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Why Aducanumab Failure Is Not The End Of Amyloid Hypothesis

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Biogen and **Eisai Co. Ltd.** will continue to test anti-amyloid agents in the treatment of Alzheimer's disease even after the failure of their most advanced and highest-profile candidate aducanumab in Phase III, but suggestions that Biogen should focus its resources elsewhere are mounting after this latest setback.

The partners said on March 21 that they will discontinue the Phase III ENGAGE and EMERGE clinical trials testing aducanumab in patients with mild cognitive impairment due to Alzheimer's disease and in patients with mild Alzheimer's disease dementia based on a futility analysis by an independent data monitoring committee, which found that the trials were unlikely to meet their primary endpoints.

A Phase II safety study and a long-term extension of the Phase Ib study that convinced Biogen to take aducanumab into Phase III also will be terminated. The company and its partner will determine after looking at the ENGAGE and EMERGE data whether to initiate a planned Phase III study for the anti-amyloid-beta antibody in secondary prevention of Alzheimer's.

Biogen closed down 29.2% at $226.88 per share on March 21 after the announcement that its most advanced and closely watch late-stage development program will be discontinued, wiping out $18.6bn worth of the company's value.

The failure of aducanumab to significantly affect even mild cognitive impairment in early-stage Alzheimer's disease patients is not particularly surprising, since several anti-amyloid antibody candidates similarly have failed in previous clinical trials. However, Biogen has projected so much confidence in its program – and Alzheimer's disease has so much unmet need – that there was a lot of hope despite multiple sets of evidence to the contrary that aducanumab would work.

"Aducanumab now joins a long list of Alzheimer's therapies that have failed to change the course of the disease, particularly those targeting beta-amyloid," William Blair analyst Matt Phipps wrote in a March 21 note.

"Despite the concerns with the amyloid hypothesis, we had hoped the Phase I data with aducanumab, particularly the correlation between removal of amyloid plaque as measured by PET scan and slowing of cognitive decline, would prove aducanumab could succeed where others have failed, but this hypothesis was obviously wrong," Phipps continued. "This is a setback for the Alzheimer's field and patients, but will hopefully catalyze increased investment in novel targets to treat the devastating disease."

BIOGEN PIPELINE DOESN'T EXCITE ANALYSTS, INVESTORS

Aducanumab's failure leaves Biogen with a research and development pipeline that analysts describe as unexciting – including multiple amyloid-targeting agents – at a time when its multiple sclerosis (MS) franchise is projected to see sales decline and when its top-selling drug, *Tecfidera* (dimethyl fumarate), is facing patent challengers seeking to launch generics of the

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from the editor

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The amyloid beta hypothesis is remarkably tenacious. Despite the many notable failures of amyloid-targeting drug candidates to show meaningful effects on Alzheimer's disease in the clinic, companies have found reasons to justify ongoing trials of the failed drugs and of rival candidates.

One of the reasons the hypothesis lingers on is the belief that it has yet to be thoroughly tested early enough in the disease's course to have an influence on clinical outcomes. Another is the dearth of promising alternative approaches. Meanwhile, developers have highlighted distinctions between their drugs and those that have failed in the clinic which could make for a difference in clinical outcomes. Hence, firms have pressed on, homing in on earlier, milder presentations of the disease when they meet with failure in more symptomatic patients. Thus, even as Biogen announces the latest failure (of aducanumab; see cover story), its partner Eisai announces the start of a new Phase III study with another beta-amyloid-targeting candidate, BAN2401. And aducanumab itself has yet to be definitively buried: a planned secondary prevention trial is still potentially in the offing.

But even if there were a point in time when targeting amyloid beta peptide accumulation in a person's brain could prevent or modify the development of Alzheimer's disease, there remains the question of how patients would be identified and treated in real-world health systems.

Clearly, the need for better understanding of Alzheimer's etiology and pathophysiology is paramount. Information sharing between industry, health systems and academia should be increased. There is no low-hanging fruit for lone companies to pluck, and team work is essential to reach further.

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Going Generic: Big Brands Poised To Lose Marketing Exclusivity In The US In 2019

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Several high-profile blockbuster brands are poised to lose their marketing exclusivity in the US in 2019 with the launch of the first generic versions of drugs like *Advair* (fluticasone/salmeterol) and *Lyrica* (pregabalin) and the first wave of oncology biosimilars, *Herceptin* (trastuzumab), *Avastin* (bevacizumab) and *Rituxan* (rituximab).

The year is expected to be a notable one for generics and biosimilars, though the commercial launch trajectory for biosimilars in the US remains unclear. The exact timing of generic and biosimilar launches is also uncertain, with the timelines tied to patent expirations, patent settlement agreements, or in some cases ongoing patent challenges.

"Since the end of the patent cliff, we have had essentially the same $15bn-$17bn of negative impact from expirees in the US, and our modeling suggests that it is supposed to pop this year," Research Director for the IQVIA Institute for Human Data Science Michael Kleinrock said in an interview. But, he also pointed to uncertainties, including the possibility that some launches are delayed or there is slower uptake for certain complex generics and biosimilars.

"You can have a generic approved. It can reach the market, and the originator can retain a fairly large share of the volume of sales," Kleinrock noted. That has been the experience with some recent entrants, such as the generic launch of **Teva Pharmaceuticals USA Inc.**'s *Copaxone* (glatiramer) or biosimilars to **Johnson & Johnson**'s *Remicade* (infliximab).

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MS drug, though probably not before 2020. *(Also see "Going Generic: Big Brands Poised To Lose Marketing Exclusivity In The US In 2019 " - Scrip, 15 Mar, 2019.)*

Even its much-hyped spinal muscular atrophy (SMA) drug *Spinraza* (nusinersen), partnered with **Ionis Pharmaceuticals Inc.**, could see its blockbuster status challenged when the **Novartis AG** gene therapy *Zolgensma* for SMA launches later this year. *(Also see "Novartis Pharma CEO Sees Zolgensma Supplanting Spinraza" - Scrip, 1 Feb, 2019.)***Roche** also is closing in on Biogen's SMA franchise with plans for mid-year filings seeking approvals of ridisplam. *(Also see "Roche Makes Case For Its Oral SMA Drug Risdiplam As Filings Beckon" - Scrip, 6 Feb, 2019.)*

Analysts expect Biogen to engage in more aggressive business development as a result of the aducanumab failure on top of the company's other challenges to build up a more interesting pipeline.

"Aducanumab was the key pipeline drug, and beyond it there was [elenbecestat (E2609)] and BAN2401, two other beta-amyloid related compounds," Mizuho Securities analyst Salim Syed said in a March 21 note. He added that the amyloid hypothesis in Alzheimer's disease is now dead, so investors should take elenbecestat, which inhibits beta-secretase cleaving enzyme (BACE) to block amyloid production, and the anti-amyloid beta protofibril antibody BAN2401 out of their models assessing Biogen's value.

Both candidates plus aducanumab are being developed in partnership with Eisai and the three assets are the foundation upon which Biogen has built its Alzheimer's-lead neurology focus. Biogen recently revealed that BAN2401 was moved from Phase II into Phase III development despite mixed mid-stage results. *(Also see "Biogen To Launch Phase III Alzheimer's Prevention Study " - Scrip, 29 Jan, 2019.)* and *(Also see "Biogen, Eisai Report BAN2401 Seemingly Positive In Alzheimer's; Others Skeptical" - Scrip, 26 Jul, 2018.)*

Eisai announced after the aducanumab Phase III trial discontinuations were disclosed that the company and Biogen have initiated the Phase III ClarityAD /Study 301 testing BAN2401 versus placebo in 1,566 patients with mild cognitive impairment due to Alzheimer's disease.

> "This is a setback for the Alzheimer's field and patients, but will hopefully catalyze increased investment in novel targets to treat the devastating disease."

"BACE inhibitors (like E2609) have not worked historically to further this argument, and BAN2401, is another beta-amyloid targeting compound," Syed noted. *(Also see "Eisai/Biogen Remain In BACE Race As Alzheimer's Contenders Dwindle" - Scrip, 6 Jun, 2018.)*

WHO MIGHT BIOGEN BUY – OR BUY BIOGEN?

Syed suggested several companies that are potential acquisition targets for Biogen, including **Sage Therapeutics Inc.**, which won US FDA approval on March 19 for its first drug, the postpartum depression (PPD) therapy *Zulresso* (brexanolone). Sage also has a promising oral drug in Phase III development with a similar mechanism of action, SAGE-217, for PPD and major depressive disorder (MDD). *(Also see "Zulresso Is Sage's First Step In Postpartum Depression Treatment" - Scrip, 19 Mar, 2019.)*

Among other companies with late-stage and commercial neurology assets that Biogen investors may see as favorable acquisition targets, Syed named **Neurocrine Biosciences Inc.**, **Acadia Pharmaceuticals Inc.**, **Biohaven Pharmaceutical Holding Co. Ltd.**, **Alder BioPharmaceuticals Inc.** and **Sarepta Therapeutics Inc.** The company previously has noted that it wants to increase its investments in gene therapy, even after the recently announced deal to acquire **Nightstar Therapeutics PLC** for $877m in cash.

"Investors wanted Biogen to buy assets ahead of this [aducanumab] news for this very scenario. The company admittedly wasn't too active on this front, at least not enough to move the needle," he wrote. "Today's news definitely weakens Biogen's seat at the negotiation table, and any strategics that Biogen engages with at this point will know that." Syed said Biogen may be a more attractive acquisition target itself with the aducanumab risk removed from its pipeline, but noted the Tecfidera intellectual property risk and coming Spinraza competition as issues that may also impact the company's value in the eyes of purchasers.

Morningstar analyst Karen Andersen was more optimistic about Biogen's prospects going forward, however, pointing to multiple 2019 catalysts in a March 21 note – approval for the MS drug *Vumerity* (diroximel fumarate), which may show better gastrointestinal tolerability versus Tecfidera in an ongoing head-to-head trial, and Phase II data in treatment-resistant epilepsy for *Tysabri* (natalizumab) and for the anti-tau antibody BIIB092 in progressive supranuclear palsy.

BTIG analyst Thomas Shrader pointed to Vumerity and other R&D programs as well, but wasn't particularly enthusiastic about any of the assets in a March 21 note.

"We like the GI friendly Tecfidera (GI news mid-year) and the stroke drug (BIIB093; in P3), but neither is really exciting. Most of the rest of the pipeline is novel and high-risk medicine – remyelination [in MS] and such," Shrader wrote. "We expect BAN2401 (always weaker data) will be stopped as well." *(Also see "Alzheimer's Early Approval? Skepticism Over Biogen/Eisai's BAN2401 Data Clouds Chances" - Pink Sheet, 26 Jul, 2018.)*

AMYLOID HYPOTHESIS REMAINS IN PLAY DESPITE SETBACKS

In addition to Biogen and Eisai's partnered programs for the amyloid-targeting antibody BAN2401 and BACE inhibitor elebecestat, the Phase III Alzheimer's disease pipeline includes two other amyloid-focused programs. They are ALZT-01, a small molecule designed to block amyloid beta aggregation and polymerization in the brain from **AZTherapeutics Inc.**, and Roche's anti-amyloid antibody gan-

tenerumab, developed in partnership with **MorphoSys AG**. *(Also see "Roche In New Phase III Bet On MorphoSys' Anti-Amyloid Agent" - Scrip, 7 Mar, 2017.)*

However, Roche's amyloid-targeting antibody crenezumab developed in collaboration with **AC Immune SA** recently came to the same end as aducanumab. The partners discontinued two Phase III studies for crenezumab in January after an interim analysis found that the antibody was unlikely to succeed if the trials were continued to their conclusion. *(Also see "AC Immune/Roche Drop Crenezumab After Phase III CREAD Alzheimer's Failure" - Scrip, 30 Jan, 2019.)*

Aducanumab and crenezumab joined 26 other antibodies, vaccines, peptides and small molecules seeking to block amyloid formation or clear it from the brain, which were all suspended at various stages of preclinical through Phase III development, according to a review of the *Biomedtracker* database.

The Biogen/Eisai and Roche/AC Immune candidates followed the same path as other high-profile, late-stage antibody therapeutics. **Eli Lilly & Co.**'s solanezumab flopped in Phase III in 2016. **Pfizer Inc.**, **Johnson & Johnson** and partners pulled the plug on bapineuzumab in 2012.

Also, development has been suspended for 15 different compounds targeting BACE, including three late-stage drugs whose development ended in 2018 – **Merck & Co. Inc.**'s verubecestat in February, J&J and **Shionogi & Co. Ltd.**'s atabecestat in May, and **AstraZeneca PLC** and Lilly's lanabecestat in June. *(Also see "M&A Pressure Mounts For Merck & Co After Alzheimer's Drug Dismissed" - Scrip, 14 Feb, 2018.)* and *(Also see "More Alzheimer's Pain As J&J Pulls Plug On BACE Inhibitor" - Scrip, 18 May, 2018.)*

ALTERNATIVE AMYLOID, ALZHEIMER'S APPROACHES

ProMIS Neurosciences Inc. Chief Medical Officer James Kupiec, who worked on the clinical trials for bapineuzumab during his tenure at Pfizer, said in an interview with *Scrip* that the now-failed amyloid-targeting antibodies, including BACE inhibitors, all went after the wrong amyloid target.

Kupiec, who was vice president and global clinical leader for Parkinson's disease as well as clinical head of the Neuroscience Research Unit at Pfizer before he joined ProMIS last year, noted that the late-stage and discontinued anti-amyloid candidates targeted amyloid plaques. *(Also see "Executives On The Move: Defectors From GSK, Pfizer, Shire, Dr Reddy's Get New Posts" - Scrip, 27 Sep, 2018.)* Those antibodies were created before research showed amyloid oligomers may be a better target and before there were technology platforms, like the one used by ProMIS, that could develop antibodies capable of precisely targeting toxic amyloid oligomers, he said.

That's what ProMIS' lead candidate PMN310, which is in preclinical development, is designed to do. The company is "hoping to get into the clinic as soon as possible" and is in "serious discussions with a lot of large pharma companies," Kupiec said.

Meanwhile, **AgeneBio Inc.** is in Phase III testing a drug with a completely different mechanism of action altogether. The private company has a $20m National Institutes of Health (NIH) grant to help fund its 830-patient Phase III trial for AGB101, which enrolled its first patient in January.

The drug is a low dose of the anti-epileptic therapy levetiracetam, which targets SV2A, a synaptic vesicle membrane protein. AGB101 is a proprietary, extended-release, once-daily formulation of levetiracetam dosed at one-twelfth of what's given to treat epilepsy.

AgeneBio's candidate is being studied in the treatment of mild cognitive impairment in Alzheimer's disease based on research from the lab of company CEO and founder Michela Gallagher at **Johns Hopkins University** that showed restoring normal brain function with AGB101 slowed the progression of Alzheimer's.

AgeneBio is talking to investors and pharma partners in an effort to secure more funding for the Phase III study, which may be registrational, since AGB101 is based on a known, approved drug, Gallagher told *Scrip* in an interview.

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Merck KGAA/Pfizer Discontinue Phase III Avelumab/Talazoparib Combo Study In Ovarian Cancer

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Merck KGaA and **Pfizer Inc.**'s decision to discontinue their Phase III study of PD-L1 inhibitor *Bavencio* (avelumab) plus Pfizer's PARP inhibitor, *Talzenna* (talazoparib) in previously untreated advanced ovarian cancer, announced March 19, was based partly on disappointing results from another study involving Bavencio reported at the end of last year.

Other reasons for the study discontinuation were the rapidly changing treatment landscape, including the approval of another PARP inhibitor in the front-line maintenance setting, the companies say. This was **AstraZeneca PLC**/**Merck & Co. Inc.**'s PARP inhibitor *Lynparza* (olaparib) which was approved by the US FDA for first-line use in BRACA-mutated ovarian cancer patients in December 2018, based on the results of the SOLO-1 study.

Lynparza's move to become the standard-of-care in first-line ovarian cancer patients is likely to be reinforced by results from the PAOLA-1 trial involving Lynparza plus **Roche**'s *Avastin* (bevacizumab), due to read-out in 2020, note analysts at Bryan Garnier & Co.

Recent progress by other companies in the ovarian cancer field include EU approval for **Clovis Oncology Inc.**'s PARP inhibitor, *Rubraca* (rucaparib) for maintenance therapy for platinum-sensitive ovarian cancer in all-comers, in January 2019.

And **Tesaro Inc.**'s PARP inhibitor, *Zejula* (niraparib) is likely to get a boost from the proposed acquisition of Tesaro by **GlaxoSmithKline PLC**.

PREVIOUS STUDIES

Merck KGaA/Pfizer explained that the Phase III JAVELIN Ovarian PARP 100 study was being discontinued based on several emerging factors since the trial's initiation in mid-2018, including the previously announced interim results from the Phase III JAVELIN Ovarian 100 study.

"The degree of benefit observed with avelumab in front-line ovarian cancer in that study does not support continuation of JAVELIN Ovarian PARP 100 trial in an unselected patient population," the two big pharma partners said. A planned interim analysis of JAVELIN Ovarian 100 found the addition of avelumab to chemotherapy or to maintenance therapy was unlikely to affect progression-free survival during the first-line treatment of ovarian cancer patients.

The two companies have been collaborating on the clinical development of avelumab under a deal signed in 2014 but have already been knocked back by disappointing results in gastric cancer and lung cancer, and now in ovarian cancer. Pfizer gained US approval for talazoparib for the treatment of breast cancer in October 2018 and is now evaluating it alone and in different combinations in a number of cancers.

THE LATEST DECISION

JAVELIN Ovarian PARP 100 was evaluating the efficacy and safety of PD-L1 inhibitor avelumab in combination with chemotherapy, followed by maintenance therapy of avelumab in combination with talazoparib, versus an active comparator in treatment-naive patients with locally advanced or metastatic ovarian cancer (Stage III or IV).

Although checkpoint inhibitors used alone have not been particularly effective in relatively non-immunogenic ovarian cancer, it was hoped that combination therapies might fare better, but a series of disappointing results in the JAVELIN series may have dashed those hopes. Top-line results from another

Competitive pressures can lead to a rethink of development strategies

study, the Phase III JAVELIN Ovarian 200 study, released in November 2018, indicated that avelumab monotherapy or its use in combination with chemotherapy missed PFS and overall survival endpoints when evaluated in platinum-resistant or refractory ovarian cancer patients.

The decision to discontinue JAVELIN Ovarian PARP 100 does not impact the remainder of the JAVELIN program which includes 30 clinical programs across 15 different tumor types including breast, gastric/gastro-esophageal junction and head and neck cancers, Merkel cell carcinoma, non-small cell lung cancer and urothelial carcinoma, the companies said.

Other combinations in other cancers have been fruitful: earlier this month, Merck and Pfizer completed the filing process for Bavencio plus Pfizer's tyrosine kinase inhibitor, *Inlyta* (axitinib), for the treatment of advanced renal cell carcinoma, based on the pivotal Phase III JAVELIN Renal 101 trial, and the combination has been submitted for priority review in the US, with a target action date of June 2019.

Currently, avelumab is approved in the US, EU and elsewhere for the treatment of metastatic Merkel cell carcinoma, and for metastatic urothelial carcinoma in the US, while talazoparib was approved for the treatment of BRCA-mutated HER2-negative locally advanced or metastatic breast cancer in the US in October 2018.

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Conatus Endures Another NASH Setback With Failure To Hit Fibrosis Endpoint

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The future of **Conatus Pharmaceuticals Inc.**'s partnership with **Novartis AG** in non-alcoholic steatohepatitis (NASH) appears uncertain after the biotech's emricasan posted its second Phase IIb miss in four months. The first-in-class pan-caspase inhibitor did not meet a fibrosis-reduction endpoint in the ENCORE-NF trial, the San Diego firm announced March 21.

Conatus did not provide detailed data for the trial other than to report that in 318 biopsy-confirmed NASH patients with liver fibrosis, emricasan failed to produce a one-stage or greater reduction in fibrosis score at a statistically significant rate compared to placebo after 72 weeks of treatment.

In a statement, the company said that while the study did not yield the desired effect in earlier-stage NASH fibrosis patients, emricasan has shown biomarker activity across a spectrum of liver disease that suggests potential utility in later-stage patients, such as those with cirrhosis.

The study randomized patients with fibrosis scores ranging from F1 to F3 at baseline (mild fibrosis to bridging fibrosis that has spread but not become cirrhosis) on a 1:1:1 basis to 5 mg or 50 mg emricasan or placebo twice-daily. A fibrosis score of F4 means the patient has cirrhosis, which can lead to hepatocellular carcinoma and/or the need for a liver transplant.

Reduction in fibrosis is one of the measures FDA recommends using as a primary endpoint in Phase III NASH trials, per its December 2018 draft guidance on NASH drug development. However, the guidance also allows for improvement in steatohepatitis as a primary endpoint, as long as there is no worsening of fibrosis.

No drugs are approved as therapy for NASH, although four have advanced to Phase III, with **Intercept Pharmaceuticals Inc.**'s obeticholic acid (OCA), a farnesoid x receptor (FXR) agonist, generally considered to be the closest to approval. There are 53 other candidates in the clinic.

Gilead Sciences Inc. was the first company to report out Phase III data in NASH, on Feb. 11, as its ASK1 inhibitor selonsertib failed to demonstrate a fibrosis-reduction in patients with F4 fibrosis scores. Intercept then reported data from its Phase III REGENERATE study of OCA on Feb. 19, showing a fibrosis benefit in the larger of two doses tested, but it missed an endpoint of NASH resolution. The New York-based firm said it will file OCA for approval in NASH during the second half of 2019.

Still to come is Phase III data for **Genfit SA**'s PPAR alpha/delta agonist elafibranor, expected during the final four months of 2019. The other Phase III candidate, **Allergan PLC**'s CCR 2/5 antagonist cenicriviroc, is expected to produce Phase III data in 2020.

THREE ROUNDS OF ENCORES

Under its 2016 option agreement with Novartis, Conatus is conducting three Phase IIb ENCORE studies with emricasan in different cohorts of NASH patients. This past December, Conatus revealed that the drug failed to meet its primary endpoint – change in hepatic venous pressure gradient (HVPG) from baseline to week 24 – in the 263-patient ENCORE-PH trial in compensated NASH cirrhosis patients at high risk of decompensation. *(Also see "In NASH Race, Bad News For Conatus, Good News For Genfit In PBC" - Scrip, 10 Dec, 2018.)*

> Conatus said it and Novartis are awaiting a chance to review the totality of the data from the three ENCORE trials to make a decision on continued development of emricasan.

A six-month extension of ENCORE-PH measuring liver function and clinical outcomes after 48 weeks of treatment is expected to report out in mid-2019, Conatus said. The firm is also conducting the 210-patient ENCORE-LF study in NASH patients with decompensated cirrhosis. An event-driven analysis of clinical outcomes is expected in mid-2019.

Conatus said it and Novartis are awaiting a chance to review the totality of the data from the three ENCORE trials to make a decision on continued development of emricasan. Overall, Emricasan has been studied in more than 950 patients across 19 completed clinical trials in a variety of liver indications. In ENCORE-NF, the drug was generally well tolerated, consistent with safety findings from the 18 previous studies, the company said.

Conatus unveiled its plans for the ENCORE studies at the American Association for the Study of Liver Diseases annual meeting in 2015, saying that it saw emricasan as offering potential in a wide swath of liver conditions from early-stage to later-stage disease. Beyond NASH, the company hoped to demonstrate that the candidate could benefit a range of cirrhosis patients and also address residual liver damage in cured hepatitis C patients.

Novartis paid $50m up front for an option to license emricasan in December 2016, under a deal that also gave Conatus a convertible loan of $15m, a potential option exercise fee of $7m and up to $650m in milestones as well as possible sale royalties. The agreement gave Novartis the right to take over development of emricasan in Phase III, where it planned to test the compound in combination with its internal NASH candidates, including FXR agonists.

Combination therapy is expected to become the standard of care, as NASH is a multi-factorial disease caused by buildup of fat in the liver that can cause fibrosis and/or inflammation.

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Latest REDUCE-IT Results Bolster Case For Amarin's Vascepa Fish Oil Pill

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Amarin Corp. PLC's latest results for the prescription-grade fish-oil product *Vascepa* in the REDUCE-IT cardiovascular outcomes trial presented at the American College of Cardiology (ACC) annual meeting boost the case for the drug's efficacy ahead of a supplemental US filing in a broader patient population.

Vascepa is a proprietary formulation of the omega-3 acid eicosapentaenoic acid (EPA). Data released on March 18 at the ACC meeting in New Orleans suggest that the drug used on top of statins provides a significant 30% reduction in risk compared with placebo for a composite of first, subsequent and total ischemic events. Investigators also reported a significant 20% reduction in risk for CV death and a 13% numerical risk reduction in total mortality (p-value of 0.09)

An early unedited copy of an article with the data was published the same day by Deepak Bhatt, executive director of interventional cardiovascular programs at Brigham and Women's Hospital, and colleagues in the *Journal of the American College of Cardiology* (JACC).

The primary composite endpoint included cardiovascular death, nonfatal myocardial infarction (MI), nonfatal stroke, coronary revascularization or hospitalization for chest pain related to blockages.

The key secondary endpoint, which is considered more robust, included cardiovascular death, nonfatal MI or nonfatal stroke. And on this measure, the drug was associated with a significant 26% reduction in risk. Vascepa was well-tolerated, with a risk profile in line with the what has been previously reported.

Vascepa is US FDA approved for use as an adjunctive treatment of patients with severe hypertriglyceridemia, defined as 500 mg/dL or above. Amarin plans to submit a supplemental NDA with results from the REDUCE-IT outcomes study, which was designed through a special protocol assessment with the agency, by the end of March in a bid to broaden the patient population.

REDUCE-IT included about 8,000 patients with triglyceride levels between 135 mg/dL and 500 mg/dL. The median triglyceride level at baseline was 216 mg/dL, but the study also included some patients with triglyceride levels as low as 81 mg/dL at baseline. The patients were well-controlled on statins, as evidenced by the median baseline LDL cholesterol (LDL-C) of 75 mg/dL.

BUILDING ON PRIOR RELEASE, TACKLING PLACEBO QUESTION

The company released data for Vascepa at the American Heart Association (AHA) annual meeting in November. On the primary efficacy endpoint of the study – the first occurrence of a composite of major adverse cardiovascular events (MACE) – the drug was associated with a significant, 25% reduction in risk compared with placebo.

As the first major study of a fish oil product to show a CV outcomes benefit, the study was groundbreaking, though there was controversy about the use of mineral oil as a comparator for placebo as this increased LDL-C, raising questions about whether this was a true placebo.

The JACC paper by Bhatt and colleagues acknowledged that some biomarkers in the placebo arm increased from baseline – median LDL was 5 mg/DL higher in the placebo group versus the Vascepa group – but added that "such changes are common in statin-treated patients within cardiovascular outcome studies."

It's unclear whether that statement along with the consistency of the latest results will be enough to reassure the cardiology community regarding a potentially negative effect in the mineral oil placebo arm that benefited the Vascepa arm of the trial.

Cedars-Sinai cardiologist Sanjay Kaul noted in emailed responses to questions from *Scrip* that the placebo/mineral oil issue has been brought up twice at the FDA with this compound and was not deemed to be a major issue.

The fact that a benefit was consistently observed in patients with an LDL increase and in those with no LDL increase in the placebo group "suggests this is not a major issue," said Kaul, who has participated as a panelist in agency reviews of cardiovascular drugs.

CONSISTENT REDUCTIONS IN RISK

In the latest release at the ACC meeting, investigators noted that first events were reduced by 25%, second events by 32%, third events by 31%, and fourth or more events by 48%.

The analysis of recurrent events was pre-specified, but a limitation of the study was that it was an exploratory analysis and one method used to evaluate the data was done on a post hoc basis, the authors acknowledged in the JACC paper.

A total of 159 primary endpoint events were prevented in the course of the five-year study, including 12 cardiovascular deaths and 42 heart attacks.

"The times to first occurrence, second occurrence, third occurrence, or fourth occurrence of the primary composite endpoint were consistently reduced with icosapent ethyl," Bhatt and colleagues wrote.

"Patients don't care just about the first event, they care about the second event especially if that one happens to be a fatal one, but even otherwise," Bhatt said during an ACC press briefing, adding that from an insurance, health economics and public health perspective the intervention would have a "very large impact."

The wholesale acquisition cost (WAC) for Vascepa in 2019 is $303.65 per month and Amarin stressed there are "numerous discounts and rebates" negotiated in the supply chain as well as coupon programs to help patients with out-of-pocket costs. Amarin reported $228m in product sales for 2018.

Bhatt also highlighted results for people in the study with a baseline triglyceride level as low as 81 mg/dL, which is lower than what might be considered the target treatment population for the drug. Study participants with a baseline triglyceride

between 81 mg/dL and 190 mg/dL had a 26% reduction in risk for the primary endpoint. That compares with 23% risk reduction for those with baseline between 190 mg/dL to 250 mg/dL, and 40% risk reduction where the baseline was between 250 mg/dL and 1,401 mg/dL.

Bhatt and two other clinicians – Duke Clinical Research Institute's Ann Marie Navar and Boston University's William Boden – questioned whether the threshold for what is considered a high level of triglycerides needs to be lowered during an investor call held by Amarin on March 18 after the market closed.

Discussing the study during the press briefing, University of Florida Research Professor Eileen Handberg said that patients with cardiovascular disease have multiple events and continuing to reduce that risk over time is extremely important.

These analyses are not that commonly done, but should be done in all trials with MACE outcomes, Handberg said, noting that REDUCE-IT represents a kind of paradigm shift for clinical trial reporting.

JACC authors credited the efficacy benefit to high EPA levels, in contrast with other fish oil products, which are composed of EPA and docosahexaenoic acid (DHA).

"EPA has unique lipid and lipoprotein, anti-inflammatory, anti-platelet, anti-thrombotic, and cellular modifying effects, all of which may contribute to benefits in atherosclerotic processes such as reduced development, slowed progression, and increased stabilization of atherosclerotic plaque," the JACC paper noted. Kaul described the time-to-first events of REDUCE-IT as "quite impressive" given that they came on top of optimal medical therapy with pre-treatment LDL levels (75 mg/dL) among the lowest recorded in LDL trials; he said the recurrent event results were "along expected lines."

"The results of this recurrent event analysis show that the benefits are preserved (for the more robust secondary endpoint of CV death, MI or stroke), and to some degree amplified (for the less robust primary endpoint), when all events are accounted for, thereby capturing the totality of treatment benefit," Kaul said.

He added that regulatory agencies appear to be "increasingly supportive of an analysis strategy based on recurrent events." For example, the primary endpoint of the PARAGON-HF study of **Novartis AG**'s *Entresto* (sacubitril/valstartan) in heart failure was the cumulative number of primary composite events of cardiovascular death (first and recurrent) and total heart failure hospitalizations, he noted.

Hadley Wilson, an interventional cardiologist at the Sanger Heart and Vascular Institute and a member of the ACC Board of Trustees, said that the study provides evidence for another agent that can be used in people with hypertriglyceridemia and lipid problems. It may also pave the way for inclusion in treatment guidelines, he said.

The ACC/AHA released new guidelines for primary prevention of heart disease and Vascepa was not included. The next version is may be released in a year or more.

Joint ACC/AHA guidelines for managing cholesterol released last November also left Vascepa out and it is unclear when they will be revised.

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Shorter Treatment Time For Chagas Could Blunt Kissing Bug Disease

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A two-week course of drugs for treating patients with Chagas disease, instead of the current 60-day regimen, could be just as effective and safer, according to a new study which researchers believe could change the paradigm for treatment of the debilitating and potentially fatal insect-borne illness.

The BENDITA study was led by the not-for-profit Drugs for Neglected Diseases Initiative (DNDi) and carried out at sites in Cochabamba, Tarija and Sucre in Bolivia. It tested six treatment arms with a variety of lengths and dosages of benznidazole, the drug most commonly used to treat Chagas, both as monotherapy and in combination with **Eisai Co. Ltd.**'s investigational antifungal fosravuconazole.

Some 80% of the patients assigned to the group which took the standard dose of 300mg/day of benznidazole, but for two weeks instead of the standard eight weeks, showed no sign of the parasite in their blood six and 12 months after finishing the treatment. A similar result was observed in the group that took the standard eight-week treatment.

Significantly, DNDi noted, none of those in the two-week reduced duration group interrupted treatment. On average, 20% of patients who followed the standard course of treatment with benznidazole abandoned it due to side effects such as gastric intolerance, rashes or neuromuscular problems.

The side effects associated with benznidazole have "often discouraged some people from seeking treatment and healthcare workers from recommending it," said Joaquim Gascon, principal investigator in the trial and director of the Chagas Initiative at the Barcelona Institute for Global Health. A fellow investigator, Faustino Torrico, president of the CEADES Foundation in Bolivia, added, "We've shown shorter treatment could be just as effective, and much safer. This could change the paradigm for Chagas treatment, by improving adherence and encouraging wider adoption by the medical community."

The results "bring new hope for people living with this silent disease and could change the reality of access to treatment in endemic countries. With a much simpler treatment regimen, there is no excuse for not treating people with Chagas," added Sergio Sosa Estani, head of the Chagas clinical program at DNDi.

Chagas is caused by the parasite *Trypanosoma cruzi* and transmitted to humans via the feces and urine of kissing bugs or triatomines. According to the World Health Organization, 8 million people are infected worldwide, mainly in Latin America where one quarter of the population is potentially at risk of contracting a disease which causes incapacity and more than 10,000 deaths per year. International travel and migration has meant that Chagas is increasingly a global health issue – according to the Centers for Disease Control and Prevention, in the US an estimated 300,000 people are infected with *T cruzi*.

As the disease typically remains asymptomatic for years after infection, most people with Chagas are unaware of their condition, noted DNDi, and for 30-40% of people infected, most will suffer cardiac damage, often leading to sudden death or progressive heart failure.

"We've shown shorter treatment could be just as effective, and much safer. This could change the paradigm for Chagas treatment, by improving adherence and encouraging wider adoption by the medical community."

NOVARTIS TESTS ENTRESTO FOR CHAGAS CARDIOMYOPATHY

It is against this background that **Novartis AG** has announced that as well as joining the Global Chagas Disease Coalition as a member, it is preparing a study to test its heart failure blockbuster *Entresto* (sacubitril/valsartan) versus enalapril in around 900 patients with chronic Chagas cardiomyopathy. Recruitment is planned to commence this year and the Swiss major noted that it will be "the first definitive morbidity and mortality study to assess a potential therapy for cardiac disease in this underserved patient population."

The primary endpoint is time to occurrence of a composite of cardiovascular events, including death or first hospitalization due to heart failure. Novartis said that the study followed an exploratory analysis from the PARADIGM-HF trial on which the appproval of Entresto was based which suggested the drug may have beneficial effects in people with chronic Chagas cardiomyopathy and heart failure with reduced ejection fraction.

The company added that it was also "working with stakeholders in endemic countries to co-develop tailored access-to-medicine programs and health system strengthening strategies to help ensure lower-income patients suffering from chronic Chagas cardiomyopathy can benefit from the best available treatment." In addition, Novartis pointed out that its proteasome inhibitor LXE408 was recently advanced as a promising drug candidate for the treatment of visceral leishmaniasis and "this novel mechanism of action is also being explored for other indications, including Chagas."

BAYER PEDIATRIC STUDY A SUCCESS

There are currently only two drugs available to treat the disease – benznidazole and nifurtimox – and the latter was discovered by **Bayer AG** which first introduced the drug in Argentina (marketed as *Lampit*) in the 1970s, and shortly afterwards in other Latin American countries. Now the German major has presented positive data from the first part of a Phase III study of nifurtimox in pediatric patients at a Chagas conference in Barcelona.

The 330-patient study met its primary endpoint, which was the serological response at one year after end of treatment, by demonstrating superiority of 60-day nifurtimox treatment compared with historical placebo control. The study was conducted at sites in Argentina, Bolivia and Colombia between 2016 and 2018.

For the trial, Bayer developed a new formulation of both the 30mg and 120mg tablets, which can be dissolved in water to form a slurry when administered to children to allow for dosing accuracy and administration to those who have difficulty swallowing tablets. Jaime Altcheh of the Ricardo Gutierrez Children's Hospital in Buenos Aires and coordinating investigator of the trial, was quoted by Bayer as saying that "an adequate dispersable formulation of nifurtimox is a big step forward toward achieving the goal of treating all infected children. Early treatment after infection is very important to prevent manifestation of the disease in adulthood."

So progress is being made and pharma has been doing the right thing in an area of great unmet need but not a lucrative one. For example, since 2002 Bayer has been providing the WHO with nifurtimox free of charge, as well as financial resources for logistics and distribution and funding awareness, education and training programs, plus surveillance activities.

However much is still to be done and Bayer noted that today, less than 1% of people infected with Chagas worldwide are treated due to low disease awareness and limited access to treatment.

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New CV Outcomes Study May Mean Big Boost For Amgen's Repatha Market

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Amgen Inc.'s plan to run a new cardiovascular outcomes study of its PCSK9 inhibitor *Repatha* (evolocumab) in high-risk patients who haven't had a cardiovascular event yet has the potential to greatly broaden the target population for the drug.

The VESALIUS-CV trial will be done in collaboration with the Brigham and Women's Hospital Thrombolysis in Myocardial Infarction (TIMI) Study Group and will start enrolling in the second quarter, the company announced March 15. Repatha is currently approved in the US for reducing the risk of myocardial infarction, stroke and coronary revascularization in adults with established cardiovascular disease, for use as an adjunctive therapy in treating primary hyperlipidemia (including heterozygous familial hypercholesterolemia), and for homozygous familial hypercholesterolemia.

With current US FDA labeling, some 11m in the US are potentially eligible for treatment (including 3.4m at the highest risk) and if those who had never had an event were included it would add another 4.5m, according to the company.

"Amgen and TIMI previously collaborated on the Repatha cardiovascular outcomes study (FOURIER), which demonstrated Repatha's efficacy in reducing low-density lipoprotein cholesterol (LDL-C) levels, as well as the relative risk for major CV events in high-risk patients with a history of heart attack or stroke. VESALIUS-CV will build on these findings by exploring the potential benefit of Repatha in preventing a first heart attack or stroke in patients with some of the most significant risk factors for a first CV event," Amgen said.

"The study will be the first to investigate long-term outcomes in this population with Repatha for a minimum of four years," the company noted. Median follow-up in FOURIER was 24 months.

Amgen's previous FOURIER cardiovascular outcomes study (CVOT) tested Repatha for secondary prevention and showed the drug was associated with a 15% reduction in risk on the primary endpoint, a composite that included cardiovascular death, myocardial infarction (MI), hospitalization for unstable angina or coronary revascularization. Investigators also reported a 20% reduction for the endpoint including risk for CV death, MI or stroke.

In VESALIUS-CV, the enrollees will not have had a heart attack or stroke, but they do have coronary, cerebral or peripheral arterial disease and may have had interventions, including a coronary arterial bypass graft (CABG) or stents and they may have diabetes with indicators of increased risk for cardiovascular disease, the company explained.

The new study tests the drug given every two or four weeks in 13,000 high-risk patients who have not had an event yet and with a baseline LDL of 100 mg/dL, whereas FOURIER tested the drug every two or four weeks after an event in 27,564 patients with a baseline LDL of less than 70 mg/dL

The primary efficacy measure also differs. FOURIER featured a five-point com-

posite of major adverse cardiovascular events (MACE). The new study has two primary endpoints – three-point MACE (cardiovascular death, MI and ischemic stroke) and four-point MACE (cardiovascular death, MI, ischemic stroke and ischemia-driven revascularization.

NOT PRIMARY PREVENTION

Mizuho Securities analyst Salim Syed stressed in a March 15 note that the VESALIUS-CV study is not considered a primary prevention trial, because the study is enrolling very high-risk patients, who have significant coronary disease.

> The VESALIUS-CV trial will be done in collaboration with the Brigham and Women's Hospital Thrombolysis in Myocardial Infarction (TIMI) Study Group and will start enrolling in the second quarter, the company announced March 15.

"Primary prevention typically refers to pre-clinically manifest CV disease (e.g. a 25-year old who is perfectly in good health taking a PCSK9 for long-term benefit). The only place in the trial design that one can really argue this is primary prevention is patients [with] diabetes with indicators of increased CVD risk, which could be considered a high-risk primary prevention population since they do not have a diagnosis of ASCVD [atherosclerotic cardiovascular disease]," Syed said, which was confirmed by Amgen.

The analyst also noted that the study design is similar to **The Medicines Co.**'s ORION-4 outcomes study of the long-acting PCSK9 inhibitor inclisiran. *(Also see "Medicines Company Gets Aggressive With Inclisiran Phase III Plans" - Scrip, 31 Aug, 2017.)* The ORION-4 study tests inclisiran in 15,000 patients who have had an event and have baseline LDL of 100 mg/dL, and features four-point MACE as the primary efficacy endpoint. The study started in October 2018 and has a primary completion date of December 2024. Top-line data from a range of Phase III trials are set for release this year and the drug is expected to launch by 2021.

The primary completion date on clinicaltrials.gov for Amgen's VESALIUS-CV study is May 2024, ahead of the ORION-4 release.

PCSK9S FINALLY GETTING OFF THE GROUND

Amgen secured the outcomes claim and indication for primary hyperlipidemia at the end of 2017, which has marked a valuable turning point for the drug. Payers and physicians had not fully embraced the pricey injectable class ahead of outcomes data. *(Also see "Outcomes Claim May Help Amgen Make Case For PCSK9 Inhibitor Repatha" - Scrip, 1 Dec, 2017.)*

Sanofi/Regeneron Pharmaceuticals Inc.'s competing PCSK9 inhibitor *Praluent* (alirocumab) is now under review at the FDA for an outcomes claim and use in first-line treatment of primary hyperlipidemia based on the ODYSSEY outcomes study, with a decision expected in April. *(Also see "PCSK9 Inhibitor Labeling Parity Is Within Reach As Praluent And Repatha Strive To Make Commercial Case" - Pink Sheet, 20 Aug, 2018.)* It is currently approved for use as an adjunctive therapy for heterozygous familial hypercholesterolemia or for patients with clinical atherosclerotic cardiovascular disease who need additional LDL-lowering.

The European Commission approved a new indication for Praluent for reducing cardiovascular risk in adults with established atherosclerotic disease as an adjunct to correction of other risk factors on March 15.

The PCSK9 class is associated with dramatic reductions in LDL on top of statins, and consequently, hopes were high for a blockbuster trajectory. The lack of outcomes data and high price at the time of launch – both initially cost about $14,500 annually – prompted insurance companies to establish heavy utilization management barriers that hindered use.

However, recent price cuts for both drugs, and the CVOT data, have helped to improve access in the market. *(Also see "Sanofi/Regeneron Cut Praluent List Price As PBMs Look To Maintain Rebate Status Quo" - Scrip, 12 Feb, 2019.)* Amgen announced plans to cut the list price for Repatha to $5,850 in October 2018. *(Also see "Amgen Drops Repatha List Price 60% To Cut Medicare Co-Pays And Boost Use" - Scrip, 24 Oct, 2018.)* Whereas Medicare patients have been paying as much as $370 per dose out of pocket, the copay cost could come down to $150 or as low as $25. And Sanofi followed suit, announcing in February that it is cutting the list price of Praluent by 60% to $5,850 per year. The goal for both drugs was to make the drugs more accessible to Medicare Part D patients, who were ineligible for copay coupons.

The changes have been helping. Amgen reported sales of $159m in the fourth quarter, up 62% from the year-ago period. Sanofi/Regeneron reported sales of €82m ($92m) in the fourth quarter, up 51% from the same period of 2017.

The consensus expectation for peak sales is $2.5bn.

AMGEN'S COUNTING ON REPATHA

Amgen highlighted Repatha as among the products driving long-term growth, during a presentation at the Cowen Health Care Conference on March 12.

Repatha sales grew 70% in 2018 and with the now-reduced price offering, Amgen is starting to see a step function in terms of upward trajectory in terms of adoption, David Meline, executive vice president and chief financial officer, told the meeting.

BMO Capital Markets analyst Do Kim said in a March 14 note that lowering the list price should "align reimbursement with physician enthusiasm to accelerate uptake."

Fourth-quarter sales figures for Praluent and Repatha suggest that the market is very under-penetrated, the analyst said, with about 106,000 in the US on therapy, Kim said.

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Zulresso Is Sage's First Step In Postpartum Depression Treatment

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The US FDA approved **Sage Therapeutics Inc.**'s *Zulresso* (brexanolone) on March 19 as the first agency-endorsed treatment for postpartum depression (PPD). It's also Sage's first approved product, helping the company establish a commercial organization as it completes Phase III development for the more broadly applicable postpartum and major depression candidate SAGE-217.

Zulresso's 60-hour I.V. infusion and requirement for continuous inpatient monitoring during administration may limit its use to the most at-risk new mothers, but it will help Sage build its presence in the PPD market ahead of approval for SAGE-217, an oral therapy with a similar mechanism of action that's being developed for PPD as well as major depressive disorder.

MARKET REACTION

Sage closed down 0.5% at $156.10 per share on March 19 as it ended the trading day without a Zulresso approval announcement on the FDA action date. However, the company rose 5.6% to $164.80 in after-hours trading when the agency announced the drug's approval later in the evening on March 19.

The FDA extended the original Dec. 19 user fee date for the Zulresso new drug application (NDA) by three months to consider a Risk Evaluation and Mitigation Strategy (REMS) proposed by the company. The REMS proposal was submitted to the agency after an advisory committee recommended approval as long as the Zulresso label included a REMS requiring close monitoring of patients for sedation or sudden loss of consciousness, which were observed in clinical trials. *(Also see "Sage's Brexanolone Could Be Transformative, But Only In Controlled Settings, US FDA Panel Says" - Pink Sheet, 2 Nov, 2018.)*

The drug rapidly and significantly improved depression scores in Phase III trials for new mothers who were experiencing moderate or severe PPD up to six months after giving birth; onset of symptoms occurred between the third trimester of pregnancy and within four weeks of delivery. Efficacy was seen at the 60-hour mark, but often within the first 24 hours of starting therapy, and treatment effects were observed for at least 30 days after administration. *(Also see "All Smiles At Sage As Phase III Postpartum Depression Data Are Positive" - Scrip, 9 Nov, 2017.)*

Sage will launch Zulresso for PPD as soon as the Drug Enforcement Administration (DEA) completes scheduling for the drug, an allosteric modulator of synaptic and extrasynaptic GABA-A receptors. The DEA process usually takes about 90 days, but company CEO Jeff Jonas told *Scrip* that Sage is ready to launch Zulresso right away if the scheduling decision comes early.

The product's list price is $34,000 for the one-time treatment, which Jonas said Sage set after discussing a range of prices with several payers.

"The feedback has been uniformly positive," he said, noting that payer attitudes about Zulresso's pricing are based on the attributes of the drug – namely its fast-acting efficacy.

"Payers understand the impact [of PPD] on the family, the cost to society, and the convenience of getting better in two and a half days," the CEO said. "We are expecting broad reimbursement for the drug."

Patient assistance programs will be revealed when Sage launches Zulresso to improve access for women who may not be able to afford the drug.

Jonas noted that PPD is a psychiatric disease that's not often diagnosed by psychiatrists, but rather by women's obstetricians, pediatricians treating the women's infants, social workers and others.

"Our focus is going to be on hospitals and centers of excellence, maybe an inpatient unit or outpatient unit where they can stay 24/7," he said. "We'll have only about 100 sales reps that will cover this market successfully."

The CEO explained that Sage will have almost as many medical science liaisons to work on informing physicians about the science behind Zulresso and the need for proper diagnosis and rapid treatment.

IV ADMINISTRATION

About one in nine new mothers experiences PPD – about 400,000 women in the US – but it's estimated that only half of affected patients are diagnosed.

Jonas said Sage does not anticipate that Zulresso's I.V. administration and the drug's REMS requirements will limit its use. Physicians and patients understand the importance of a rapid-acting therapy for a condition that, he said, "is the leading medical complication of pregnancy, and the most common cause of death after childbirth is suicide."

In speaking with women who have participated in Zulresso clinical trials, Sage has found that "the opportunity of a drug that provides benefit within hours and is a one-time treatment that is completed in two and a half days … is not an inconvenience," Jonas said.

"We have to administer the drug properly, but we don't see that as a barrier in terms of actual administration of the drug," he added.

The REMS for Zulresso requires the drug to be administered by a health care provider in a certified health care facility. Patients must be enrolled in the REMS program prior to administration of the drug then monitored during the 60-hour I.V. administration for excessive sedation and sudden loss of consciousness with continuous pulse oximetry monitoring. Patients also must be accompanied when interacting with their infants during administration of Zulresso.

Patients must be counseled about the risks associated with the drug and instructed about the REMS monitoring requirements prior to administration, and

should not drive, operate machinery, or do other potentially dangerous activities until Zulresso-induced sleepiness has resolved.

Analysts from Cowen wrote in a March 18 report following the investment bank's recent health care conference that investors and psychiatrists see a role for Zulresso even for moderate PPD patients based on Phase III results for the drug. The I.V. administration and the requirement for inpatient treatment during administration is viewed as a limiting factor for the drug, however.

MARKET POTENTIAL

That's why there's a lot of optimism around the oral drug SAGE-217, a next-generation positive allosteric modulator optimized for selectivity to synaptic and extrasynaptic GABA-A receptors that also had a rapid and significant effect on PPD – without loss of consciousness – in the Phase III ROBIN trial. Somnolence was among the most common side effects, however.

Sage has completed one Phase III study for SAGE-217 in major depressive disorder (MDD) and has another under way with results expected in late 2019 or early 2020.

"Our experts and audience continued to be encouraged by the potential of SAGE-217 given the promising data and [Phase II/III] progress in MDD and PPD," Cowen analysts said in the March 18 note.

"As the PPD treatment landscape continues to evolve, investors and experts increasing[ly] acknowledge the opportunity for pharmacologic treatments, including that of Sage's Zulresso, in patients whose symptoms are not well controlled on current treatment alternatives," they said. "Successful development of an oral formulation clearly has a role in the minds of investors and specialists. Our panelists were more definitive in their view that an effective oral could be a game changer, displacing an I.V. therapeutic in PPD."

Jonas noted that SAGE-217 is not an oral formulation of Zulresso but a novel drug with a slightly different formulation. He acknowledged, however, that Zulresso will pave the way for SAGE-217 with its similar mechanism and efficacy.

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Dermira's Lebrikizumab Data Set Up AD Showdown With Dupixent

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Dermira Inc.'s Phase IIb data for its IL-13 inhibitor lebrikizumab in atopic dermatitis showed efficacy across three dosing regimens, with a profile similar to market leader *Dupixent*. Now, the company hopes to initiate a Phase III study by year's end that could set up the therapy with a dosing-convenience advantage compared to **Sanofi**/**Regeneron Pharmaceuticals Inc.**'s IL-4/IL-13 receptor antagonist.

Dupixent (dupilumab) became the first biologic approved for atopic dermatitis in 2017, and in its first full year on the market in 2018 approached the blockbuster sales threshold (€788m/$894m), while picking up an additional US indication for moderate-to-severe asthma. *(Also see "Dupixent Approved For Severe Asthma With Broader Label Than Other Biologics" - Scrip, 21 Oct, 2018.)* Dermira executives cited multiple reasons during an investor call March 18 as to why they think lebrikizumab can compete viably with Dupixent in dermatology's largest indication, predicted to reach $15bn in aggregate sales by 2025.

Lebrikizumab already demonstrated proof-of-concept in a Phase II study at **Roche** when the Swiss pharma outlicensed the compound's development rights outside respiratory disease in 2017 to Dermira. The antibody yielded mixed results in severe asthma, hitting its Phase III primary endpoint in one trial but failing in another.

However, Dermira saw best-in-class potential in atopic dermatitis because of lebrikizumab's extended coverage and developed a Phase IIb protocol, including a loading dose and three different dosing cohorts.

Dermira noted in top-line data from the 280-patient Phase IIb study unveiled March 18 that all three treatment arms achieved statistical significance on the primary endpoint of improvement from baseline in Eczema Area and Severity Index (EASI) score from at 16 weeks compared to placebo. The improvement in EASI score was 62.3% for patients getting a 250 mg loading dose followed by 125 mg every four weeks, 69.2% for a 500 mg loading dose followed by 250 mg every four weeks, and 72.1% for a 500 mg loading dose followed by 250 mg every two weeks.

Dupixent is dosed every two weeks and Dermira seeks to demonstrate that lebrikizumab can yield similar or better efficacy with a monthly dose. Warning about variables that can confound cross-trial comparisons, SVB Leerink analyst Pasha Sarraf said in a March 18 note that lebrikizumab's Phase IIb data appear similar to the 71% EASI improvement shown by Dupixent in its Phase IIb program.

The Phase IIb data, while not conclusive, leave open the door for the possibility of monthly dosing, analysts agreed.

EASI-75 DATA COULD OFFER IMPORTANT DIFFERENTIATION

Of the three doses tested by Dermira, the two larger doses also hit statistical significance on multiple secondary endpoints, while the 125 mg monthly dose did not. Key among these might be EASI-75, which measures the percentage of patients achieving 75% clearance of atopic dermatitis by a specified time point. Cowen analyst Ken Cacciatore said KOLs have pinpointed this measure as "an important endpoint and differentiator of efficacy" in a March 18 note on the data.

In the 250 mg dosing cohorts, 56.1% treated monthly with lebrikizumab and 60.6% treated every two weeks achieved EASI-75, while the Dupixent Phase III SOLO studies achieved 51% and 44% EASI-75 rates. "We believe that the 250 mg bi-weekly dosing efficacy and safety of lebrikizumab demonstrates differentiation, since previously our consultants have indicated that to prove superiority to Dupixent a competitor would need to demonstrate a 60% or better EASI-75 score," Cacciatore wrote.

Dermira execs said they hope to initiate a Phase III program for lebrikizumab before the end of 2019, pending an end-of-Phase IIb meeting with the US FDA. Chief Development Officer Luis Pena told the call that the company's hypothesis right now is to design a protocol that would include a 250 mg dose every two weeks during the induction phase, with flexibility to continue dosing every two weeks or transition to monthly dosing during the maintenance period.

Chief Commercial Officer Lori Lyons-Williams added, however, that dosing convenience would not come at the expense of efficacy. Efficacy is the most important factor in atopic dermatitis therapy, she said, but a dosing edge could provide an important measure of differentiation in a competitive space.

"Based on extensive market research, we know that, of course, efficacy is the most important therapeutic attribute," she said. "We really think the trial design that [Pena] described would potentially allow us to have that and disease efficacy and a more convenient maintenance schedule, which, we think, would drive additional commercial value. So, I mean, honestly, from a commercial perspective, this is the best outcome we could have hoped for."

CEO Thomas Wiggans asserted that the Phase IIb dataset indicate lebrikizumab could prove to be both best-in-class and best-in-disease, supporting a thesis that IL-13 inhibition can address atopic dermatitis pathology by ameliorating both skin manifestations and itch, he said.

"IL-13 is a validated target and believed to be an important mediator in atopic dermatitis," Pena noted. "IL-13 expression is up-regulated in AD patients and correlates with disease severity. It promotes type 2 inflammation and drives multiple aspects of AD pathophysiology such as impaired skin barrier function, increased sensitivity to itch, fibrosis and an elevated risk of infection." Lebrikizumab appears to inhibit IL-13's biological effects in a targeted and efficient manner, he added.

Dermira previously guided that the costs of a Phase III program for lebrikizumab in atopic dermatitis would total approximately $200m. The company recently has taken steps to cover some of those costs, both by selling **Almirall SA** an option to European commercial rights to the product and also by adjusting the earnout provisions of its 2017 deal with Roche. [See Deal]

In its deal with Almirall, Dermira got $30m up front for the option rights to lebrikizumab, with the Spanish firm in line to pay $50m to exercise its option with potential milestone and royalty payments to follow. *(Also see "Almirall Extends Dermatology Reach With Dermira Lebrikizumab Deal" - Scrip, 12 Feb, 2019.)*

Meanwhile, Dermira reduced its near-term costs under its agreement with Roche by arranging for $16m in study drug free of charge, while eliminating a $30m milestone fee for the first regulatory filing of lebrikizumab in atopic dermatitis and halving what was a $40m start-of-Phase III milestone. In return, Roche obtained rights to tiered royalties into the high teens for lebrikizumab if the drug's sales exceed $3bn.

Along with a financing agreement with Athyrium Capital Management, these arrangements could reduce Dermira's Phase III costs by as much as $110m and give the Menlo Park, Calif.-based firm financial runway into the second half of 2020, SVB Leerink's Sarraf pointed out.

Dermira investors seem enthused, as the company's stock finished trading on March 18 up 82% at $12.61 per share.

The company will take advantage of investor goodwill to raise additional capital in preparation for its Phase III lebrikizumab program. It announced after the market closed that it may raise up to $126.5m in a forthcoming sale of common stock, although the total could change when Dermira prices the offering.

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Price 'Anchoring'? Zolgensma And The Art Of Managing Gene Therapy Sticker Shock

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Novartis AG and **AveXis Inc.** may be following a well-known approach to shaping the public's reception of the price of their upcoming one-time gene therapy for spinal muscular atrophy, *Zolgensma* (onasemnogene abeparvovec).

For the first cell and gene therapies, **Spark Therapeutics Inc.**'s *Luxturna* (voretigene neparvovec) and Novartis' *Kymriah* (tisagenlecleucel), the approach has included: 1) announcing a launch price that is notably lower than forecasts; and 2) engaging with payers on novel reimbursement arrangements that make coverage feasible. Zolgensma is expected to be approved in May.

Spark priced its therapy for inherited blindness at $850,000 (for treatment in both eyes) after widespread pre-launch speculation about a $1m price point. And Novartis' Kymriah chimeric antigen receptor T-cell (CAR-T) therapy originally launched at a list price of $475,000, well below published estimates of as much as $650,000.

Although Novartis/AveXis have not announced a price for Zolgensma, the companies have publicly suggested a price of up to $5m could be considered cost effective.

Analysts are predicting a list price of around $2m, which still would put Zolgensma in the ranks of the most expensive drugs ever. But it's a lot less than $5m.

"The psychological bias they are employing is called 'anchoring' – once they socialize the idea of a very high price as being 'worth it' they will then settle for a lower list price (but not that much lower) as being 'reasonable'," Boston University's Rena Conti suggested in an email.

She noted the approach has also been used in the past for cancer drugs and "in other luxury markets – most notably art." Conti is associate research director for biopharma and public policy at the Institute for Health System Innovation and Policy at BU.

SUPPORT FOR HIGH PRICE FROM ICER?

During its earnings presentation Jan. 30, Novartis said that a $5m price for Zolgensma is supported by a recent analysis by the Institute for Clinical and Economic Review. AveXis reiterated that position in a statement following an ICER-convened advisory panel meeting on the cost effectiveness of Zolgensma and **Biogen Inc.**'s *Spinraza* (nusinersen) March 7.

ICER challenges the characterization. While its report notes Zolgensma could be value-priced at $5m at a willingness to pay threshold of $500,000 per quality-adjusted life year (QALY), the organization does not believe that threshold would apply to setting US prices.

"Our report notes that decisionmakers often give special considerations for ultra-rare diseases such as SMA, and therefore we display thresholds that range all the way up to $500,000/QALY," an ICER spokesman said in an email.

"Our experience, however, is that public and private payers in the US do not typically accept cost-effectiveness thresholds that high as appropriate, even for treatments of ultra-rare conditions."

Novartis "has a real opportunity here to demonstrate both scientific and ethical leadership by setting the launch price of Zolgensma in line with the benefits patients will likely receive," the organization said.

ICER concludes that $900,000 would be a value-based price for Zolgensma in the infantile-onset Type 1 SMA population using the traditional US cost effectiveness threshold of $150,000 per quality-adjusted life year (QALY).

Using a complementary measure of benefit called "life year gained" (LYG), the report suggests that Zolgensma could be priced up to $1.5m, marking the first time ICER has supported a value-based price of more than $1m for a drug.

ICER has begun to feature the LYG metric more prominently in its reports to address concerns that use of the QALY alone could undervalue treatments that extend length without improving quality of life. (The estimates in the report are based on a $2m "placeholder" price for Zolgensma.)

With regard to Spinraza, the report concludes the therapy would require "a substantial discount to meet traditional cost-effectiveness ranges." Biogen's treatment has a list price of $750,000 for the first year and $375,000 per year thereafter.

NEW REIMBURSEMENT MODELS

As with Luxturna and Kymriah, AveXis has been working with payers on novel reimbursement approaches for Zolgensma.

"Payers are very interested in talking with us about exploring different payment models" including "outcomes-based models to ensure there's an effective balance between high upfront costs and managing the costs and benefits that would come down the road," according to AveXis VP Clinical Development Douglas Sproule.

Sproule commented on discussions with payers at the March 7 meeting, which was held by ICER's New England Comparative Effectiveness Public Advisory Council.

Avexis has been in negotiations with commercial payers in Massachusetts about piloting an annuity payment model for the treatment that includes a performance-based component. *(Also see "Annuity Payment Model For Cures May Get Test Drive In Massachusetts" - Pink Sheet, 19 Feb, 2019.)*

However, negotiations are still in the early stages and plans for the model may not be finalized in time for the drug's initial launch. Sticking points include how to define outcomes and how to avoid triggering Medicaid "best price."

"Medicaid is an important issue for all companies in this space," Sproule pointed out. "Certainly, we're working with [the Centers for Medicare and Medicaid Services] trying to pilot an effective solution that would be most equitable for the system and allow appropriate flexibility to work with payers to have the most optimal set of scenarios for payments."

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Pfizer Buys Option For Vivet In Latest Gene Therapy Tie-Up

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The gene therapy business development space has been active, and **Pfizer Inc.** is the latest to announce a deal in the research area with an option to buy the privately-held French gene therapy developer **Vivet Therapeutics**s. The companies announced March 20 that Pfizer has acquired a 15% equity stake in Vivet and secured an exclusive license to acquire outstanding shares in exchange for €45m ($51m) up front.

The deal will further expand Pfizer's footprint in gene therapy, where it has been building a significant presence, with several programs now in clinical development.

The partnership will add a new program advancing toward clinical development, VTX-801, a treatment for Wilson disease, a rare and potentially life-threatening liver disorder that causes copper poisoning. A faulty gene in liver cells encoding the ATP7B protein reduces the ability for the liver to regulate copper levels, causing severe hepatic and neurological symptoms.

There are an estimated 12,000 diagnosed patients undergoing treatment in the EU and US, but there are believed to be as many as 8,000 undiagnosed patients, according to Pfizer. Also, more than half of patients who are being treated aren't compliant with their

Pfizer has built much of its gene therapy pipeline through business development

medications. Among the drugs approved for treating the condition are copper chelating therapies including **Bausch Health Companies Inc.**'s (formerly Valeant's) *Cuprimine* (penicillamine) and *Syprine* (trientine), but they are associated with serious adverse events.

VTX-801 uses a modified AAV vector to transport a truncated functional version of the ATP7B gene to the liver cells carrying the defective gene. Pfizer said it expects an investigation new drug (IND) application will be filed with the US FDA in the first quarter of 2020, putting off the initiation of a human trial until at least some time next year.

Vivet raised €37.5m in a Series A round in 2017, led by Novartis Venture Fund and Columbus Venture Partners and including Roche Venture Fund, HealthCap, Kurma Partners and Ysios Capital, with plans to advance VTX-801 into the clinic. The company has other gene therapy programs in development for other rare liver disorders, including programs for progressive familial intrahepatic cholestasis type 2 (PFIC2), PFIC3 and citrullinemia type 1.

Pfizer could pay up to €560m ($635.8m), including the option to acquire Vivet outright, under the companies' agreement. The big pharma can exercise its option after Phase I/II data for VTX-801 is available. Pfizer VP-Worldwide Business Development Monika Vnuk will join Vivet's board of directors.

PFIZER'S GROWING GENE THERAPY PIPELINE

Pfizer has built much of its gene therapy pipeline through business development. In 2016, the company acquired **Bamboo Therapeutics Inc.** for $645m, bringing in adeno-associated virus vectors for neuromuscular conditions, including what is now a clinical-stage candidate for Duchenne muscular dystrophy. Data from the first human trial is expected in the first half of 2019.

The partnership with Bamboo came about in a similar manner, in that Pfizer initially acquired a 22% stake for $43m and then later the same year acquired the company outright for $150m plus $495m contingent on certain milestones.

Pfizer is also partnered with **Spark Therapeutics Inc.**c. on the development of a gene therapy to deliver the human coagulation factor IX gene to liver cells in patients with hemophilia B under a 2014 alliance. The program, SPK-9001, is in Phase III development, although Spark is in the midst of an ownership transition. Big pharma rival Roche announced plans to buy Spark for $4.85bn in February.

Under another partnership, Pfizer is developing a hemophilia A gene therapy with Sangamo under a 2017 agreement in which it paid $70m up front. The two partners signed a second agreement in 2018 for a gene therapy collaboration in amyotrophic lateral sclerosis (ALS).

Business development in gene therapy has been booming recently, as many industry observers forecast it would be as big players line up to get their foot in the maturing development area. Roche's deal for Spark turned out to be a competitive bidding process, according to filings with the Securities & Exchange Commission.

Biogen revealed earlier in March a deal to buy ophthalmology gene therapy developer Nightstar for $877m.

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Biohaven Pays $105m For Turbo Boost In Migraine Drug Review Race

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Connecticut-based **Biohaven Pharmaceutical Holding Co. Ltd.** has paid $105m for a US FDA priority review voucher that it intends to use in the second quarter of 2019 to speed the regulatory review of its oral migraine candidate rimegepant. Use of the voucher could cut the review period from 10 to six months.

Since the use of a voucher to expedite a new drug application requires 90 days' notice, it would appear that Biohaven intends to file rimegepant in the latter part

of June 2019. Such a filing would provide for a speedy six-month review of the drug, which is being filed as rimegepant Zydis ODT (orally disintegrating tablet) for the acute treatment of migraine.

Biohaven is in a race against **Allergan PLC** with its similar oral CGRP inhibitor ubrogepant.

On March 13, Biohaven revealed it had concluded pre-NDA meetings with the FDA for both orally dissolving tablet and tablet formulations of rimegepant for the acute treatment of migraine, and planned to proceed with a filing in the second quarter.

Allergan, meanwhile, announced the FDA's acceptance of its own NDA for ubrogepant to treat acute migraine on March 11.

Ubrogepant is subject to a standard 10-month review period with a PDUFA date in the fourth quarter of 2019. Rimegepant's submission before the end of June could would potentially mean it would receive approval in the first quarter of 2020, since the six-month review period would take effect after the 60-day filing date.

While Allergan has talked up the lack of hepatic side effects in trials of ubrogepant, something which has hampered previous attempts to develop oral CGRP inhibitors, Biohaven has been emphasizing the speed of onset of its fast-dissolving tablet and its long durability, claiming that ubrogepant's four-hour half-life compares unfavorably to rimegepant's 8-12 hours. It has also talked up the fact that patients treated with Zydis ODT had not required rescue medications or a second dose, unlike ubrogepant in its Phase III program. Biohaven also believes the orally dissolving tablet formulation is preferable to tablets that must be taken with water, since migraine patients often experience nausea and vomiting.

Separately, **Eli Lilly & Co.**'s lasmiditan, another oral drug candidate for the acute treatment of migraine, was submitted for FDA review in the third quarter of 2018. Lasmiditan is a serotonin receptor agonist that selectively targets 5-HT1F receptors in the trigeminal nerve pathway. An approval decision for lasmiditan is likely sometime in October or November 2019.

Both Allergan and Biohaven are also developing oral CGRP receptor antagonists for migraine prevention, but Allergan is more advanced as its atogepant is in Phase III while Biohaven plans to complete enrolment in its Phase III trial of rimegepant for migraine prevention in the second quarter of 2019, and begin a Phase II/III trial of its third-generation CGRP-receptor antagonist BHV-3500 in the first quarter of 2019.

The firms are hot on the heels of a raft of recently approved injectable monoclonal antibody migraine prevention products also targeting calcitonin gene-related peptide from **Amgen Inc./Novartis AG** (Aimovig/erenumab), **Teva Pharmaceutical Industries Ltd.** (Ajovy/fremanezumab) and Lilly (Emgality/galcanezumab).

VOUCHER MARKET

Biohaven's priority review voucher was apparently purchased from **GW Pharmaceuticals PLC**, which was awarded the voucher under the FDA's incentive program for the development of treatments for rare pediatric diseases. GW Pharma received the PRV when it won approval for *Epidiolex* (cannabidiol) in June 2018 for the treatment of seizures in two rare, severe, childhood-onset epilepsies, Lennox-Gastaut syndrome and Dravet syndrome. The UK-domiciled firm intends to invest the $105m proceeds in the commercial launch of Epidiolex in Europe and the US, and in advancing its pipeline of cannabinoid product candidates.

The market value of priority review vouchers has fluctuated since the first acquisition in 2014, when **Regeneron Pharmaceuticals Inc.** and **Sanofi** bought **BioMarin Pharmaceutical Inc.**'s for $67.5m, still the lowest price on record. The highest price paid was $350m, paid by **AbbVie Inc.** to **United Therapeutics Corp.** in 2015.

Details of such purchases are not always disclosed: **Novo Nordisk AS**, for example, recently revealed that it had booked the purchase of a PRV in fourth-quarter accounts, to expedite the filing for its oral GLP-1 analogue semaglutide, but it did not disclose the source of the voucher, nor the price paid. However, since 2016 the going rate appears to have stabilized at around $100-130m, with the odd outlier. Lilly managed to pick one up for $80m in November 2018, acquiring that obtained by **Siga Technologies Inc.** under the material threat medical countermeasure program in July 2018 with the approval of its oral smallpox treatment. And Teva paid up to $150m for a PRV in 2017, which it subsequently used to expedite the approval of Ajovy.

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Cancer, Rare Disease Drugs To Be Covered As China Expands Reimbursement

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Pharmaceuticals that have gained approvals before Dec. 31, 2018 will be subject to consideration for a new expansion of China's National Reimbursement Drug List (NRDL), with priority to be given to national essential drugs, cancer and rare disease medicines, treatments for chronic disorders, pediatric medications and urgent care products.

Outlined in the 2019 National Healthcare Product coverage adjustment work plans, released by the country's Medical Insurance and Support Administration (MISA), the reimbursement of the products will be divided into two categories under the list.

One is direct inclusion, comprising regular products priced lower or similarly to currently listed drugs, meaning that the inclusion will not impact the bottom line of the existing medical insurance funding pool.

The other category will be high-priced products, which must go through the national price negotiation system to have their prices lowered before they can be included in the NRDL.

LARGE EXPERT POOL

To ensure a fair process, the NRDL inclusion procedure will involve tens of thousands of experts in roles ranging from consultants to selection committee members, health technical assessment experts and other negotiators.

Among these, 300 will serve as consultants to compile a comprehensive list of the drugs for the initial selection process. After that, 20,000 experts from different provinces and local hospitals will vote to select which final products to include in the NRDL.

Also, the state medical insurance agency plans to involve 30 insurance experts and health technology assessment (HTA) analysts to evaluate the cost-effectiveness of the products and impact on insurance funding. Especially for the high-priced drugs, past price negotiations have seen price reductions on average exceeding 50%.

For the drug price negotiation rounds, an unspecified number of negotiators selected from the local and central medical reimbursement agencies and outside experts will work to oversee the negotiation process with the drug makers.

Despite the large expert pool required for the NRDL expansion process, the timeframe is quite tight. The whole procedure will be divided into five phases -preparation, evaluation and voting, release of direct inclusion products, negotiations, and release of the inclusion of high-priced drugs.

The preparation period will be the first three months in 2019, requiring the selection of the experts and setup of product databases. From April to May, the consulting experts will compile candidate products, and the 20,000 selection experts brought together from different levels of hospitals in two-thirds of China's 31 provinces.

Meanwhile, the consulting experts will finalize the products to be included in the direct inclusion list and release the list in June. Also, consulting experts will decide on high-priced products that are subject to price negotiations, and send negotiation requests to manufacturers.

These discussions then kick off in July and the final list will be released in August.

Expanding patient access to innovative new drugs has been a top priority for the reimbursement agency, as well as one of the top catalysts for the development of the healthcare sector in China in the years to come.

WHO WILL BENEFIT?

Since many newer oncology and rare diseases treatments are imported by multinationals, many see the NRDL coverage expansion as opening market access for such firms.

Some oncology products that are likely to be included are: **Roche**'s lung cancer drug *Alecensa* (alectinib; licensed from Chugai Pharmaceutical Co. Ltd.), for anaplastic lymphoma kinase-positive disease, **Hutchison MediPharma Ltd.**'s *Elunate* (fruquintinib) for colorectal cancer, and **Eisai Co. Ltd.**'s *Lenvima* (lenvatinib) for patients with inoperable hepatocellular carcinoma who have not received any prior systemic therapy.

Domestic maker **Jiangsu Hengrui Medicine Co. Ltd.** has its TKI inhibitor *Iruini* (pyrotinib), indicated for breast cancer patients with HER2 and EGFR mutations, and Tianqing Chiatai Pharma's *Fukewei* (anlotinib) is for lung cancer.

Rare disease treatments could include: Roche's *Hemlibra* (emicizumab; licensed from Chugai) for hemophilia, and **Alexion Pharmaceuticals Inc.**'s *Soliris* (eculizumab) for paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome, as well as **Actelion Pharmaceuticals Ltd.**'s *Uptravi* (selexipag) for pulmonary hypertension.

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From the editors of PharmAsia News.

What Brexit Effect? UK Biotech Start-Ups Reach Record Numbers

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Despite the uncertainty over the UK's withdrawal from the European Union, the number of new British biotechnology companies has soared by 65% in the last three years, and investment in the industry has reached new highs.

Official data from Companies House, the UK executive agency that incorporates and dissolves limited companies, show that there are 3,456 active companies currently involved in biotech R&D activities. This represents a 65% increase from Q1 2016, when 2,095 active companies were classed as engaging in the same activity.

New analysis from investment manager Downing LLP suggests that 44% of the total number of active biotechnology businesses have been incorporated in the past three years, since January 2016. This includes 127 in the first two months of 2019, which is the equivalent to three every working day during January and February 2019.

One reason for this is the growth in genomic and data-driven science, Will Brooks, investment director at Downing told *Scrip*, which allows more powerful data and computation to improve the drug development path and in doing so decreases time and cost of development, as well as allowing more accurate diagnosis and treatment of patient populations. "This combination of data-driven technology and healthcare also means that the pool of capital is expanding with technology funds and companies now targeting the healthcare sector," he said.

The uncertainties of the UK's withdrawal from the European Union is clearly not having an impact on the confidence of UK biotech companies to raise capital, or to recruit employees with the right skills from the EU.

"The government has been very proactive with investment in R&D spending to support any EU shortfall, although how

long this may last is uncertain," said Brooks. "There has been a lot of investment both in new funding, but also in incubators and research parks that help offset costs."

Uncertainty over EU funding such as Horizon 2020 had caused some grant funds to drop off, he said. "Traditionally, the UK has not had high levels of EU investment from venture capital and so, while some funding sources may be cautious in the short term, UK-based companies should still continue to attract investment."

Echoing global trends, in which the biotech sector raised $23bn in venture capital in 2018, data from the BioIndustry Association (BIA) and Informa Pharma Intelligence's report *Confident capital: backing UK biotech* show that the UK claimed a new high of £2.2bn from investors in 2018, up by 85% from 2017. Venture capital has contributed 51% of UK biotech funding from 2016-2018, increasing by 63% from £681m in 2016 to £1.1bn in 2018. *(Also see "Biotech Sector Raises $23bn In Venture Capital In 2018" - Scrip, 3 Jan, 2019.)*

Steve Bates, CEO of the BIA, told *Scrip*: "Our finance report shows that the UK life sciences sector is thriving and remains attractive to investors. This further good news shows that companies feel confident starting their business in the UK and that infrastructure remains strong.

"2018 was a record year for investment in the UK life science ecosystem and despite the uncertainty of Brexit it's clear that the Government's Industrial Strategy and Life Sciences Sector Deal is moving our sector forward."

Brooks dampens the idea that this rate of funding is a bubble that will burst shortly after Brexit is complete. Once the terms of the Brexit withdrawal deal are understood, in whatever form it takes, he expects funding of the British biopharma industry to continue at its current rate, due to confidence in the "underlying technology".

While private limited companies still make up a large chunk of active businesses in the biotech sector – 96% – Downing's analysis shows the number of public limited companies has grown from 30 to 42. BIA figures show that IPOs contributed 15% of funds raised by UK biotech companies from 2016-2017, increasing to 20% in 2018, when over £1bn was raised on public markets: £432m in initial public offerings and £658m in all other public financing.

London is the lead location in Britain's biotech Golden Triangle

THE GOLDEN TRIANGLE

Over one-third of all biotech companies are now headquartered in the 'Golden Triangle' of UK innovation: London, Oxford and Cambridge. The number of biotech R&D businesses based in the capital has increased by 120% over the last three years, and it now plays host to nearly one in four registered businesses, compared to fewer than one in five in 2016.

Cambridge ranks second after London with 7.5% of biotech businesses located there in Q1 2019, followed by Oxford with 2.3% – the city's biotech business population has increased by 95% in just over three years.

Outside of the Golden Triangle, Nottingham and Manchester continue to make up the top five UK locations for biotech R&D activities.

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Merck KGaA: China E-Health Push A 'Long-Term Strategy'

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Merck KGaA aims to position itself as a key player in China's evolving digital healthcare system and will use recently established alliances with Chinese internet giants **Tencent** and **Alibaba Health** to do so, the German group's head of international operations told *Scrip*.

CHINA'S E-HEALTHCARE 'EVOLVING FAST'

Merck KGaA, which has a strategic interest in chronic diseases in China, tied up with Tencent in January to explore digital services aimed at raising awareness of allergic disorders and improve treatment compliance for allergy sufferers. "China is a market I know quite well and I think what is often underappreciated is the sheer level of digital progress that China has made in its internal markets," Chris Round said in an interview.

Chris Round

He said there was huge healthcare potential in Tencent's WeChat platform, which offers text messaging, voice messaging, voice and video calls in China.

"WeChat is very widely used in China, perhaps by as many as 700 million Chinese citizens. They are using it as a form of communication which often gets used in group discussions and as a plat-

form for online payments and online commerce," explained Round. "We've linked up with Tencent after trying to see if there are ways that we can provide targeted information – in a compliant and appropriate way that's not branded – to various groups in the Chinese healthcare system, and we're exploring opportunities for Tencent's platform and our commercial and medical teams to come together and to figure out ways that we can help support the roll-out of healthcare in China and the evolution of healthcare there."

Tencent, which launched a major strategic upgrade in 2018, is now actively embracing the so-called industrial internet in China, with the healthcare field being an important focus.

"We've got some really clear, defined, concrete proposals at this stage. It's a long-term collaboration and we're exploring all sorts of opportunities," Round said. He declined to say what those proposals were, however, saying that would be premature.

Round has responsibility for Merck Group's international businesses, comprising China, APAC, EMEA and LATAM, a role he took on under a regrouping of the family-controlled German conglomerate's healthcare executive committee last summer.

"As the environment in China gets more connected it will also become increasingly interesting what opportunities lie in the big databases and how they can lead to effective interaction – with physicians, with patients, with payers or with others."

Merck KGaA is also developing a strategic business collaboration with Chinese internet healthcare company Alibaba Health, to provide Chinese patients and their families with improved access to patient-centric healthcare services.

The collaboration will focus on the areas of drug track-and-trace and internet health services, and to jointly explore areas such as pharmaceutical e-commerce and artificial intelligence.

The collaboration will start with Alibaba Health's drug tracking platform, combining Merck's expertise in diabetes, thyroid disorders and cardiovascular diseases with Alibaba Health's online healthcare services to help ensure safety and security of drug use, while generating consistent value for patients through a series of add-on services.

The two companies will also explore online healthcare service applications, direct-to-patient models as well as artificial intelligence enabled healthcare applications.

> "We're exploring opportunities for Tencent's platform and our commercial and medical teams to come together and to figure out ways that we can help support the roll-out of healthcare in China and the evolution of healthcare there."

Asked if a similar digital health approach could be taken in other developing regions of the world, such as Latin America, Round replied: "It's a great idea. We would be open to taking this approach in other developing areas in theory once they are capable of doing so."

He explained: "Some of the principles such as how can one more efficiently use technology to communicate and disseminate the products would, in principle, be possible. But WeChat as a platform is somewhat unique to China. We could look for ways to replicate those aims and ambitions but essentially we're just trying to do what we've done in the past, but just more efficiently using technologies that may open up new opportunities for us as we move forward."

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Celgene/Bristol's Revlimid Patent Risk Incrementally Lower After PTAB Denies Alvogen IPR

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The final request for an *inter partes* review (IPR) of a **Celgene Corp.** *Revlimid* (lenalidomide) patent by the US Patent and Trademark Office (USPTO) Patent Trial and Appeal Board (PTAB) was denied March 14, somewhat reducing the intellectual property risk associated with **Bristol-Myers Squibb Co.**'s pending $74bn acquisition of the company.

Bristol-Myers has tried to keep investors focused on Celgene's research and development pipeline, which is designed to eventually replace the loss of Revlimid's blockbuster revenue stream, as an April 12 shareholder vote on the Celgene deal approaches. Regardless, shareholders can't get over the fact that the multiple myeloma drug, which will continue to account for about two-thirds of Celgene's revenue for at least another year or two, will begin to face generic competition in the US starting in 2022.

However, the risk of multiple Revlimid generics hitting the market before a single limited competitor in 2022 was reduced by the PTAB's decision regarding an IPR sought by **Alvogen Inc.** The PTAB said it was unlikely that the generic drug maker would prevail on at least one of the claims in a review of the 7,968,569 patent, which covers administration of Revlimid in combination therapy regimens to treat relapsed multiple myeloma.

Bernstein analyst Ronny Gal said in a March 14 note that this was the last of the

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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, 15–21 MARCH 2019

Event Stage	Lead Company/Partner	Drug Name	Indication	Comments	Change To LOA (%)	LOA (%)
Phase III Published Results	Amarin Corporation plc	Vascepa (icosapent ethyl)	Cardiovascular Disease	REDUCE-IT; Journal of the American College of Cardiology, March 18, 2019	0	51
Phase III Published Results	AstraZeneca/Bristol-Myers Squibb	Farxiga (dapagliflozin)	Diabetes Mellitus, Type II	DECLARE-TIMI58 (CV Events); Circulation, March 18, 2019	0	100
Phase III Published Results	Evolus, Inc.	Jeuveau (prabotulinumtoxinA)	Wrinkles	TRANSPARENCY; Dermatologic Surgery, March 21, 2019	0	100
Phase III Discontinuation	Biogen/Eisai	aducanumab	Alzheimer's Disease	ENGAGE, EMERGE; Unlikely To Meet Primary Endpoint	-35	19
Phase III Updated Results	GenSight Biologics S.A.	GS010	Leber's Hereditary Optic Neuropathy	REVERSE; Durable Responses	0	45
Phase III Updated Results	Esperion Therapeutics, Inc.	bempedoic acid	Dyslipidemia	CLEAR Wisdom; Met Endpoints	0	84
Phase III Updated Results	Samsung Bioepis/Merck & Co	Ontruzant (trastuzumab)	Breast Cancer	Biosimilar, Similar Efficacy To Reference	0	100
Phase II/III Updated Results	Amgen, Inc.	Repatha (evolocumab)	Dyslipidemia	TAUSSIG; Long-Term Safety Confirmed	0	100
Phase IIIb Top-Line Results	Roche Holding AG	Tecentriq (atezolizumab)	Bladder Cancer	SAUL; Safety Confirmed	0	100
Phase IIIb Top-Line Results	Daiichi Sankyo Co., Ltd.	Savaysa (edoxaban)	Stroke Prevention in Atrial Fibrillation	ELIMINATE-AF; Positive Results	0	100
Phase III Top-Line Results	Biofrontera AG	Ameluz (5-aminolevulinic acid)	Actinic Keratoses	w/BF-RhodoLED; Met Primary Endpoint	0	100
Phase III Top-Line Results	Farmacéuticos Rovi, S.A.	Doria (risperidone ISM), once-monthly Inj.	Schizophrenia	PRISMA-3; Met Endpoints	2	53
Phase III Top-Line Results	Urovant Sciences, Inc.	vibegron	Overactive Bladder	EMPOWUR; Met Co-Primary Endpoints	1	67

Source: Biomedtracker | Informa, 2019

CONTINUED FROM PAGE 21

outstanding IPR requests related to Revlimid, so its denial gives a little more assurance that an additional generic launch before 2023 is unlikely. The PTAB also denied an IPR request in February from **Dr. Reddy's Laboratories Ltd.** related to a Revlimid patent for treating myelodysplastic syndrome (MDS).

However, patent uncertainty is far from erased in the US with the denial of these IPR attempts. Celgene has multiple lawsuits pending against generics companies that filed abbreviated new drug applications (ANDAs) with the US FDA seeking approval for Revlimid copies.

These cases will take a few more years to work their way through the trial and appeal process unless Celgene enters into settlement agreements with its competitors, including Alvogen and Dr. Reddy's, the latter of which is the plaintiff in the most advanced of these lawsuits.

Even so, Gal said in his note that the benefit of the PTAB denial of Alvogen's IPR request "is two-fold: 1) the decision closes the loop one of the two potential venues to invalidate the Revlimid patent (before 2023). 2) As the same arguments will presumably be presented at trial, odds of eventual win by Celgene are higher."

"Critically," he continued, "a quick read of the IPR shows the IPR decision was made on the merits, i.e. the judges considered the evidence presented by Alvogen and found it insufficient to meet the minimal threshold for review. This view (by judges with background in the field) will have weight before the court."

BILLIONS IN REVLIMID SALES AT STAKE

What's at stake if Celgene loses in any of these cases is billions of dollars in sales and a majority of the company's revenue, which will take years to rebuild through sales of new products. None of these are guaranteed to be approved or to quickly become big sellers.

That's why investors in both Celgene and Bristol want to make sure, if the companies' transaction closes in the third quarter as anticipated, the merged entity will be able to hold on to as much Revlimid revenue as they can for as long as possible. Revlimid generated global sales of $9.69bn in 2018, which was 63% of Celgene's total revenue of $15.28bn last year.

The company insists that Revlimid revenue will continue to grow by double digits annually at least through 2022, when **Natco Pharma Ltd.** and partner **Teva Pharmaceutical Industries Ltd.** are allowed under a 2015 US patent litigation settlement to begin a limited generic Revlimid launch. Full generic market entry in the US isn't expected until 2026.

Alvogen recently claimed a lead in the race to bring generics to the European market with the first launch of Revlimid generics in Europe in February, but this occurred in small markets – Central and Eastern European markets, including Romania, Croatia, Bulgaria and the Baltic states.

Bernstein's Gal sees US sales peaking at $11.76bn in 2023 assuming no generics other than a Natco-Teva product launch before 2027.

Published online 14 March 2019

To read this story in full please go to:
https://bit.ly/2JJxLWu

APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
Joachim Fruebis	BlueRock Therapeutics	Chief Development Officer	Bioverativ	Senior Vice President, Clinical Development	18-Mar-19
Bryan Reasons	Mallinckrodt plc	Chief Financial Officer	Impax Laboratories	Senior Vice President and Chief Financial Officer	18-Mar-19
Hsiao D. Lieu	NGM Biopharmaceuticals Inc	Chief Medical Officer and Senior Vice President	Genentech	Vice President, Early Clinical Development	20-Mar-19
Ran Zheng	Orchard Therapeutics	Chief Technical Officer	Amgen	Vice President, Development Supply Chain	18-Mar-19
Martin B. Brenner	Pfenex Inc	Chief Scientific Officer	Recursion Pharmaceuticals	Chief Scientific Officer	18-Mar-19
John Temperato	RDD Pharma Ltd	Chief Executive Officer	Atlantic Healthcare plc	President, US and Chief Operating Officer	20-Mar-19
Andrew Pucher	Tilray	Chief Corporate Development Officer	Goldman Sachs	Managing Director	13-Mar-19

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