Assets Options

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Immatics Biotechnologies GmbH has signed its first cell therapy-focused deal by entering into a strategic collaboration and option agreement with Celgene Corp. to develop novel adoptive cell therapies targeting solid cancers. Celgene has secured exclusive options to three Immatics TCR-T targets and has agreed to pay the German biopharma $75m upfront, with the potential of a further $505m per program in option exercise payments and milestones, plus tiered royalties on net sales. Moreover, Immatics also retains options to co-develop or co-fund certain licensed products.

Under the terms of the deal, Immatics will attempt to develop T-cell receptor engineered T-cell therapy programs against solid tumor targets discovered using its XPRESIDENT platform, using its proprietary TCRs identified by its XCEPTOR TCR discovery and engineering platform.

"There is still an enormous unmet medical need for solid cancers. We believe that intracellular pMHC (Major-Histocompatibility-Complex-restricted peptide) targets are the key to unlocking solid cancers in immunotherapies. The targets most companies have in discovery are often restricted to the surface but the pMHC pathway allows us to tap into the entire target space and it is an area that we have been active in for the past 15 years," Harpeet Singh, Immatics CEO, told *Scrip*.

In the past decade, Immatics has identified more than 160 million peptide sequences and initially prioritised 4,000 candidates, honing this down in the past two years to 100 candidates that have shown significant target properties.

"It is this bucket of 100 targets that we are using for our own proprietary programs and seven of them we are focusing on in clinical development, while the rest are unencumbered and available for partnering. Before this Celgene deal we had only partnered a handful of targets," added Singh.

FIRST TRUE PARTNERSHIP

Using quantitative mass spectrometry, Immatics has been able to show that the targets are truly presented on tumor cells and in sufficient copy numbers. Moreover, data from its collaboration with the MD Anderson Cancer Center, presented at the recent AACR meeting, confirms that the approach is safe and well tolerated and can drive dramatic T-cell responses in cancer patients.

This deal is the first one which sees Immatics retaining co-development or co-funding options. "The other deals we have signed – with Roche, Amgen Inc., Genmab AS and MorphoSys AG – were licensing deals. This is our first industry partnership in cell therapy, it is the largest upfront we have received for targets, and it is the first time we have retained an option to co-develop and co-fund certain licensed products and so have the opportunity to participate more in the downstream value generation," he noted.

Under the terms of the deal, Immatics will deliver the initial targets and then develop TCR programs through to lead candidate stage, at which time, Celgene can exercise opt-in rights and assume sole responsibility for further worldwide development, manufacturing and commercialization of the T-cell therapies.

Immatics continues to pursue the two-pronged strategy of developing its own pipeline and working with partners. "We will run the two horses in a sensible way not compromising the progress that we want to make in our proprietary pipeline nor impacting the quality we wish to deliver to our partners. We have 185 employees – 120 in Germany and 65 in Houston, Texas – and do not anticipate a dramatic increase in our size in the coming 12 months. We want to grow sensibly and will take a balanced approach to allocation of resources," he added.

Declining to disclose either cash burn or runway, Singh noted that the company has raised some $420m since its inception; $220m of this has come from private equity sources and the balance from upfront payments and grants. "At the moment, we are in a comfortable position financially and do not need to raise money although we still may do so. We have a tight leash on cash spending and are in a position to be able to raise money when we choose," he added.

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GSK Opts In On Ionis' Antisense Candidates For Hep B

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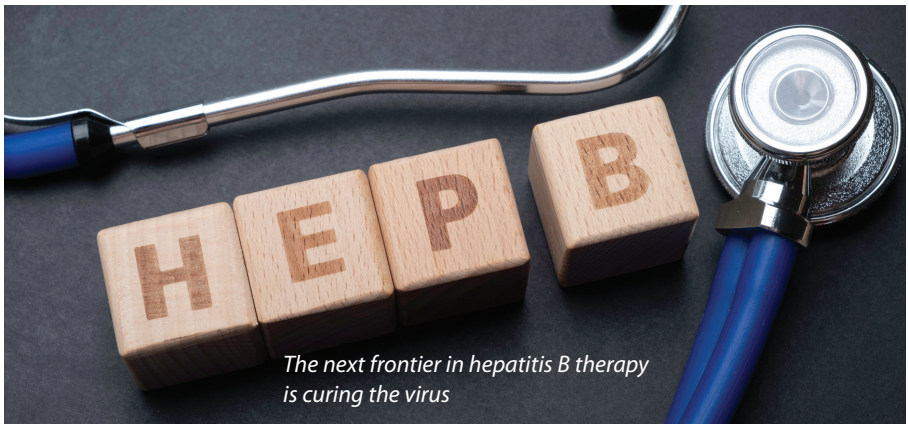
The winding terrain of the long-standing collaboration between GlaxoSmithKline PLC and Ionis Pharmaceuticals Inc. took another turn on 27 August, as the pharma elected to opt in on a pair of antisense candidates for hepatitis B, paying the biotech $25m in licensing fees with the potential for milestone payments and sales royalties.

Overall, it was only the second licensing deal around HBV assets announced in 2019, according to Strategic Transactions. In an HBV *Market Spotlight* report issued on 6 August, Datamonitor Healthcare noted that there had been 37 licensing and asset-acquisition deals in the HBV space between 2014 and 2019, including nine deals in both 2015 and 2018.

Carlsbad, CA-based Ionis said GSK exercised its option on multiple candidates, presumably including both the Phase II IONIS-HBV$_{RX}$ and a different formulation, IONIS-HBV-L$_{RX}$, which incorporates the biotech's second-generation LICA (ligand conjugated antisense compound) technology. GSK plans to present Phase I/II data on IONIS- HBV$_{RX}$ at a medical meeting later this year, likely November's American Association for the Study of Liver Disease (AASLD) conference in Boston.

Ionis said the milestones it could earn as GSK takes over development, regulatory and commercial responsibilities for the candidates could reach as high as $237m, along with tiered net sales royalties in the low double digits. Then known as Isis Pharmaceuticals, the biotech partnered with GSK in 2010 to discover and develop antisense candidates against targets selected by the pharma, getting $35m up front. The deal originally covered five targets, with GSK eligible to add a sixth; the HBV program was added to the deal in October 2013.

Ionis said it was interested in GSK's development and commercial know-how in infectious diseases, which make it the ideal entity to bring a potentially curative agent for HBV to patients. While current therapies kill the viral the infection but leave traces of the disease in the body, several companies, including Johnson & Johnson, are working to develop curative therapies to completely clear the virus. Ionis believes its candidates could do that by targeting all four HBV transcripts.



The next frontier in hepatitis B therapy is curing the virus

In a 27 August note, Laidlaw & Co. analyst Yale Jen said the deal with GSK is meaningful, even if less lucrative than other recent deals Ionis has negotiated. Last October, Ionis got $75m up front with potential for $684m in milestones and sales royalties as high as 20% from Roche for the rights to the ophthalmic IONIS-FB-L$_{RX}$, which the Swiss giant plans to develop for geographic atrophy and possibly later for advanced wet age-related macular degeneration. That candidate is one of two GSK elected not to option in August 2017 under the 2010 collaboration.

"Although the overall deal size for the [HBV] program is relatively modest compared to some other recent Ionis deals, the opt-in by GSK for future development exemplifies the technical and clinical success of Ionis' antisense program in this increasingly meaningful competitive treatment market," Laidlaw's Jen said. "It could also provide a very meaningful commercial upside to Ionis given the large patient population, especially in Asia."

The Datamonitor Healthcare report on HBV notes that as of 2017, there were an estimated 294.5m cases of HBV worldwide, although fewer than 10% (about 29.1m) were diagnosed. Of those, roughly 4.8m patients were treated with one of the currently available antiviral therapies that year. In the US, the five largest EU markets, Japan and China, there were an estimated 89.4m prevalent cases (diagnosed and undiagnosed), but more than 96% of those (about 86m) patients were in China.

Successfully treating or possibly curing HBV can have important ramifications for health care systems around the globe, Datamonitor Healthcare pointed out, as chronic HBV is a leading cause of cirrhosis, liver failure and hepatocellular carcinoma. The infection led to an estimated 887,000 deaths worldwide in 2015, and between 20% and 30% of cases advance to complications such as HCC and cirrhosis.

Regarding deal-making in the HBV space, the report states that the 37 licensing and acquisition deals tracked since 2014 have an average deal value of $305.1m. The variation in deal value is significant, as little as $2m in total projected value at one end of the spectrum and as high as $1.775bn at the other end. The latter is an October 2018 deal between J&J and Arrowhead Pharmaceuticals Inc., in which the pharma paid $250m up front and made a $75m equity investment for Phase I/II ARO-HBV, which, like the Ionis candidates, employs a gene-silencing approach to hopefully cure the virus.

Earlier this year, China's Ascletis Pharma Inc. licensed exclusive development and commercial rights to a PD-L1 antibody candidate (KN035/ASC22) for HBV from Alphamab. Specific financial terms weren't disclosed, but Alphamab got upfront cash with the potential for development and commercial milestones, sales royalties and profit-sharing outside greater China.

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AbbVie Might Be Most Affected By FDA's HCV Drug Safety Warning

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The US Food and Drug Administration issued a drug safety communication that warns of rare incidences of serious liver injury seen in hepatitis C patients treated with three combination products marketed by AbbVie Inc., Gilead Sciences Inc. and Merck & Co. Inc. However, AbbVie appears to have more to lose than its two peers as its product, Mavyret, remains one of its top sellers despite declining sales.

The FDA reported on 28 August that it has identified 63 cases of worsened liver function in patients with the hepatitis C virus (HCV) who were treated with Mavyret (glecaprevir/pibrentasvir), Gilead's Vosevi (sofosbuvir/velpatasvir/voxilaprevir) or Merck's Zepatier (elbasvir/grazoprevir). In most cases, liver decompensation occurred during the first four weeks of treatment, the agency said.

Each of those fixed-dose regimens contains a protease inhibitor – glecaprevir, voxilaprevir and grazoprevir, respectively – and the FDA warning notes that most of these cases occurred in patients with moderate-to-severe liver impairment (Child-Pugh B or C), for whom HCV therapy with a protease inhibitor is contraindicated.

"In many of the reported cases, liver failure occurred in patients who … should not have been treated with these medicines," the letter states. It recommends that physicians prescribe Mavyret, Zepatier and Vosevi "as indicated in the prescribing information," which recommends therapy for patients without liver impairment or with only mild liver impairment (Child-Pugh A). Doctors are advised to assess a patient's severity of liver disease at baseline and then monitor for signs and symptoms of worsening disease such as liver enzyme increases, jaundice and encephalopathy.

Sales of Mavyret, AbbVie's second-generation direct-acting antiviral combo for HCV, declined 20.4% year-over-year to $780m during the second quarter of 2019. Likewise, for the first six months of 2019, Mavyret brought in $1.57bn, down nearly 21% year-over-year. Nonetheless, Mavyret is AbbVie's third-largest seller behind immunology titan Humira (adalimumab) and hematologic cancer drug Imbruvica (ibrutinib). *(Also see "AbbVie's Five Biggest Priorities, Apart From Allergan" - Scrip, 26 Jul, 2019.)* The HCV combo posted sales of $3.43bn in 2018.

Gilead, once the dominant player in HCV, reported sales of only $75m during the second quarter for Vosevi and $109m for the first six months of 2019. Upon Vosevi's approval in July 2017, Gilead told investors that would be its final HCV product as the company began emphasizing cancer cell therapy and HIV as its priority therapeutic areas. *(Also see "Gilead Completes HCV Clinical Development With Vosevi Approval" - Scrip, 18 Jul, 2017.)*

Merck, which has struggled to carve out a clear niche in HCV for much of the past decade, realized sales of $221m for the first six months of 2019 from Zepatier, including $108m during the second quarter.

> "In many of the reported cases, liver failure occurred in patients who … should not have been treated with these medicines."
> – FDA

SOME DEATHS, BUT MOST CASES RESOLVED AFTER THERAPY ENDED

The FDA noted in its warning that in most patients who experienced serious liver injury, the symptoms resolved or the worsening of liver function stopped shortly after HCV therapy was ceased. "These medicines have been widely used and are safe and effective in patients with no or mild liver impairment," the agency added.

However, some of the 63 cases reported – either through submission to the FDA or by being recorded in the medical literature – led to liver failure and death. The agency pointed out that there could be other such cases that were not reported, noting that 72,000 patients were dispensed prescriptions for one of the three combination pills in 2018.

This is not AbbVie's first experience with an HCV therapy-related safety warning. Labeling for its first-generation combo Viekira Pak (ombitasvir/paritaprevir/ritonavir/dasabuvir) and follow-on product Technivie, which included all those ingredients except for dasabuvir, was revised in October 2015 to contraindicate therapy in Child-Pugh B patients. Both products already were contraindicated for Child-Pugh C patients. *(Also see "AbbVie Downplays Impact Of Viekira Pak Safety Issues" - Scrip, 30 Oct, 2015.)*

The label update resulted after the FDA noted several post-marketing reports of liver failure and death in HCV patients who had received Viekira or Technivie.

Roughly one year later, several direct-acting antiviral therapies for HCV, including Viekira and Technivie, Gilead's Sovaldi (sofosbuvir), Epclusa (sofosbuvir/velpatasvir) and Harvoni (sofosbuvir/ledipasvir) and Bristol-Myers Squibb Co.'s Daklinza (daclatasvir) got an FDA black box warning noting 24 cases of hepatitis B reactivation in patients who had received those drugs, including two deaths.

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After Two Jury Verdicts, Court Finds Repatha Patents Invalid

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Amgen Inc. was dealt a blow in its long battle with Sanofi/Regeneron Pharmaceuticals Inc. as a US district court found that its Repatha (evolocumab) patents were invalid for lack of enablement. The decision means that, for now, Sanofi and Regeneron will continue to market their competing PCSK9 inhibitor Praluent (alirocumab) in the US without worrying about potential damages.

In a 28 August opinion, Delaware District Judge Richard Andrews granted Sanofi and Regeneron's request to overturn portions of a second jury verdict, which found that a claim in one Amgen patent, No. 8,859,741, and claims in a second patent, No. 8,829,165, are valid and that two claims in the '165 patent are invalid. However, he denied their request for a judgment that the claims lacked adequate written description and their request for a new trial.

"We disagree with the court's decision in reversing the jury verdict on enablement and will seek review by the appellate court," Amgen said in a statement.

Sanofi and Regeneron said the ruling invalidates asserted patent claims targeting PCSK9. The decision "validates our position that Amgen's patents are overly broad and invalid," Regeneron General Counsel Joseph LaRosa said in a release. "Praluent was developed using Regeneron's proprietary science and technology and the judge has confirmed our position by issuing this ruling."

The dispute has gone through many twists and turns since Amgen filed an infringement suit against the two companies in October 2014. Amgen won the first trial when a jury found Sanofi and Regeneron failed to prove Amgen's patents were invalid for lack of written description and enablement. They had stipulated that Praluent infringed the patents. Amgen then won a permanent injunction blocking the marketing and sale of Praluent, which was stayed and never went into effect.

On appeal, the US Court of Appeals for the Federal Circuit vacated the judgment and remanded the case for a new trial, finding that the district court's erroneous evidentiary rulings and jury instructions necessitated a new trial on Sanofi and Regeneron's written description and enablement defenses.

MARKET BATTLE CONTINUES

The second jury trial was held in February. Prior to that trial, Amgen petitioned the US Supreme Court to review the standard the Federal Circuit used for determining the adequacy of an invention's written description. But the court declined to take up the case.

The companies have been simultaneously engaged in a market battle. The US Food and Drug Administration approved Praluent in July 2015 and Repatha a month later. Repatha had an edge when it obtained a cardiovascular risk reduction label claim from FDA in late 2017. But Sanofi and Regeneron nabbed an outcomes claim for Praluent in April.

Repatha sales totaled $152m globally in the second quarter versus $148m the quarter after the company introduced a lower list price version of the biologic in October to help lower out-of-pocket costs for US patients covered by Medicare Part D plans. *(Also see "Amgen Drops Repatha List Price 60% To Cut Medicare Co-Pays And Boost Use" - Scrip, 24 Oct, 2018.)* In 2018, Repatha sales jumped 72% to $550m for the year.

Sales of Praluent totaled $306.8m in 2018, but Sanofi/Regeneron's decision in February to also lower their drug's cost by 60% could improve uptake in 2019. *(Also see "Sanofi/Regeneron Cut Praluent List Price As PBMs Look To Maintain Rebate Status Quo" - Scrip, 12 Feb, 2019.)* Praluent still may be hit by sales declines in ex-US markets, however, given patent court decisions that have gone in Amgen's favor in Germany and other countries. *(Also see "In A Win For Amgen, Court Blocks Sanofi/Regeneron's Praluent Sales In Germany" - Scrip, 11 Jul, 2019.)*

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Mandy Jackson contributed to the article.

Shadow On Novartis' Ceritinib In India After Patent Revoked

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New twists and turns have emerged in the ceritinib case in India, where the patent office revoked Novartis AG's patent on the product, after which a local court has put on hold an interim order against challenger Natco Pharma Ltd., which had previously launched its own version of the lung cancer drug. But the Swiss multinational isn't backing off and has appealed against the revocation order. However, with the patent struck down, the Delhi High Court last week suspended a previous interim order dated 2 May that restrained Natco from carrying out any fresh manufacturing using the ceritinib active pharmaceutical ingredient (API). *(Also see "Novartis Ceritinib India Case: Court Rebuke Amid Wait For Patent Decision" - Scrip, 22 Jul, 2019.)*

Novartis said that the decision of the Deputy Controller of Patents and Design

to revoke the patent for ceritinib was disappointing. "We have decided to appeal this decision before the Intellectual Property Appellate Board [IPAB] and are hopeful that the patent will be reinstated," Novartis told *Scrip*.

The indications now are that a hearing before the IPAB is expected in early September, with the court hearings in the case also listed for next month. This could potentially give Natco a window of opportunity to resume activities around ceritinib, though it's not immediately clear if the Hyderabad-based firm will exercise the option and replenish stocks of its product.

NOXALK LAUNCH

Natco had commercialized its ceritinib (sold as Noxalk) on 20 March 2019. While the Delhi High Court had in its 2 May order noted that the company "ought not to have launched the product" while the decision was pending in the Indian Patent Office, the court had, at the time, allowed "drugs already manufactured" by the firm to be sold during the pendency of the particular hearing and until further court orders.

"Considering that this is a drug for treating non-small cell lung cancer, stopping the sale of the defendant's products which are already manufactured would not benefit the patient community in any manner," the court observed at the time.

It's not immediately clear how Noxalk has fared thus far on the Indian market versus Novartis' ceritinib (marketed as Spexib in India and Zykadia internationally). Natco had during the course of the case undertaken to file an affidavit with a complete statement of stock, including the batch numbers of the products which have been manufactured.

The revocation of Indian Patent number 276026 pertaining to ceritinib comes as a significant setback to Novartis after an Opposition Board had previously held that the patent was novel and inventive, and not hit by Section 3(d) of the India Patent Act. This broadly deals with incremental inventions that are not patentable unless they show improved efficacy or unless a known process results in a new product or employs at least one new reactant.

> "We have decided to appeal this decision before the Intellectual Property Appellate Board and are hopeful that the patent will be reinstated." – Novartis

The Opposition Board, constituted by India's Patent Controller, conducts the examination of the notice of opposition along with documents such as statements and evidences, and submits a report with reasons on each ground in the notice of opposition with its joint recommendations in a specified time-frame.

But Deputy Controller of Patents and Designs Kavita Taunk struck down Novartis' 276026 patent and held that Natco had succeeded in the grounds (of opposition) under sections 25(2) (b), 25(2) (e) and 25(2) (f) of the Patents Act, 1970.

"I do not agree with the recommendations of the Opposition Board. Having considered all the relevant documents and pleadings of both the parties, and in view of my findings, as per Section 25(4) of the Patents Act 1970, I hereby revoke the Patent numbered 276026 granted on the Patent Application No. 3951/DELNP/2009," Taunk said in an order dated 16 August.

Among a string of observations, Taunk held that the '026 patent lacks inventive step and that the priority date of the patent was 8 December 2006 - therefore, it lacked novelty on the "date of filing of first convention application filed in the US i.e. 8 December 2006."

Details of the Deputy Controller's order were presented by Natco in the Delhi High Court, which then observed that once a patent is revoked, a "suit for infringement of the patent itself would not be maintainable."

"Considering the development, i.e., the passing of the order dated 16 August, 2019, revoking the patent, the interim order restraining the defendant (Natco) from carrying out any fresh manufacturing of pharmaceutical preparations comprising the API ceritinib, as directed vide order dated 2 May 2019, stands suspended," Judge Prathiba Singh said in an order dated 20 August.

EARLY SEPT HEARING?

However, with Novartis initiating an appeal against the deputy patent controller's order before the Intellectual Property Appellate Board, which was to list before the board on 19 August, it requested the Delhi High Court to not pass an order till 22 August - the date of a court hearing on the matter.

Details of the listing of the appeal before the IPAB could not immediately be verified, but sources indicated that matter is now expected to be heard in early September. Hearings before the Delhi High Court are also expected to come up next month.

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Kolon TissueGene Faces Delisting In Korea On Invossa Uncertainties

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The Korea Exchange has decided to delist the depositary receipts of US-based Kolon TissueGene Inc. from the second-tier Kosdaq market following a ministry decision to cancel the approval of its lead product Invossa (TC-C; tonogenchoncel-L), an allogeneic cell and gene therapy for knee osteoarthritis. The move is expected to have a significant impact on the company's business.

The Kosdaq review committee will finalize the initial delisting decision within 15 days, and if this goes forward it is expected to seriously hurt shareholders in the company, whose stock has already plunged because of uncertainties over Invossa and its future business. This move could also lead to further lawsuits from investors and add to the financial burden on the company. Kolon TissueGene launched its offshore IPO on Kosdaq in November 2017.

Shares of parent Kolon Life Science Inc., which are also traded on Kosdaq, fell 22% on 27 August on the decision by the exchange. Shares of Kolon TissueGene were suspended from trading in late May after South Korea's drug ministry announced the Invossa approval revocation decision, after it concluded the company submitted false data to support the approval, and asked prosecutors to press criminal charges against the company.

Kolon Life has filed for an administrative lawsuit to withdraw and suspend the administrative measures by the ministry. *(Also see "Kolon Ends One Asian Invossa Contract, But Hopes To Keep Others" - Scrip, 30 Jul, 2019.)*

Kolon TissueGene, previously known as TissueGene Inc., has also been progressing clinical trials of Invossa in the US. In July 2017, Kolon Life Science Inc., TissueGene's exclusive licensee for Asia, received marketing approval in South Korea for Invossa; both Kolon Life Science Inc. and Kolon TissueGene belong to mid-sized South Korean conglomerate Kolon Group.

DELISTING TO FUEL LEGAL ACTION?

DB Financial Investment said in a research note that Kolon TissueGene is likely to be delisted from the stock market whether or not Invossa resumes clinical trials in the US. The company is already facing more than KRW7bn ($5.8m) in compensation lawsuits from patients who have been administered Invossa in Korea, as well as KRW53bn worth of lawsuits from shareholders who claim to have suffered from plunging stock prices.

In addition, Kolon Life Science has to handle the cost of 15-year follow-up studies on patients who have been administered Invossa, as well as indemnity insurance payments related to the gene therapy. There is also a possibility of legal action from Mundipharma International Corp. Ltd. and other partners which had licensed in Invossa for the return of upfront payments Kolon had received.

The brokerage saw a very slim chance for the resumption of the Phase III clinical trials of Invossa in the US and resumption of sales of the product.

NEW DATA TO ADDRESS US CLINICAL HOLD

Kolon TissueGene said that it has now submitted additional data required by the US FDA to remove the clinical hold on the Invossa trials. These included the results of a confirmation test on characteristics of Invossa's cell components, plans to improve quality management of the product and data evaluating safety. The US FDA usually completes such reviews of data within 30 days.

> Kolon TissueGene is likely to be delisted from the stock market whether or not Invossa resumes clinical trials in the US.

Meanwhile, a paper on the safety and efficacy of Invossa was recently published in *Surgical Technology International*, the authors of which included doctors who participated in clinical trials.

According to the abstract, the safety and efficacy of the therapy was demonstrated in laboratory studies as well as in Phase I-III clinical trials. Due to a mis-identification error, there have been concerns that the cell-based gene therapy is actually based on a different cell than the one initially approved, confusion over which led to the withdrawal of the Korean approval.

However, the paper noted that Invossa's safety profile has been demonstrated by over 10 years of data that revealed no evidence of tumorigenicity or other long-term safety concerns. In all studies to date, there have been no treatment-related serious adverse events, it noted. Although the nomenclature of one component of the drug product has changed, the product itself has not, it added.

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Concerns Over Alleged Lapses By Sun Fading?

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Things may be settling down for Sun Pharmaceutical Industries Ltd., which has been in the eye of a storm over allegations of market-related and governance lapses, after an initial inquiry by the Securities and Exchange Board of India (SEBI) appears to have yielded little to support the charges.

Sun's shares spurted by over 5% to end at INR434.65 ($6.07) on 29 August on the Bombay Stock Exchange, after a local media report said that a preliminary inquiry by SEBI had found "no merit" in certain allegations made by a whistleblower and that an investigating team felt that the "matter does not require further probe."

SEBI, the report said, had sought details from Sun over allegations of "fund diversion" through Aditya Medisales Ltd, a related party through which Sun routed its domestic business (the arrangement has since been changed), and certain questions around the firm's foreign currency convertible bond (FCCB) issue back in 2004. Details of the investigation have been sent to a committee of the regulator for vetting, the report claimed.

Sun however told *Scrip* that it had "not received any intimation from SEBI regarding the outcome of the investigation."

Some analysts tracking the development said a potential clean bill for Sun wasn't very surprising since some of the allegations, to begin with, did not appear to be "on a strong wicket [basis] technically and legally." They also underscored that Sun's dull run on Indian bourses over the recent past has more to do with the mismatch in the firm's performance versus general investor expectations, rather than just concerns over governance issues.

"The specialty business hasn't yet shaped the way some of us thought it would and an impactful uptick with the Halol's site recent NAI [no action indicated] status following the June inspection by the FDA is awaited," one analyst told *Scrip*.

Another industry expert, however, observed that allegations of governance lapses erode confidence sharply and "these things tend to stick in the investor's mind."

ALLEGATIONS AGAINST SUN

Sun has been firefighting allegations of governance and other market-related lapses flagged last year by the Australian brokerage Macquarie and followed by a complaint to SEBI by a whistleblower.

Macquarie had, at the time, questioned why Sun chose to use London-based Jermyn Capital to manage its $275m FCCB issue; it also claimed that the Indian arm of Jermyn was found to have links with certain tainted market players, accused in an Indian stock market scam of 2001. Sun's rebuttal, however, pointed out that Macquarie seemed to have failed to mention that J.P. Morgan was the sole book runner for the FCCB issue and Jermyn Capital Partners PLC was only the co-manager to the issue.

The whistleblower's complaint to SEBI had also made a string of damning allegations against India's top ranked company, including that between 2014 and 2017, Aditya had "over INR58bn [$811m at the time] of transactions" with Suraksha Realty, controlled by Sudhir Valia, Sun chief Dilip Shanghvi's brother-in-law.

Sun, which has all along claimed that it has played by the rule book, had previously clarified that its relationship with AML has been on an arm's length basis and that the financials of Aditya are available in the public domain. Sun had also stressed that it does not have any financial transactions with Suraksha Realty.

Subsequently Sun fine-tuned certain business transactions that were a sticking point with investors. In January this year, the company said it would "transition" distribution related to its domestic formulations business from Aditya to a wholly owned subsidiary of Sun Pharma.

"This change will be made effective by Q1FY20, post receipt of all requisite regulatory approvals," Sun said in a filing to the Bombay Stock Exchange on 22 January. *(Also see "Sun Firefights Governance Concerns " - Scrip, 22 Jan, 2019.)*

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Patience Pays Off For Kyowa Kirin As Nourianz Finally Gets US FDA OK

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Kyowa Kirin Co. Ltd. never gave up on Nourianz (istradefylline) for Parkinson's disease (PD) and now the company's patience has paid off with US Food and Drug Administration approval on 28 August for the adenosine A2A receptor antagonist – the first drug approved in its class for PD.

Nourianz is indicated as an adjunctive treatment to levodopa/carbidopa for adults with PD who are experiencing "off" episodes – periods of time when levodopa/carbidopa wears off before patients can take another dose of the standard-of-care drug combination. Kyowa Kirin originally sought approval for its oral small molecule in 2007 as an adjunct to levodopa/carbidopa to improve motor function in PD patients, but the US FDA rejected Nourianz in 2008, requesting more preclinical and clinical data.

The drug has since been approved in Japan, where it has been marketed since May 2013 as Nouriast. Meanwhile, Kyowa Kirin made plans to resubmit its new drug application (NDA) to the FDA and completed the filing in March of this year. The NDA included data from a new Phase III study that generated mixed results, showing an improvement in off episodes, but not a statistically significant change.

"These mixed results did not give the impression of a strong case for approval of Nourianz, but Kirin has worked with the FDA in preparation for the most recent submission," Biomedtracker said in a 28 August note. The commentary cited pooled data from eight randomized, controlled studies presented at the World Parkinson Congress in June, which showed statistical improvement in off episodes with Nourianz versus placebo across five of the clinical trials.

"The PD disease area has seen few new treatments emerge over the past few decades, and although this treatment isn't the huge breakthrough the PD field space is calling out for, it does offer PD patients a novel non-dopaminergic pharmacologic approach to alleviate the adverse effects of 'off' episodes," Biomedtracker noted.

Kyowa Kirin intends to launch Nourianz in the US before the end of the year, president and CEO Masashi Miyamoto said during the company's 1 August second quarter earnings conference call. In Japan, Nouriast sales totaled JPY4.8bn ($45.3m) in the first half of 2019 versus JPY4.4bn ($41.5m) in the first half of 2018.

The company has a second A2A antagonist called KW-6356 that it is studying in a Phase IIb Parkinson's clinical trial in Japan.

According to the US FDA, 50,000 Americans are diagnosed with PD each year and about 1m people in the US have the neurodegenerative disorder. The agency said the Kyowa Kirin drug was approved based on four 12-week placebo-controlled trials enrolling 1,143 patients that showed statistically significant improvements for Nourianz-treated patients in off episodes.

The most common adverse events associated with Nourianz are dyskinesia, dizziness, constipation, nausea, hallucination and insomnia. Patients should be monitored for development or exacerbation of dyskinesia; 1% of PD patients treated with the drug in clinical trials discontinued treatment due to onset or worsening of involuntary muscle movements. Doctors should consider reducing or stopping Nourianz treatment if hallucinations, psychotic behavior, or impulsive/compulsive behaviors occur.

US COMPETITION POSSIBLE FROM NEUROCRINE NEXT YEAR

Another oral drug for levodopa/carbidopa off episodes could join Nourianz on the US market in about eight months, but it's the fourth drug of its kind for Parkinson's disease. Neurocrine Biosciences Inc. is next in line for FDA approval of an adjunctive PD therapy with Ongentys (opicapone), a selective and reversible catechol-O-methyltransferase (COMT) inhibitor that has a 24 April user fee date.

Neurocrine, which also has a Phase II gene therapy for PD in development with Voyager Therapeutics Inc., licensed North American rights for opicapone in 2017 from its European marketer Bial Pharmaceuticals. *(Also see "Voyager Nabs Neurocrine As Partner In CNS Gene Therapy" - Scrip, 29 Jan, 2019.)* Voyager and AbbVie Inc. have an earlier-stage Parkinson's gene therapy agreement. *(Also see "AbbVie Validates Voyager's One-Shot Approach With Parkinson's Collaboration " - Scrip, 25 Feb, 2019.)*

Biomedtracker's database shows six PD drug candidates in Phase III, but five are various formulations of levodopa/carbidopa, including AbbVie's ABBV-951, a levodopa/carbidopa prodrug delivered via subcutaneous injection. *(Also see "AbbVie Spotlights Its Early-Stage R&D Pipeline" - Scrip, 1 May, 2019.)* Also in Phase III, Intec Pharma Ltd. is developing a gastric-retentive levodopa/carbidopa candidate in immediate-release and extended-release formulations, Amneal Pharmaceuticals LLC has an extended-release capsule, and two different subcutaneous versions of levodopa/carbidopa are being developed by Mitsubishi Tanabe Pharma Corp.

Pharma Two B Ltd. also is testing P2B001, which combines low-dose pramipexole and low-dose rasagiline, in Phase III.

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Tecentriq Takes EU Lead In Triple-Negative Breast Cancer

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Although its development may initially have trailed behind other checkpoint inhibitors, Roche's PD-L1 inhibitor, Tecentriq (atezolizumab), has now taken a large step forward by becoming part of the first combination immunotherapy regimen to gain an approval from the European Commission to treat triple-negative breast cancer, a condition poorly served by other therapies.

The approval for the additional indication is the first of three expected imminently for Tecentriq in the EU – the triple-negative breast cancer indication was recommended after the CHMP's June meeting, while the CHMP's July meeting recommended approval for Tecentriq plus chemotherapy as an initial (first-line) treatment for advanced non-squamous non-small cell lung cancer and, separately, as an initial treatment for extensive-stage small cell lung cancer.

There is a substantial unmet market for effective therapies for triple-negative breast cancer. The condition is defined by the lack of receptors for estrogen, progesterone and HER2 amplification, is more common in women aged under 50, and is characterized by rapid progression and shorter survival times than other breast cancer subtypes. Around 15% of all breast cancers are triple-negative.

The market opportunity in triple negative breast cancer is expected to undergo significant growth in the next five years, with the market in the US, Japan and the top-five EU countries

Roche is ahead of the field in triple-negative breast cancer

expected to reach $1bn by 2024, according to analysts at Datamonitor Healthcare. The growth will be led by checkpoint inhibitors such as Tecentriq, and products like AstraZeneca PLC's capivasertib and Imfinzi (durvalumab), both of which are in Phase III in the condition.

Roche announced on 29 August that the European Commission had approved Tecentriq in combination with Celgene's nanoparticle chemotherapy, Abraxane (paclitaxel albumin, or nab-paclitaxel), for adult patients with unresectable locally advanced or metastatic triple-negative breast cancer whose tumors have PD-L1 expression (≥1%) and who have not received prior chemotherapy for metastatic disease. A similar extension to Tecentriq's indications was approved by the US FDA in March.

On the same day, Roche also launched commercially a CE-marked companion diagnostic, the Ventana PD-L1 (SP142) Assay, in European countries where Tecentriq is approved for triple-negative breast cancer, in order to identify patients eligible for the immunotherapy. The assay is also already available in the US.

France's regulators have already recognized that there are few therapeutic options for patients with the condition, and recently issued temporary use authorizations (ATUs) for Tecentriq in triple-negative breast cancer and for Kadcyla (trastuzumab emtansine) in early HER2-positive breast cancer. *(Also see "Roche Wins Two French Early Access Programs In Breast Cancer " - Pink Sheet, 28 Aug, 2019.)*

EU INDICATION DETAILS

The approval of Tecentriq in triple-negative breast cancer was based on the results of the Phase III IMpassion130 study which showed Tecentriq plus nab-paclitaxel significantly reduced the risk of disease worsening or death (progression-free survival) by 38% compared with nab-paclitaxel alone (median PFS of 7.5 months versus 5 months; hazard ratio of 0.62, 95% CI: 0.49-0.78, p<0.0001) in people who were tested positive for PD-L1 expression on tumor-infiltrating immune cells.

At a second interim analysis there was a clinically meaningful improvement of seven months in overall survival versus placebo in the PD-L1 positive population, although due to the design of the study, survival was not formally tested in that population because statistical significance was not met for overall survival in the intent-to-treat population.

Roche is continuing to study Tecentriq in patients with triple negative breast cancer, and has seven ongoing Phase III studies in early and late stage disease. The Switzerland-headquartered big pharma has considerable expertise in the breast cancer sector through the development of Herceptin (trastuzumab), Perjeta (pertuzumab) and Kadcyla for early and advanced HER2-positive breast cancer, and is also developing an AKT targeted drug, ipatasertib (with partner, Array BioPharma Inc.), in triple negative breast cancer.

In a Phase Ib study reported in April 2019, a combination of Tecentriq, nab-paclitaxel and ipatasertib showed promising antitumor activity in patients with triple-negative breast cancer.

Other companies are also active in this area: topline results from the KEYNOTE-522 Phase III study reported at the end of July indicated that Merck & Co. Inc.'s Keytruda (pembrolizumab) plus chemotherapy met one co-primary endpoint.Also, the KEYNOTE-355 trial is evaluating Keytruda in first-line locally recurrent inoperable or metastatic triple-negative breast cancer – this study is due to complete this year. However the checkpoint inhibitor when used as a second- or third-line monotherapy missed its overall survival endpoint in top-line results from the Phase III KEYNOTE-119 study.

G1 Therapeutics Inc. has reported improved survival with trilaciclib in triple-negative breast cancer in Phase II results.

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Alexion's Soliris To Treat EU Patients With NMOSD

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European patients with neuromyelitis optica spectrum disorder (NMOSD) will now have an approved therapy for their condition, with Alexion Pharmaceuticals Inc. announcing on 27 August that the European Commission has extended the indications for Soliris (eculizumab) to include NMOSD; Soliris becomes the disease's first and only approved medication in the EU.

It's the second EU approval for an Alexion drug in the past two months – the company's longer-acting C5 complement inhibitor, Ultomiris (ravulizumab), was approved for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) in July.

In Europe, Soliris's indications now include the treatment of NMOSD in adult patients who are anti-aquaporin-4 (AQP4) antibody-positive with a relapsing course of the disease, adding to its previously granted indications in paroxysmal nocturnal hemoglobinuria, atypical uremic syndrome, and generalized myasthenia gravis in patients who are anti-acetylcholine receptor antibody positive.

An NMOSD indication was approved for Soliris in the US in June 2019, and a supplemental NDA is under review in Japan, and Alexion looks set to dominate this particular therapeutic sector for a while, in a global market estimated by analysts to peak at around $500m per year.

There are around 4,000 to 5,000 patients with NMOSD in the US, and likely a similar number in the EU, and Alexion chief commercial officer Brian Goff noted that patients live in a "world of fear" given the unknowns and devastating impact of NMOSD attacks.

Each NMOSD attack results in a stepwise accumulation of irreversible disability, including blindness, paralysis and sometimes premature death. The condition disproportionately affects young women, with the average age of first onset of 39 years. NMOSD is often confused with multiple sclerosis. The results of the PREVENT study showed that Soliris prolonged the time to relapse and reduced the risk of relapse.

The indication is important to Alexion. "With the launch of NMOSD and growing contribution from generalized

myasthenia gravis (gMG), we expect neurology to be our biggest franchise by patient volume in the US by year end," said Alexion's CEO Ludwig Hantsen during the company's second-quarter earnings call. In the second-quarter, Soliris revenues were $981m, up by 17% on the previous year, while Ultomiris revenues were $54m.

That said, there are current and future competing products likely in the NMOSD market. Rituximab and its generics are used off-label in NMOSD, eculizumab biosimilars are in development at other companies, and other potential therapies to treat NMOSD are racing to get to the market.

Such potential competitors include Alexion's own product Ultomiris, which is expected to enter a Phase III study in NMOSD later this year, according to R&D head John Orloff. Ultomiris maintenance therapy is administered every eight weeks compared with every two weeks with Soliris, and Alexion is hoping that it can persuade patients and doctors to switch to Ultomiris therapy.

Such a switch would make current concerns around patent protection and biosimilar competition less relevant to Alexion's strategy – analysts at Morgan Stanley note that an oral hearing on 5 September at the European Patent Office will decide whether new patents on Soliris can be issued, extending its protection from 2021 to 2027. And on 6 September, a US patent appeal board is expected to decide whether US patent protection already extended to 2027 should be reviewed. Alexion executives expect biosimilar competitors to become available in around three years from now.

INEBILIZUMAB FILED IN US

Other companies are also developing drugs for NMOD, including Gaithersburg, MD-based Viela Bio Inc., which announced on 27 August that the US Food and Drug Administration had accepted the company's BLA for an anti-CD19 monoclonal antibody, inebilizumab, for the treatment of NMOSD.

In the pivotal N-MOmentum trial in 231 patients with and without the AQP4-IgG antibody, inebilizumab met its primary and a majority of the secondary endpoints, Viela Bio reported. Inebilizumab reduced the risk of developing an NMOSD attack by 77% when compared with placebo in AQP4-IgG seropositive patients after 28 weeks of treatment.

Roche/Chugai Pharmaceutical Co. Ltd. are developing the anti-IL-6 monoclonal antibody, satralizumab, for NMOSD, and the companies have asked the EU regulatory authorities to fast track the marketing application when it is made, which would reduce its evaluation time from 210 days to 150 days.

EXTENDED INDICATION FOR BMS'S EMPLICITI

Separately, Bristol-Myers Squibb Co. announced on 27 August that the European Commission had approved Empliciti (elotuzumab) plus pomalidomide and low-dose dexamethasone (EPd) for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies, including lenalidomide and a proteasome inhibitor (PI), and have demonstrated disease progression on the last therapy.

This is the second EU approved indication for an Empliciti-based triplet combination therapy in relapsed and refractory multiple myeloma. The drug is already approved in the EU for use in combination with lenalidomide and dexamethasone for the treatment of multiple myeloma in adult patients who have received at least one prior therapy. Elotozumab has been jointly developed by BMS and AbbVie Inc., with BMS being solely responsible for commercialization

The new indication is based on data from the ELOQUENT-3 trial, in which the elotuzumab-containing triplet combination doubled both median progression-free survival (PFS) and overall response rate (ORR) among patients with relapsed and refractory multiple myeloma, compared with patients treated only with pomalidomide and low-dose dexamethasone.

The US FDA approved EPd for the treatment of adult patients with multiple myeloma who have received at least two prior therapies, including lenalidomide and a proteasome inhibitor, in November 2018. It was initially approved in the US in November 2015.

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AbbVie Puts Final Nail In Rova-T's Coffin After Another Trial Failure

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The end of all research and development for rovalpituzumab tesirine (Rova-T) was pretty much a foregone conclusion after AbbVie Inc. said in January that it wrote off $4bn of the $5.8bn acquisition of Stemcentrx Inc. that brought the antibody-drug conjugate (ADC) to the company – but now it's official.

AbbVie announced on 29 August that it discontinued the entire Rova-T R&D program after an independent data monitoring committee (IDMC) recommended terminating the Phase III MERU clinical trial testing the ADC as first-line maintenance therapy for advanced small-cell lung cancer (SCLC). The IDMC determined in a preplanned interim analysis that Rova-T, which targets the cancer stem cell-associated delta-like protein 3 (DLL3), provided no survival benefit compared with placebo.

The company noted that Rova-T's overall safety in MERU was generally consistent with prior studies and said results from the trial will be presented at a future medical meeting and/or published in a peer-reviewed medical journal.

AbbVie took a $4bn impairment charge in January to write off assets from the Stemcentryx purchase. The financial equivalent of admitting defeat was announced after the company said in December that it halted the Phase III TAHOE trial for Rova-T in second-line SCLC.

The TAHOE results followed data revealed earlier in 2018 from the Phase II TRINITY study in third-line SCLC that showed no benefit for patients treated with Rova-T. *(Also see "Weak Rova-T Data May Imperil AbbVie's Larger Cancer Ambitions" - Scrip, 22 Mar, 2018.)* Those studies compounded earlier concerns that AbbVie paid too much for Stemcentrx back in April 2016 as it sought to aggressively expand its oncology portfolio ahead of the loss of patent exclusivity for its blockbuster anti-inflammatory biologic Humira (adalimumab).

With the Rova-T program behind it, AbbVie said it will prioritize other oncology R&D programs within its portfolio of investigational and marketed drugs. The company has more than 300 clinical trials under way in more than 20 different tumor types.

Imbruvica (ibrutinib) and Venclexta (venetoclax) for various hematological malignancies continue to be AbbVie's keystone cancer drugs, along with Empliciti (elotuzumab) for multiple myeloma, but the company has several therapeutic candidates in the clinic for multiple solid and liquid tumors.

AbbVie announced in July that a partial clinical hold was lifted for the Phase III CANOVA trial testing Venclexta in relapsed or refractory multiple myeloma patients with a translocation (11;14) abnormality, but other studies of the drug in myeloma remain on hold. *(Also see "Cautious Restart To Venetoclax's CANOVA Trial In Multiple Myeloma" - Scrip, 25 Jun, 2019.)*

The company also said when it announced second quarter earnings on 26 July that it has discontinued development of the epidermal growth factor receptor (EGFR)-targeting ADC depatuxizumab mafodotin (Depatux-M) after it showed no overall survival benefit for newly diagnosed glioblastoma patients in an interim analysis of the Phase III INTELLANCE-1 study.

Going forward, AbbVie will continue to prioritize oncology and immunology even as it incorporates the marketed products and R&D programs from Allergan PLC into its portfolio.

AbbVie announced its plan to purchase Allergan for $63bn in June and said it will use revenue from the Allergan's blockbuster wrinkle-reducer and migraine prophylactic Botox (onabotulinumtoxinA) to help fund its ongoing R&D and business development activities.

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AbbVie Oncology Pipeline: Key Highlights

DRUG, TARGET	PHASE	INDICATION(S)
Imbruvica, Bruton's tyrosine kinase (BTK)	Phase III	First-line follicular lymphoma (FL), relapsed or refractory (R/R) FL or marginal zone lymphoma (MZL), and first-line mantle cell lymphoma (MCL)
Venclexta, B-cell lymphoma 2 (BCL2)	Phase III	Multiple myeloma (MM) and MCL
	Phase II	Myelodysplastic syndrome (MDS)
	Phase I	Acute lymphoblastic leukemia (ALL)
Empliciti, signaling lymphocyte activation molecule (SLAMF7)	Phase III	First-line MM
Veliparib, poly ADP ribose polymerase (PARP)	Phase III	Non-small cell lung cancer (NSCLC), BRCA-mutated breast cancer and ovarian cancer
Navitoclax, BCL2	Phase II	Myelofibrosis
Telisotuzumab vedotin, c-Met	Phase II	Solid tumors
ABT-165, vascular endothelial growth factor (VEGF) and delta-like 4 (DLL4)	Phase II	Solid tumors

Lilly's Latest Olumiant Data Raise Question Of JAK Inhibitor Role In Atopic Dermatitis

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Eli Lilly & Co. reported positive results for its JAK1/2 inhibitor Olumiant (baricitinib) in combination with topical corticosteroids in the third of five Phase III clinical trials in atopic dermatitis (AD) with data readouts this year. However, a pulmonary embolism experienced by a patient treated with the drug in the ex-US trial raises questions about whether JAK inhibitors are viable treatments for AD given safety concerns.

JAK inhibitors, including Olumiant, already are under scrutiny because of pulmonary emboli observed in studies of rheumatoid arthritis (RA) – the first approved indication for the Lilly product. But while the company said when it reported results for Olumiant in AD from the Phase III BREEZE-AD1 and BREEZE-AD2 studies in February that there were no thromboembolic events or major cardiovascular adverse events (MACE), that was not the case in the BREEZE-AD7 data announced late on 23 August.

SVB Leerink analyst Geoffrey Porges said in a same-day note for Regeneron Pharmaceuticals Inc. investors in response to Lilly's Phase III BREEZE-AD7 results that ongoing safety concerns for JAK inhibitors mean that the drug class should not pose a threat to AD sales for Regeneron/Sanofi's blockbuster interleukin-4 (IL-4)/IL-13 inhibitor Dupixent (dupilumab).

"We believe that we now know enough about the current generation of JAK inhibitors to more or less dismiss them as threats to [Dupixent] in benign dermatological and atopic indications," Porges said. "In these diseases, there is no reason, or real inclination, for physicians and patients to take the risk of a JAK inhibitor, even when they offer the convenience of daily oral formulation. In our view, Regeneron's Dupixent will continue to dominate the AD market with its superior risk-benefit profile."

HIGHER OLUMIANT DOSE MOST EFFECTIVE IN BREEZE-AD7

The highest dose of Olumiant tested in BREEZE-AD7 was the most effective dose in the study, in which the primary endpoint was the proportion of patients who achieved an improvement in disease severity at 16 weeks, defined as a validated Investigator's Global Assessment for AD (vIGA) score of clear or almost clear skin.

Secondary endpoints included the proportions of patients who achieved a 75% reduction in AD appearance and symptoms Eczema Area and Severity Index (EASI75) and a four-point improvement in the Numerical Rating Scale (NRS) for itching, both at week 16.

Lilly did not get into specifics about the adverse events (AEs) observed in the trial, but said safety data were consistent with Olumiant's known profile with nasopharyngitis, upper respiratory tract infection and folliculitis as the most common treatment-emergent AEs. There were no malignancies, MACE or deaths in BREEZE-AD7, but there was one pulmonary embolism among Olumiant-treated patients and one opportunistic infection in the placebo group.

Patients Achieving Primary and Secondary Endpoints At 16 Weeks

	Placebo (n=109)	Olumiant 2mg (n=109)	Olumiant 4mg (n=111)
vIGA	16 (14.7%)	26 (23.9%)	34 (30.6%; p≤0.01)
EASI75	25 (22.9%)	47 (43.1%; p≤0.01)	53 (47.7%; p≤0.001)
NRS	21 (20.2%)	37 (38.1%; p≤0.01)	44 (44%; p≤0.001)

Source: Eli Lilly & Co.

The BREEZE-AD7 study – conducted in Asia, Europe, South America and Australia – is one of five Phase III clinical trials for Olumiant in AD. More detailed results from this study will be shared at scientific meetings and in peer-reviewed journals later this year. Top-line data from the final two studies of the drug in this indication are expected in late 2019 or early 2020.

LESS EFFECTIVE THAN DUPIXENT, WITH TROUBLING SAFETY

Biomedtracker's analysis of the BREEZE-AD7 results noted that Olumiant added to topical corticosteroids did not perform as well as Dupixent as an add-on therapy.

"The IGA response of 31% does not quite match the 39% response seen in dupilumab's add-on CHRONOS study. Additionally, the EASI75 responses of 38% and 44% on low and high doses do not match dupilumab's 64% and 69% responses," Biomedtracker noted. "Importantly, the low 2mg baricitinib dose did not reach statistical significance, while the high dose has historically been plagued with safety concerns that have limited its rheumatoid arthritis approval in the US to a maximum 2mg daily dose."

Olumiant was approved for RA in June 2018, but only the lower 2mg daily dose was cleared for marketing and not the 4mg dose, because of thrombosis concerns. *(Also see "Lilly Prices Olumiant For JAK Battle, But Misses Approval For Higher Dose" - Scrip, 2 Jun, 2018.)*

However, Biomedtracker's analysis notes, "Lilly's history of competitively pricing baricitinib in rheumatoid arthritis may improve the outlook for this product, if approved in atopic dermatitis. Although the lower dose did not demonstrate statistical significance on IGA in this ex-US add-on study, that may not necessarily preclude a European label expansion where the drug is available at the higher 4mg dose."

JAK SAFETY IN AD WILL BE INFORMED BY RA EXPERIENCE

The label for Xeljanz (tofacitinib) – Pfizer Inc.'s first-to-market JAK inhibitor for inflammatory conditions – includes warnings about serious infections and malignancies, but labels for Olumiant and AbbVie Inc.'s newly approved JAK1 inhibitor Rinvoq (upadacitinib)

in RA caution prescribers about thrombosis risks in addition to malignancies and infections. *(Also see "AbbVie's Post-Humira Strategy Continues Taking Shape With Rinvoq Approval" - Scrip, 16 Aug, 2019.)*

Pfizer's disclosures about a post-marketing study for Xeljanz in February added to concerns that all JAK inhibitors carry a thrombosis risk. The occurrence of pulmonary embolism and mortality rates were higher among RA patients who took 10 mg of Xeljanz two times daily – twice the approved dose – than in individuals treated with 5mg twice daily or a TNF inhibitor.

Lilly's Olumiant partner Incyte Corp. may have a way around safety concerns for systemic JAK inhibitors in atopic dermatitis with a topical version of its blockbuster oral JAK1/2 inhibitor Jakafi (ruxolitinib), which is approved for myelofibrosis, polycythemia vera and graft-versus-host disease. The topical formulation is in Phase III for AD with data expected in early 2020. After Phase II success in vitiligo, Incyte also is moving the topical therapy into Phase III for that indication. *(Also see "Forging Ahead In Vitiligo: Incyte's Ruxolitinib Cream Scores Phase II Win" - Scrip, 17 Jun, 2019.)*

Lilly and Incyte announced in their first quarter earnings reports at the end of April that Incyte has opted out of its research and development funding obligations for Olumiant and will now receive lower royalties from the Lilly-marketed drug, to focus its financial resources on its own R&D programs, which would include topical ruxolitinib. *(Also see "Lilly Says Volume Growth Strategy, Launches Working Despite Price Pressures" - Scrip, 30 Apr, 2019.)*

Published online 27 August 2019

AstraZeneca's COPD Triple Combo Drug Succeeds in ETHOS Phase III, Setting Up GSK Showdown

The Phase III ETHOS study of AstraZeneca PLC's triple-combination chronic obstructive pulmonary disease (COPD) therapy Breztri Aerosphere has met its primary endpoint, adding to the evidence for the product in this disease.

The therapy, formerly known as PT010, contains three active ingredients: the inhaled corticosteroid (ICS) budesonide; the long-acting muscarinic antagonist (LAMA) glycopyrronium; and the long-acting beta2-agonist (LABA) formoterol fumarate.

Authorities including Cochrane have found dual LABA-LAMA treatments, such as GlaxoSmithKline PLC's Anoro Ellipta and Novartis AG's Ultibro Breezhaler, are often the most effective of the well-established long-acting inhalers. However, there is also a group of COPD products that combine a LABA with an ICS. That group includes GSK's Seretide.

AstraZeneca is one of a number of companies to explore combining all three types of COPD drug in a single inhaler. GSK and Chiesi Farmaceutici SPA are at the front of the pack, having already won approvals for triple-combinations called Trelegy Ellipta and Trimbow, respectively, but AstraZeneca is close behind.

The push to establish Breztri Aerosphere as a rival to Trelegy Ellipta and Trimbow in Western markets took a step forward today with the positive ETHOS data. AstraZeneca is yet to share full data from the 8,500-patient trial but the top-line finding is that Breztri Aerosphere is better than dual LABA-LAMA and LABA-ICS combinations at reducing the rate of moderate-to-severe exacerbations.

In ETHOS, AstraZeneca limited enrollment in the study to people who had suffered one or more exacerbations over the previous 12 months. Success in that population follows positive data from another Phase III trial, KRONOS, that enrolled patients regardless of whether they had suffered an exacerbation over the previous year. In that broader population, use of Breztri Aerosphere was associated with a 52% reduction in the rate of moderate to severe COPD exacerbations.

The results from KRONOS are now under review at the US Food and Drug Administration and its European counterpart, putting AstraZeneca on track to win approvals in both territories next year. AstraZeneca won approval of Breztri Aerosphere in Japan in June and is on track to secure clearance to sell the product in China, where it has been granted a priority review, by the end of the year.

While that means Breztri Aerosphere could soon be available in two major markets, AstraZeneca only expects sales to start properly ramping up after it is approved in the US and Europe.

"It's probably more for 2021 and beyond in term of cash flow generation," AstraZeneca CEO Pascal Soriot said on a conference call with investors in April.

AstraZeneca will need to pay out before starting to generate significant sales. The terms of the 2013 takeover of Pearl Therapeutics that added the COPD triple combination to AstraZeneca's pipeline call for the payment of a $150m milestone upon US regulatory approval. That is the final development or regulator milestone mandated in the terms of the agreement.

If Breztri Aerosphere makes it to the US and European markets, AstraZeneca will face the challenge of how to win market share from existing triple-combination therapies. GSK won US and EU approval for Trelegy Ellipta in the second half of 2017, giving it more than a two-year headstart on Breztri Aerosphere.

Sales of Trelegy Ellipta totalled £207m ($253m) over the first six months of the year and are rising quickly. In 2018, Trelegy Ellipta sales were £156m for the full year. The upward trajectory is partly a consequence of GSK's success in expanding the US label of the drug. GSK recently filed another FDA supplemental NDA based on evidence that Trelegy reduces all-cause mortality compared to an older Ellipta product, Anoro, setting it up to cement its first-mover advantage.

In trying to make up lost time, AstraZeneca may be able to argue its product is more efficacious. The 52% reduction in exacerbations seen in the Breztri Aerosphere trial far exceeds the 25% achieved by Trelegy Ellipta during its development. However, the use of different comparator drugs in the studies, plus the usual caveats about the unreliability of cross-trial comparisons, means the data may not be true reflection of the efficacy of the therapies.

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New Life For AstraZeneca's SLE Treatment As Second Study Succeeds

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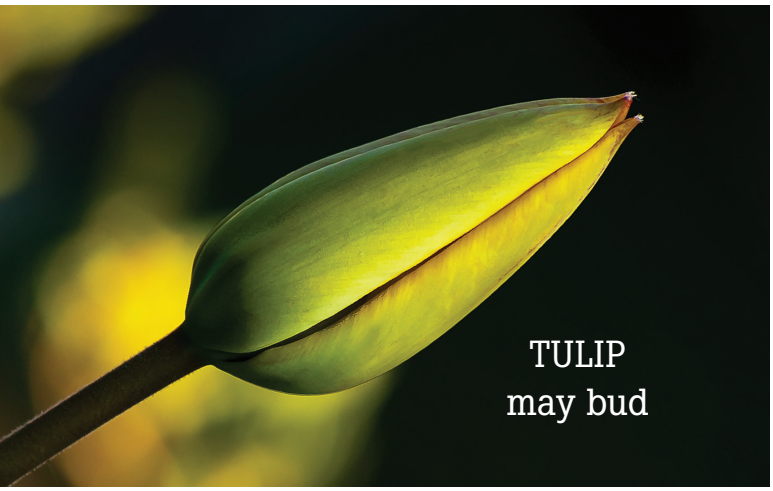

New life has been breathed into AstraZeneca PLC's potential treatment for systemic lupus erythematosus (SLE), anifrolumab, after a different primary endpoint was used in its second Phase III trial, TULIP 2. The program had looked in trouble after the first study, TULIP 1, which tested a different primary endpoint, failed a year ago.

Topline TULIP 2 data show the investigational product achieved a statistically significant and clinically meaningful reduction in disease activity versus placebo, when given on top of standard of care, as measured by the British Isles Lupus Assessment Group based Composite Lupus Assessment (BICLA) at week 52. AstraZeneca noted that the BICLA requires improvement in all organs with disease activity at baseline with no new flares.

No new safety signals were seen in the TULIP 2 study in which 373 patients with moderately-to-severely active autoantibody-positive SLE were randomized (1:1) to receive a fixed-dose intravenous infusion of 300mg anifrolumab or placebo every four weeks.

Whether the results will be enough to totally revive the product remains to be seen. Mene Pangalos, AstraZeneca's executive vice president of biopharmaceuticals R&D, said that the firm would now "review the full data set and explore pathways to bring this potential new treatment to patients."

Last August, results from the 460-patient TULIP 1 study showed that anifrolumab missed its primary endpoint using the SLE Responder Index 4 (SRI4), but anifrolumab had more success on a pre-specified analysis of the BICLA scale in the earlier study.

AstraZeneca said the BICLA was chosen as the primary endpoint for TULIP 2 "following a full evaluation of TULIP 1 and is an established measurement for disease activity in adults with SLE." Data from both trials will be submitted for presentation at a forthcoming medical meeting, it added.

The Phase III TULIP program was based on promising Phase II data which also looked at SRI4 and presented at the American College of Rheumatology meeting in 2015 and while its uncertain why this was not replicated in TULIP 1, the new data provides new hope for anifrolumab, analysts say. *(Also see "Real Hope For Lupus As AZ's Anifrolumab Impresses In Phase II" - Scrip, 10 Nov, 2015.)*

Datamonitor Healthcare analyst Karolina Kujawa told *Scrip* it would be interesting to see what regulators make of the combined data given the limited data available which make it hard to draw any conclusions on the contrasting results as yet.

The use of the BICLA score, instead of the previously used SLE Responder Index 4, "shows just how important the choice of the right primary endpoint is when it comes to lupus. SLE is notorious for failed clinical trials, with many failures attributed to inadequate or incorrect trial design. With so many drugs previously failing Phase III trials, the achievement of statistical significance for a primary endpoint is great news."

In SLE, the immune system attacks healthy tissue in the body causing chronic symptoms affecting many organs including pain, rashes, fatigue, swelling in joints and fevers. It is associated with a greater risk of death from causes such as infection and cardiovascular disease. This wide variation in symptoms makes developing effective treatments tricky.

The only drug to be licensed for SLE is GlaxoSmithKline PLC's Benlysta (belimumab), but its performance has been hindered by modest efficacy. In the second quarter, sales of Benlysta in the quarter were up by 25% at constant exchange rates to £150m, including sales of the subcutaneous formulation. In the US, Benlysta grew by 24% CER to £132m.

Anifrolumab is a fully human monoclonal antibody that binds to subunit 1 of the type I interferon receptor, blocking the activity of all type I interferons including IFN-alpha, IFN-beta and IFN-omega. Type I interferons are involved in the inflammatory pathways, and 60%-80% of adult lupus patients have an increased type I interferon gene signature, which has been shown to correlate with disease activity.

The TULIP 2 principal investigator Eric Morand of Monash University, Australia, said: "As clinicians we need new medicines for this complex and difficult-to-treat disease. These exciting results from the TULIP 2 trial demonstrate that, by targeting the type I interferon receptor, anifrolumab reduced disease activity in patients with systemic lupus erythematosus."

Other failed investigational lupus products like AstraZeneca's sifalimumab and Genentech Inc.'s rontalizumab targeted interferon alfa itself, not the receptor. AstraZeneca discontinued sifalimumab in favor of anifrolumab.

Anifrolumab lies outside AstraZeneca's core therapy areas but has been seen by the company as a promising candidate in an underserved area.

Previous sales estimates had the product pitched as a potential blockbuster with peak sales in SLE at $1.5bn.

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InDex's Lead TLR9 Agonist Shows Promise In Ulcerative Colitis

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A potential first-in-class Toll-like receptor 9 (TLR9) agonist, InDex Pharmaceuticals AB's cobitolimod, has met its primary clinical remission endpoint in top-line results from a Phase IIb study, CONDUCT, in patients with active moderate to severe ulcerative colitis, giving a boost to the small Swedish company's share price and promising a potential option for patients who do not respond to other therapies.

Cobitolimod could also be of particular interest for use in combination with other agents, according to InDex's CEO, Peter Zerhouni, speaking at an analysts' briefing on the results on 27 August. Big pharma companies are increasingly looking to combination therapies to really make an impact in this disease and combining their systemic therapies with a topical (enema) compound like cobitolimod is attractive, Zerhouni added.

Cobitolimod is an oligonucleotide which previously attracted Almirall SA as a development partner, but the Spain-headquartered company returned the European rights after fine-tuning its business strategy to focus on dermatology products in 2015.

Since then, InDex has been evaluating cobitolimod in early-stage clinical studies and has become a publicly traded company through an IPO on the junior market, Nasdaq First North Stockholm, in October 2016, with cobitolimod, also known as Kappaproct or DIMS0150, as its lead product. The TLR9 agonist is thought to modify the mucosal immune system in the gastrointestinal tract and has s a local anti-inflammatory effect on the colonic mucosa.

Zerhouni said InDex was moving towards Phase III studies, and would be evaluating company-financing alternatives, the best route to commercialization for cobitolimod, and where the molecule might fit in the treatment paradigm for ulcerative colitis in the future. At some point, the company will talk to potential partners.

LEFT-SIDED ULCERATIVE COLITIS

The company's share price rose by 36% to reach SEK11.5 early on 27 August before settling back to SEK10.0 per share, on the day top-line results from the CONDUCT study were announced. The study involved 213 patients with left-sided moderate to severe ulcerative colitis non-responsive to other therapies.

The dose-ranging Phase IIb study found that the efficacy of the highest dose of cobitolimod, 250mg given by enema on weeks 0 and 3, in terms of clinical remission was 15 percentage points higher (21.4% versus 6.8% remission rate) than the efficacy of placebo ($p = 0.0495$, OR = 3.8). Clinical remission was defined by the Mayo score at week six.

The proportion of patients in clinical remission at week six in the other arms of the study were as follows: 9.5% with 125mg doses at week 0, 1, 2 and 3; 4.7% for 125mg doses at week 0 and 3; 12.5% for 30mg doses at week 0 and 3; and 6.8% for patients treated with placebo. All doses of cobitolimod were well tolerated, with a safety profile similar to placebo, the company noted.

Disease specialist Walter Reinisch, a professor at the Medical University Vienna, Austria and the study's principal investigator Raja Atreya, professor at the University of Erlangen-Nürnberg, Germany, highlighted the finding of clinically meaningful responses to therapy after six weeks as important. Such responses are a signal that patients undergoing an active flare-up of their disease are likely to continue their responses to cobitolimod over the long-term during maintenance therapy. There is room to increase the dose further which might increase the clinical response rate, company executives noted.

Cobitolimod appears to be the leading TLR9 agonist being evaluated for ulcerative colitis, although the mechanism is being evaluated by other companies in different indications; Mologen AG recently reported that its candidate TLR9 agonist, lefitolimod, missed its primary endpoint as a monotherapy in colorectal cancer patients, and the company expects to conduct combination studies in cancer.

Checkmate Pharmaceuticals Inc. has a TLR9 agonist, CMP001, in Phase I for advanced melanoma and non-small cell lung cancer.

Biological drugs represent the largest market segment in ulcerative colitis in terms of value, noted InDex, with annual sales estimated to more than $5bn.

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Novartis's Ofatumumab Pursues Entrenched Competitors In MS

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Novartis AG's next-generation multiple sclerosis candidate, a subcutaneous ofatumumab injection, has met primary endpoints in two Phase III studies, ASCLEPIOS I and II, when compared with Sanofi's Aubagio (teriflunomide). The CD20-targeted monoclonal antibody could give a boost to the big pharma's waning MS franchise as a patient-convenient therapy that can be self-administered once monthly at home.

The company expects to submit ofatumumab for use in multiple sclerosis to regulatory authorities by the end of 2019;

ofatumumab is licensed from Genmab AS and was previously developed and marketed in a different formulation, as an intravenous infusion, Arzerra, in cancer indications, but struggled to gain traction; it was withdrawn from non-US markets in January 2018.

Roche's recently launched MS therapy, Ocrevus (ocrelizumab) is also an anti-CD20 monoclonal antibody and is making significant inroads in the MS sector, with sales of CHF1.7 bn ($1.72bn), up by 63%, in the first half of 2019. Another potential competitor to ofatumumab could be TG Therapeutics Inc.'s anti-CD20 antibody, ublituximab, which is in Phase III clinical studies in multiple sclerosis.

However, analysts say that more clinical details are needed from the ASCLEPIOS studies in order to assess the market opportunity for ofatumumab; intravenous infusions of Ocrevus every six months may be as convenient as once-monthly subcutaneous injections of ofatumumab to some patients.

That said, 2025 sales of ofatumumab could reach $1.6bn, say analysts at Deutsche Bank Research, who anticipate discussions at the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) meeting in Stockholm, Sweden, on 11-13 September about how the ofatumumab data compares with that from clinical studies involving Ocrevus. They also believe Roche is looking at shortened infusion times for Ocrevus, and is developing a subcutaneous formulation.

More clinical details are needed from the ASCLEPIOS studies in order to assess the market opportunity for ofatumumab.

ANNUALIZED RELAPSE RATES

In ASCELPIOS I and II, ofatumumab significantly reduced the annualized relapse rate when compared head-to-head with teriflunomide, and also met the key secondary endpoint of delaying the time to confirmed disability progression, Novartis announced on 30 August. Further top-line data will be presented at ECTRIMS, the company added.

The difference between the two drugs on the primary endpoints was highly significant and clinically meaningful, and the safety profile was in line with observations from Phase II results, the company said, without going into details.

The last point is important because patients on a number of other MS therapies have to be monitored for potential side effects and require doctors' visits. If a relatively benign safety profile is confirmed in further data releases and combined with its potential for self-administration at home, it could be positioned as a convenient therapy for first-line use in a broad swathe of the MS population.

"The results are wonderful news for patients who would like to take an effective B-cell therapy with low requirement for monitoring, avoiding visits to an infusion center," commented Stephen Hauser, professor and director at the UCSF Weill Institute for Neurosciences.

ASCELPIOS I and II were two Phase III studies which enrolled 1,882 patients in total with relapsing multiple sclerosis and compared the safety and efficacy of ofatumumab 20mg monthly subcutaneous injections with Aubagio 14mg oral tablets taken once daily, for up to 30 months. Patients had expanded disability status scale (EDSS) scores between zero and 5.5, and were treated at 350 sites in 37 countries.

Novartis has a leading position in MS through the S1P modulator, Gilenya (fingolimod), which has been a top-selling blockbuster drug for the company, although sales have been in decline due to increased competition in the MS sector; generic versions are also nearing the market. Gilenya sales dipped by 2% in the second quarter to $825m.

However, Novartis has been developing several next-generation products, including Mayzent (siponimod), which was approved for marketing in the US this March for the treatment of relapsing forms of MS to include clinically isolated syndrome (CIS), relapsing-remitting disease and active secondary progressive diseases.

Marketing submissions have been made in other countries for Mayzent, which is the first and only treatment specifically approved for patients with active secondary progressive MS for more than 15 years. The generics subsidiary, Sandoz International GMBH, also markets Glatopa, a generic version of Teva Pharmaceutical Industries Ltd.'s MS therapy, glatiramer acetate.

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Scotland's MGB Bags More Funds To Tackle Antibiotic Resistance

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Antibiotics resistance specialist MGB Biopharma Ltd. has completed its latest funding round which will enable the Scottish firm to progress an ongoing Phase IIa clinical trial with its lead antibiotic MGB-BP-3**,** a completely new class of anti-infective medicine designed to tackle *Clostridium difficile*-associated disease.

MGB said that the over-subscribed fund raise was supported by new and existing backers, led by Archangel Investors and including the Scottish Investment Bank (the investment arm of national development agency Scottish Enterprise), Glasgow-based venture capital company Barwell and TriCapital, a group of 40-50 angel investors most of whom are based in the south

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

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

PIPELINE WATCH, 23–29 AUGUST 2019

Event Stage	Lead Company/Partner	Drug Name	Indication	Comments
Phase III Suspension	AbbVie	Rova-T (rovalpituzumab tesirine)	Small Cell Lung Cancer	MERU; Development Ended
Phase II/III Updated Results	BeyondSpring Pharmaceuticals	plinabulin	Neutropenia Prevention	Protective-1; Improves Quality Of Life
Phase III Top-Line Results	AstraZeneca	Breztri Aerosphere (budesonide/formoterol/glycopyrronium)	COPD	ETHOS; Met Primary Endpoint
Phase III Top-Line Results	Eli Lilly/Incyte	Olumiant (baricitinib)	Atopic Dermatitis	BREEZE-AD7; Met Primary Endpoint
Phase III Top-Line Results	The Medicines Company/Alnylam	inclisiran, SC, Twice-Yearly	Atherosclerosis	ORION-11; Met All Endpoints
Phase III Top-Line Results	AstraZeneca	anifrolumab	Systemic Lupus Erythematosus	TULIP SLE 2 (IV); Positive Data
Phase III Trial Initiation	Mitsubishi Tanabe Pharma Corp.	ND0612L (continuous levodopa/carbidopa)	Parkinson's Disease	BouNDless; A Liquid SC Formulation
Phase II/III Trial Announcement	Zosano Pharma Corp	Qtrypta (zolmitriptan) microneedles	Migraine, Cluster	For Acute Therapy
Phase II/III Trial Announcement	Merck KGaA/GlaxoSmithKline	M7824 (bintrafusp alfa)	Biliary Tract Cancer	As First-Line Therapy

Source: Biomedtracker | Informa, 2019

CONTINUED FROM PAGE 21

of Scotland and north of England. The company is being coy as to how much has been raised and in an interview with *Scrip*, MGB chief business officer Chris Wardhaugh said that "we decided not to disclose the figure and we have our reasons for that," but the cash would finance operations "through to the end of 2020 comfortably."

He added that investors had been very supportive of MGB, telling the firm "to carry on doing what you're doing" with MGB-BP-3 and focus on the trial that is evaluating the oral antibiotic, which is based on minor groove binder technology. The Phase IIa study is assessing incremental doses of MGB-BP-3 in patients with *C diff*, with the cure rate assessed after completion of 10-day therapy and at follow-up of up to eight weeks.

Wardhaugh noted that recruitment of patients at sites in Canada and the US was progressing well and headline results are anticipated in the fourth quarter of this year. "There's been nothing new for *C diff* in years," he pointed out, adding that MGB-BP-3 "would be a totally new class, a totally new mode of action, and what we're aiming for is quite exciting: superiority over current agents as well as superiority to other drugs that are currently in development. We hope to bring something to market that is genuinely differentiated."

MGB-BP-3 is different in that rather than just stopping bugs growing, it is, to date, the only antibiotic to have shown in earlier-stage testing that it actually kills the bugs, Wardhaugh said, eradicating *C diff* within the first few hours of exposure and helping to prevent the bacteria evading therapy via sporulation. The company noted that MGB-BP-3 had very strong bactericidal activity against the BI/NAP1/027 strain, the most virulent strain of *C diff* which is largely resistant to current therapy.

The need for more treatments for *C diff*, which causes infection of the large intestine and is the most frequent cause of diarrhea in hospitals and care homes, is clear. In the US alone, there are almost half a million cases every year leading to around 30,000 deaths per annum.

As to how far MGB, which was spun out of the University of Strathclyde in 2010, can take the antibiotic, Wardhaugh said the firm was looking at all possibilities. "We just need to see how the trial performs and because it's open label, we will have a very good idea of what's happening as the study is going on. Frankly, when we see the results of that, then a decision will need to be taken by the management team about more investment, partnering or a blend of the two. We are genuinely keeping our options open."

Wardhaugh, who joined MGB in February this year and has over 25 years of experience in the industry including senior roles at Quintiles Transnational Holdings Inc., ProStrakan Group PLC and Clyde Biosciences, spoke glowingly about Scotland's vibrant life sciences community. "One thing that we've got up here, which is huge for us and just about every other company that I've worked with in Scotland, is that we have the support of the Scottish government and the Scottish Investment Bank, and they're very supportive institutions. They can help leverage investment from elsewhere, whether it's angel investment or VC."

He went on to say that "you are always one step away at most from a person who is going to make a decision and that's really helpful." Wardhaugh added, "I'm evangelical about the Scottish life sciences sector because there's so much coming out of our universities, there's a lot of innovation and the core quality of the science here is outstanding."

Published online 2 September 2019

APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
Anthony Yanni	Astellas Pharma US Inc	Senior Vice President, Patient Centricity	Sanofi Medical	Global Head, Patient Insights, Solutions and Outcomes	27-Aug-19
Phil Tennant	Astellas Pharma US Inc	Brand General Manager, New Oncology Products	Bristol-Myers Squibb	Head, Hematology Marketing, US Oncology	27-Aug-19
Jonathan Emms	Circassia Pharmaceuticals plc	Chief Operating Officer and Executive Director	Pfizer	Chief Commercial Officer	12-Aug-19
Priya Chaturvedi	Eisai Inc	Vice President, Global Clinical Quality Assurance	Merck Research Labs	Executive Director, Clinical Quality Assurance, and Head, Global GCP, Infectious Disease and Vaccines	26-Aug-19
Dana Hilt	Frequency Therapeutics	Chief Medical Officer	Lysosomal Therapeutics	Chief Medical Officer	22-Aug-19
Helen Giza	Fresenius Medical Care AG & Co KGaA	Chief Financial Officer	Takeda Pharmaceuticals	Chief Integration and Divestiture Management Officer	1-Nov-19

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

Source: Medtrack | Informa, 2019

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