



## Merck KGaA Plays Down Mavenclad Label And \$99,500 Annual Price For 10 MS Pills

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After a long, circuitous journey, Merck KGaA's oral multiple sclerosis drug *Mavenclad* (cladribine) has finally won approval in the US, but analysts are uncertain whether its mixed label will hinder uptake there.

The US label says *Mavenclad* is for second-line use in relapsing forms of multiple sclerosis (MS), to include relapsing-remitting disease (RRMS) and active secondary progressive disease (SPMS). (Also see "Keeping Track: Approvals For Mayzent, *Mavenclad*, *Duaklir*, *Jatenzo* And *Cimzia*" - *Pink Sheet*, 31 Mar, 2019.) The treatment requires a maximum of 20 days of oral

therapy to deliver two years of efficacy to a patient. No top-up use will be allowed in years three to four, a point that may some analysts said make value-based contracting more difficult.

It also carries black box warnings on malignancies and teratogenicity risks for pregnant women, so contraception is recommended during *Mavenclad* dosing and for six months after the last dose.

### LABEL MAKEUP

Analysts at Bernstein said the inclusion of SPMS on *Mavenclad*'s US label was a positive "surprise", but added: it is "likely

to reflect a changing in FDA language and disease classification, nothing more."

They did however voice disappointment the therapy was being limited to second-line treatment, saying that they had "seen some potential for its use as first-line treatment [in MS]."

The analysts noted, "With the exception of the notoriously unsafe *Lemtrada* (alemtuzumab), *Mavenclad* is the only MS product recommending use in latter lines, something that we feel unfairly draws attention to what is actually not that bad a safety profile." Adding that the *Mavenclad* label's teratogenicity warning is 'a first' from a MS black box warning perspective, analysts at Bernstein said its inclusion was "not helpful, and could be considered a hindrance to uptake, although we do question to what extent."

### 'DEMOCRATIZING' PILL

Merck KGaA will charge \$99,500 annually for 10 *Mavenclad* pills. Despite that high price per pill, the German group expects the drug to have a good reception in the US.

"The reason is, that this drug is taken as oral tablets with a maximum of 20 treatment days over two years. The way this is administered is in two treatment courses in years one and years two. So this means a total of 10 days of treatment this year and 10 days of treatment next year for a total of 20 treatment days over two years," Rehan Verjee, global head of Merck KGaA's innovative medicine franchises, told an analyst call on April 1.

Verjee noted that since 2017, *Mavenclad* has been approved in over 50 countries, comprising the US, across Europe, in Canada, Australia and Switzerland.

"So we now have a lot of experience, actually, in doing this and we think that this

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from the editor

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With the rapid expansion in cell and gene therapy comes the need for rapid scale-up of production.

Responding to this demand, contract development and manufacturing organizations (CDMOs) are expanding their own specialized manufacturing capacities, whether through acquisition like that of Brammer Bio by Thermo Fisher last month, or through internal investment, like Lonza, Yposkesi or Fujifilm.

At the same time, pharma and biotech are building in-house capacity. Novartis's strategy of expanding the production under its own roof continues with its latest purchase of an advanced biologics manufacturing facility in Colorado from AstraZeneca (see p7). It's also building a new site in North Carolina and expanding a facility in San Diego, as well as investing in Europe and APAC.

The AZ site purchase is aimed at meeting demand for Zolgensma, the gene therapy for spinal muscular atrophy that is expected to be approved by the US FDA this year, as well as for new gene therapies coming through its pipeline. It may also provide manufacturing services to third parties.

At this early stage in the development of this segment of industry, companies like Novartis retain flexibility and control by keeping manufacturing in-house, and with the escalation in demand for such facilities the opportunity to offer contract manufacturing is attractive.

But Novartis found out the hard way how critical manufacturing is in the new era of advanced therapies. Problems with its manufacturing process for the CAR-T therapy Kymriah have held it back while Gilead Sciences' rival CAR-T treatment Yescarta has seen sales gather pace much more quickly (see p13).

# Scrip

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## NGM Bio Is Second NASH IPO In Two Weeks

MANDY JACKSON [Mandy.Jackson@informausa.com](mailto:Mandy.Jackson@informausa.com)



**NGM Biopharmaceuticals Inc.** launched the ninth biopharmaceutical initial public offering in the US this year and was the second non-alcoholic steatohepatitis (NASH) drug developer to initiate an IPO in 2019, but the company's stock didn't fare as well as NASH company **Genfit SA's** shares a week earlier.

South San Francisco-based NGM Bio priced 6.67m shares at \$16 each on April 3 to net \$95.7m before the sale of additional shares to meet overallocments; it also will net \$65.9m from a concurrent private placement of shares with its partner **Merck Sharp & Dohme Ltd.** But while the offering went to the market at the top of a proposed \$14 to \$16 range, NGM Bio's stock closed its first day of trading below the IPO price at \$14.70 on April 4, regaining some of its value to close at \$15.10 on April 5.

Genfit's NASH pipeline is more advanced than NGM Bio's, with a top-line Phase III readout for Genfit's lead candidate elafibranor expected later this year, which may be why its stock has traded above its March 26 IPO price of \$20.32 per American depository share (ADS) since the offering to close at \$23.94 on April 5. The French firm closed the offering on March 29, bringing the gross proceeds to \$155.4m, including overallocments.

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is going to be actually quite unique and again, a real opportunity for patients here in the US, particularly when you consider the vast geography and sometimes the difficulty for patients in terms of actually being able to come in and see their neurologist," Verjee added.

"You can talk about patients traveling hundreds of miles and so again, this is really going to offer, in a sense, the democratization of high efficacy therapy," he said.

**"It will face a tough competitive environment with Roche's disease-modifying agent Ocrevus (ocrelizumab) approved in March 2017 and generating CHF2.4bn (\$2.3bn) in annualized sales in the US alone."**

#### COMPETITION CLOUDS

The timing of Mavenclad's US approval is consistent with Merck Group's previous expectations. The drug will be rolled out in coming days there.

Merck has pinned much of its recovery prospects on the medicine, a nucleoside analogue whose novel mechanism of action disrupts DNA synthesis, selectively depleting B and T lymphocytes, or white blood cells. The company on its analysts call confirmed its aim is to deliver €2bn in pipeline sales by 2022.

Still, many analysts say that goal is over ambitious, and that Mavenclad will face stiff competition. Bryan Garnier & Co said in a reaction note that "even though Mavenclad is now approved in the US, it will face a tough competitive environment with Roche's disease-modifying agent Ocrevus (ocrelizumab) approved in March 2017 and generating CHF2.4bn (\$2.3bn) in annualized sales in the US alone."

Merck KGaA said it still projects global Mavenclad sales this year coming in at "mid-triple-digit millions of euros". ▶

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## Galapagos Flies As Filgotinib Soars In FINCH Studies

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The JAK inhibitor class is getting crowded but new data from two high-profile rheumatoid arthritis trials on Galapagos NV and Gilead Sciences Inc.'s filgotinib suggest their drug can compete, especially as its safety profile appears superior to rival therapies.

The companies have reported headline results from the FINCH 1 and FINCH 3 trials which showed that filgotinib, an oral selective JAK1 inhibitor, achieved its primary endpoints of ACR20 (ie a 20% improvement in symptoms) at weeks 12 and 24 in both studies. Specifically, in FINCH 1, daily oral dosing with filgotinib 100 mg and 200 mg demonstrated significantly higher ACR20, 50 and 70 responses than placebo in patients with moderate-to-severe RA who were not responding to methotrexate alone, and also showed non-inferiority to AbbVie Inc.'s mega blockbuster Humira (adalimumab).

In FINCH 3, filgotinib monotherapy was as effective as methotrexate on the ACR20 measure, but was significantly better for the ACR50 and ACR70 scales. Full details will be presented at a forthcoming scientific conference, possibly the EULAR meeting in Madrid in June.

The results add to the positive data presented last year from FINCH 2 and represent a much-needed boost for Gilead as it addresses sliding sales from its lucrative hepatitis C franchise and the disappointment of a failed Phase III study of its non-alcoholic steatohepatitis (NASH) treatment earlier this quarter. As for Galapagos, its shares shot up March 29 as the Mechelen-headquartered firm, which is celebrating its 20th anniversary, took a big step closer to bringing its first medicine to the market. (Also see "In NASH, Gilead Swung For The Fences And Struck Out Again" - *Scrip*, 12 Feb, 2019.)

In an interview with *Scrip*, Galapagos CEO Onno van de Stolpe said that "the nice reception from the markets and analysts" to the latest FINCH results supports Galapagos' view that filgotinib "will make a big difference because of the safety con-



Onno van de Stolpe

cerns seen with others in the JAK class" and "ours clearly has a different profile from the competition." He added that if one combines that with the efficacy and convenience filgotinib offers, "we will have a great chance to capture a sizeable part of the market."

Van de Stolpe said that "if you want to be seen as serious as a company you need to have a commercialization organization," noting that the firm plans to promote filgotinib independently in the Benelux region (Belgium, the Netherlands and Luxembourg), "where we will book sales, medical affairs, everything," and co-promote in the four largest European countries alongside Gilead; the latter will be responsible for commercialization in all other geographies.

This approach "gives us an opportunity to build this out with relatively little risk. I think it's a good move for us to do it step by step." In terms of filing filgotinib, van de Stolpe said "as fast as possible," noting that the firms are working on a dossier that will go to the European Medicines Agency in the summer and "we hope to get approval by the end of the summer next year."

While its focus is mainly on RA at the moment, Galapagos sees filgotinib as a franchise in a product. Evaluated in over ten indications, it is also in Phase III for Crohn's disease and ulcerative colitis, while in September 2018, the TORTUGA Phase II trial of filgotinib in ankylosing spondylitis met its primary endpoint, with again favorable safety data. Readouts of Phase II trials in Sjögren's syndrome and cutaneous lupus are anticipated this year and a Phase III trial in psoriatic arthritis is expected to begin before the end of 2019. (Also see "Filgotinib Shaping Up To Be Success Story For Gilead and Galapagos" - *Scrip*, 31 May, 2018.)

Van de Stolpe told *Scrip* he believes JAK small molecules "are going to take over from the antibody markets, the TNFs and IL-6s, because of the fast onset action - you see activity with one week, not two months like with some of the biologics - and the convenience of oral versus injections. And, as all the analysts are saying today, we're the best in class based on safety."

If approved, filgotinib will probably be the fourth JAK inhibitor for RA after **Pfizer Inc.**'s blockbuster *Xeljanz* (tofacitinib), **Eli Lilly & Co.**'s *Olumiant* (baricitinib) and **AbbVie**'s upadacitinib which has been submitted for US approval, with a decision expected in the third quarter. Analysts at Jefferies issued a note saying FINCH 1 and 3 data are positive with efficacy broadly similar to upadacitinib but "crucially, we see safety as impressive, which is an important differentiator and could be key to drive uptake despite likely being the fourth JAK inhibitor to market."

Baird analyst Brian Skorney noted that composite safety data from the FINCH 1, 2 and 3 trials show that across the 2,088 patients enrolled, less than 0.1% experienced deep venous thrombosis/pulmonary embolism and only 0.2% had a major adverse cardiac event during the 24 week-long trials. Notably, both of these rates were lower than those observed in the 1,039 patients randomized to placebo/standard of care in which the

rate of events were 0.3% and 0.5% for DVT/PE and MACE, respectively. Galapagos also unveiled a 2,203 patient year safety analysis of patients who were enrolled in the Phase IIb DARWIN 3 long-term extension trial and had taken filgotinib for a minimum of three years. It found that annual rates of DVT/PE and MACE were both 0.1%.

Skorney noted that when approved, *Olumiant* was slapped with a black box warning for thrombosis, and *Xeljanz* was recently found to increase rates of thrombosis in a postmarketing trial. He believes all the safety data "should provide strong assurance to the FDA with regard to the cardiovascular safety of filgotinib." (Also see "Lilly Prices *Olumiant* For JAK Battle, But Misses Approval For Higher Dose" - *Scrip*, 2 Jun, 2018.)

The Jefferies analysts are predicting \$6bn peak sales, with \$3bn of that coming from the RA indication. They said that US filing timelines will depend on FDA discussions by Gilead and the availability of Phase II MANTA male safety data, expected around the third quarter, while van der Stolpe told *Scrip* its partner will be speaking to the agency about the FINCH studies and hopes to go as fast as possible with the US submission.

It all looks pretty positive for filgotinib and analysts at Leerink said its large registrational trials "could potentially make this drug the poster child for JAK inhibitors, as they were intended to perform, but have fallen short due to lack of dose response, poor safety profiles and incremental real world efficacy." Analysts at Credit Suisse issued a note saying that the "Galapagos story is now more than just filgotinib," pointing to Phase III trials for proprietary therapy GLPG1690 in idiopathic pulmonary fibrosis and Phase II studies in osteoarthritis (GLPG1972) and atopic dermatitis (**MorphoSys AG** co-developed MOR106), partnered with **Servier SA** and **Novartis AG** respectively. ▶

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## Expert View: No-Deal Brexit's Legal Fallout For Pharma

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There is some trepidation around how things will unfold with respect to legislative, patent-related and other norms for pharma in the event of a "no-deal" Brexit, despite preparatory steps by various agencies in the UK and EU to ensure a generally smooth transition. The rejection of UK Prime Minister Theresa May's Brexit deal by MPs for the third time on March 29 has only led to more uncertainty in an already highly complex situation. (Also see "UK Industry Skeptical Of Govt's No-Deal Brexit Filing Expectations" - *Pink Sheet*, 18 Feb, 2019.)

In a wide-ranging interview with *Scrip*, Dr Jonathan Atkinson, a partner at the UK-based intellectual property law firm HGF Ltd, clarifies the current and expected situation for pharma around some key aspects, in areas ranging from patent litigation and trademarks to new regulatory nuances that could impact pharma M&A deal value.

Atkinson, who has been associated with some high profile pharma issues, including being part of the patent drafting/procurement team for *Viagra* (sildenafil citrate) and being involved in prosecution and litigation pertaining to *Augmentin* (amoxicillin-

clavulanate), also outlined the complexities around the UK's participation in the Unified Patent Court (UPC). The proposed court common to the contracting member states of the EU is expected to limit costly parallel litigation and improve legal certainty.

**Q:** In terms of M&A, what are the key regulatory changes in store for Asian firms making acquisitions in the EU or UK, in a post Brexit era?

**A:** The key regulatory changes which impact M&A deal value are: 1) Marketing Authorisation - Centrally Authorised Product and products approved in the UK via a decentralized procedure, become UK marketing authorized (MA); 2) orphan drugs - the UK is to introduce a system for rare disease medicinal products with orphan status determined at the point of MA as is the case in the current EU system but based on UK-specific criteria. The EU pre-MA orphan designation will not be replicated in the UK on the basis it would not offer an additional incentive; 3) pediatric therapies - the same SPC/exclusivity rewards for pediatric

investigation plan (PIP) compliance will be available; 4) data/market exclusivity – no changes are currently proposed, but the UK government has said that it will review this within two years of the exit from the EU in order to make sure the UK remains competitive. The start of exclusivity is currently proposed to be the date of authorization in the EU or UK, whichever is earlier. There is lobbying for it just to be the date of authorization in the UK; 5) abridged applications – from exit, in the UK these can be based only on UK authorized reference products; and 6) legal presence – the following must have a legal presence in the UK (and vice versa for the EU) - a) a marketing authorisation holder (MAH) b) Qualified Persons (QP) for batch release/pharmacovigilance/orphan drug sponsor (PV)/clinical trial sponsor c) MAH in UK by end of 2020/QPPV immediately (EU QPPV allowed until end of 2020).

In the case of a UK MAH, this can be delayed until the end of 2020. In the case of a QPPV for the UK, an EU QPPV will be allowed until the end of 2020. Further guidance note on the regulation of medicines, medical devices and clinical trials if there's no Brexit deal is here. The Human Medicines (Amendment etc.) (EU Exit) Regulations 2019 will govern most of these changes.

**Q:** The EU Clinical Trials Regulation is expected to be implemented from 2020; what would this mean for Asian or other companies that expect to place trials in the UK and the rest of the EU in terms of separate approvals, Ethics Committees, legal requirements, etc?

**A:** Separate approvals will be needed in the EU and in the UK. The UK will, however, continue to recognize existing approvals - both for regulatory and ethics approvals – and there will be no need to re-apply. The EU requires the sponsor or legal representative of a clinical trial to be in the EU. The UK would require the sponsor or legal representative of a clinical trial to be in the UK or on an approved country list, which would initially include EU/EEA countries. The import of the investigational medicinal product into the EU is subject to the holding of an authorization, where any part of the manufacturing is performed outside of

the EU. The holder of this authorization has to have a qualified person in the EU to deal with batch release. MHRA has indicated that the UK government's present intention is to seek to mirror the EU Clinical Trials Regulation in the UK so far as is possible.

**Q:** Have there been any major challenges for foreign/Asian firms in activities like transitioning all decentralized procedures where the UK was a Concerned Member State into national registrations with UK as MAH?

**A:** The MHRA is seeking to make the transition as smooth as is possible. All medicinal products approved in the UK on or before the day the UK leaves the EU via a Decentralised Procedure have been issued with a UK marketing authorisation. This happens automatically unless the MAH opts out. MHRA has already contacted MAHs about this. Where the procedure has not been completed when the UK exits the EU, MHRA will complete the assessment as a UK national procedure, with no additional charges. Undecided EU procedures will not be valid in UK, but MHRA will take EU decisions into account where possible. MHRA has issued Guidance on handling of Decentralised and Mutual Recognition Procedures in a no deal scenario. There may be some

delays as MHRA takes on an increased workload.

**Q:** And will EU trademarks already registered by pharma firms in Asia or elsewhere continue to be enforceable in the UK or will there be re-registration requirements? Can these be cloned for the UK as suggested by some experts?

**A:** At the point that the UK exits the EU, the UKIPO [Intellectual Property Office] will automatically convert the UK part of an EUTM [or Community Registered Design] to an equivalent UK TM [trademark] or DR [design right]. The converted TM or DR will be treated as if it had been applied for an registered under UK law. There will be the ability for owners to opt out. In terms of validity and enforcement, use of the EUTM in any of the EU27 countries within five years before exit day will be considered as proof of use of the equivalent UK trademark. For EU trademark and Community design applications pending at the date of exit, applicants will be able to refile with the UKIPO. This opportunity will be available for nine months after exit [at the applicant's expense] and the UKIPO will recognize filing dates, claims to earlier priority and UK seniority recorded on the equivalent EU application.

**Q:** Would a no-deal Brexit/extension of Article 50 in any way impact the UK ratification of the Unified Patent Court (UPC) Agreement that enables a single judgment on patent disputes across its contracting states?

**A:** Potentially. The UK has ratified the UPC Agreement and stated its intention to stay in the UPC and unitary patent system after Brexit. The UPC is not yet operational, however, as Germany - one of three required signatories with the UK and France - has not ratified. The German parliament has recently recommended rejecting a complaint made in relation to the national UPC legislation but the constitutional complaint to the German courts remains pending. If the UK exits in the next few months on a no-deal scenario then it is likely to make participation more difficult than if the UPC were to launch while the UK was still an EU Member



“Separate approvals will be needed in the EU and in the UK. The UK will, however, continue to recognize existing approvals”

State or in a transitional arrangement. There has been discussion about amending the UPC Agreement to allow the UK to continue to participate after Brexit [including hosting the London Central Division Court]. Even if a deal is agreed and there is the political will to amend the agreement to allow a post-Brexit UK to participate, there remains uncertainty as to the ability of the UK to participate when it would be outside of the CJEU's [Court of Justice of the European Union] jurisdiction. I have personally submitted an application to be a London Central Division Court judge but the recruitment process has been put on hold pending resolution of the above issues.

**Q:** What would it mean for pharma disputes ongoing in the UK or EU?

National EP [European Patent] patent litigation will remain unaffected as the EPC [European Patent Convention] is not an EU agreement. However, where EU Directives or Regulations are also engaged [eg, SPCs - Supplementary Protection Certificates] then there is potential for disruption to ongoing cases in the event of a no-deal Brexit as the UK Courts standing for referrals will no longer exist nor will UK Courts be required to implement CJEU decisions. The transitional arrangements [if engaged as part of a deal] provide for existing cases to carry on and for UK judges to have regard to existing CJEU case law up to the date of exit.

**Q:** There is also the Falsified Medicines Directive that introduces EU-wide rules for the importation of active substances. In the event of a no-deal

Brexit and against the backdrop of the UK's Statutory Instruments The Human Medicines (Amendment etc.) (EU Exit) Regulations 2019 draft legislation, how would exporters to the UK need to prepare? Do you see any risk of confusion/ undue detention of consignments?

**A:** In relation to the Falsified Medicines Directive [FMD], the MHRA has indicated that it is likely that a UK-specific scheme will be introduced along the same lines as the directive. We do not foresee any issues with the detention of consignments because of the FMD. In a no deal Brexit situation, the UK will no longer be covered by the system. In any event, there is currently no mechanism for the detention of consignments that do not comply with the FMD. ▶

Published online 3 April 2019

## Novartis Prioritizes Gene Therapy Production With AZ Facility Buy

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With US approval expected next month of Zolgensma, its eagerly anticipated gene therapy for spinal muscular atrophy, **Novartis AG** is buying another manufacturing plant, this time from **AstraZeneca PLC**, so it is ready to meet the challenges of producing the treatment and future gene therapies.

The Swiss giant's **AveXis Inc.** unit, bought last year for \$8.7bn, has signed an agreement to purchase an advanced biologics therapy manufacturing campus in Longmont, CO, from AstraZeneca. The UK major announced earlier this year that it was planning to shutter two Colorado plants (Longmont and Boulder) and lay off 210 workers, but the Novartis purchase means many of them will not have to go job-hunting. (Also see "Novartis Goes Big On Gene Therapy With \$8.7bn AveXis Acquisition" - *Scrip*, 9 Apr, 2018.)

AveXis said that it planned to offer positions "to all approximately 150 employees previously employed at the site, and to announce further expansion of new jobs in the near term." Financial details of the purchase have not been disclosed but Novar-



Novartis builds up gene therapy manufacturing capacity

tis noted that the six-building Longmont campus with about 700,000 square feet would become the largest of the company's four facilities involved in the manufacturing of gene therapies.

AveXis currently has a fully-operational facility in Illinois and is building another in North Carolina, which is scheduled to be operational in 2020. The latter, in Durham,

is costing \$115m, while product development capacity at a facility in San Diego is also being expanded.

Longmont, along with the other three sites "will play a crucial role in helping us achieve the future manufacturing capacity required to meet the global patient need for novel gene therapies," Andrew Knudten, head of global strategic opera-

tions, said in a statement. First up will be *Zolgensma* (onasemnogene abeparvovec-xioi), which was granted a priority review by the FDA for SMA type 1 and a decision is expected in May. The drug is due to receive approval in Japan and the European Union later this year. (Also see "Price 'Anchoring'? *Zolgensma* And The Art Of Managing Gene Therapy Sticker Shock" - *Scrip*, 19 Mar, 2019.) (Also see "Novartis Pharma CEO Sees *Zolgensma* Supplanting *Spinraza*" - *Scrip*, 1 Feb, 2019.)

The incidence of SMA is approximately one in 10,000 live births and is the leading genetic cause of infant mortality. Meeting demand with a gene therapy is a complicated business and last month, Greg Gara, vice president of technical operations and engineering for AveXis, noted at a meeting attended by *Scrip's* sister publication *Pink Sheet* that manufacturers should consider that gene therapy processes "can require a significant amount of labor."

He added that "I am a stainless steel biologics guy and when I first came into gene therapy, I was amazed at how much labor it takes to run these processes. I'm used to transfer panels and opening things up. Not with this process. Our process uses disposable equipment and is very labor intensive."

AveXis president Dave Lennon said the company's success "requires not just medical breakthroughs, but innovations in R&D and manufacturing. With the opening of our fourth location in the US, we will create more than 1,000 high-tech biologics manufacturing jobs by the end of 2019."

He went on to say that the firm "has now established leading technical manufacturing capabilities with the capacity to deliver our robust pipeline." After *Zolgensma*, AveXis plans to develop treatments for other rare neurological diseases, including Rett syndrome and a genetic form of amyotrophic lateral sclerosis caused by mutations in the superoxide dismutase 1 (SOD1) gene.

Having assembled such expertise and invested heavily, AveXis will also look to offer its services to other players in the field. Lennon argued that the expanded capability being put in place gives the firm "the flexibility to enter into multiple external partnerships as the development and manufacturing partner of choice in gene therapy." ▶

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# Hemophilia A Gene Therapy Race Intensifies With Updated Sangamo/Pfizer Data

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Positive early data on Sangamo Therapeutics Inc./Pfizer Inc.'s gene therapy for hemophilia A at a higher dose cohort have put momentum behind the program, but the partners are up against rivals BioMarin Pharmaceutical Inc. and Spark Therapeutics Inc., two companies that are further ahead in the race to bring the first gene therapy for the blood disorder to the market.

Pfizer and Sangamo reported interim data April 2 from the Phase I/II Alta study, showing SB-525 was well tolerated and demonstrated a dose-dependent increase in Factor VIII levels across four dosage cohorts. A safety monitoring committee recommended the high dose cohort – 3e13 vg/kg – be expanded. The data are only in a small number of patients; eight patients in total were dosed, including two at the highest dose.

"An optimal hemophilia A product should be safe, reliable and predictable," Sangamo CEO Sandy Macrae said in a same-day conference call. "SB-525 demonstrated a dose-dependent relationship between SB-525 and Factor VIII levels, evidence of sustained Factor VIII levels and low Factor VIII level variability, both within each patient and within each cohort, therefore showing reliability and predictability in the data observed to date."

The trial enrolled two patients each in four cohorts: 9e11 vg/kg, 2e12 vg/kg, 1e13 vg/kg and 3e13 vg/kg. The two patients treated with the 3e13 vg/kg arm achieved normal Factor VIII levels in week six. A dose dependent reduction in the use of Factor VIII replacement therapy was also observed. Neither of the patients treated with the 3e13 vg/kg dose needed Factor replacement therapy after initial use and they have not experienced a bleeding event to date.

## A POTENTIAL ADVANTAGE OVER THE COMPETITION

The new data strengthens Pfizer/Sangamo's position in the hemophilia A gene

therapy market, where BioMarin and Spark Therapeutics have a lead.

As Evercore ISI analyst Umer Raffat pointed out, "Investors have been focused majorly on Biomarin and Spark's Factor VIII gene therapy data to date. Meanwhile, Sangamo's first three dose cohorts had been underwhelming on Factor VIII expression."

The fact that the two patients in the fourth and higher dose cohort achieved normal Factor VIII levels as early as week five could be notable, Raffat said in a same-day research note. "In fact, you may argue that this was materially faster than competitor gene therapies, which took 8-12 weeks," he said, but cautioned that long-term follow up data will be required.

Jefferies analyst Maury Raycroft said the data help establish a clearer picture of SB-525 and the company's platform more broadly. "We believe Sangamo/Pfizer's SB-525 stacks up very well," he said. "Sangamo is not the most advanced hemophilia A gene therapy program in development, but their argument to be best-in-class has gotten stronger with today's updates."

But Credit Suisse analyst Martin Auster forecast the update would have little impact on BioMarin. Sangamo's SB-525 appears to be viable, he said, but BioMarin has a several-year lead on the development of a gene therapy.

Being first to market when it comes to potential one-time use gene therapies could be critically important to capturing the market. BioMarin so far appears well positioned in that regard.

BioMarin has a 130-patient Phase III trial underway for its gene therapy valoctocogene roxaparvovec. The trial is expected to be fully enrolled in the third quarter of 2019, and the company is exploring an accelerated approval pathway.

Spark also initiated a Phase III trial for its gene therapy SPK-8011 at the end of 2018, and will soon have the regulatory and commercial expertise of Roche behind it.

“This single patient data indicated ST-400 successfully reconstituted hematopoiesis following conditioning in the hardest to treat patient genotype”

Roche announced plans to buy Spark for \$4.8bn in February in a deal that is expected to close in the second quarter. (Also see “Roche \$4.8bn Buy Sparks Hemophilia Gene Therapy Race” - *Scrip*, 25 Feb, 2019.)

#### VALIDATION FOR SANGAMO'S PLATFORM

For Sangamo, the news was nonetheless a positive development and the gene editing company used the opportunity to provide other updates as well. As Jefferies' Raycroft pointed out, “the positive SB-525 hemophilia A data revealed doses for cross-comparing, but more importantly helped de-risk the company's gene therapy platform.”

Sangamo's stock price opened 45% higher at \$13.83 on April 2.

The company also provided an update on the first patient treated with ST-400, an *ex vivo* gene-edited cell therapy for beta-thalassemia, in the Phase I/II THALES study. The program is partnered with **Sanofi**.

The results of treatment have been encouraging for the patient, after an initial serious adverse event – a transient allergic reaction that resolved. The patient had the most severe form of transfusion-dependent beta-thalassemia and was required to receive blood transfusions every other week.

At seven weeks post ST-400 infusion, the patient's total hemoglobin levels remain stable and levels of fetal hemoglobin have continued to rise from approximately 1% of total hemoglobin at the time of infusion to 31% at the most recent measurement. The patient received several blood transfusions at approximately two weeks after treatment, but no further transfusions have been required in the five following weeks, Sangamo reported.

“While the beta-thalassemia data are very early and only one dosed patient, this single patient data indicated ST-400 successfully reconstituted hematopoiesis following conditioning in the hardest to treat patient genotype,” Macrae said.

An investigational new drug (IND) application for another gene therapy, ST-920, for Fabry disease was accepted by the FDA in February; Sangamo expects to initiate clinical studies later this year, the chief executive added.

The therapy is wholly owned by Sangamo, while much of the company's pipeline is partnered. The company also has unpartnered therapies in early clinical development for MPS1 and MPS II. Macrae talked to *Scrip* about the company's partnering strategy at the J.P. Morgan Healthcare Conference earlier this year. (Also see “J.P. Morgan Notebook Day 3: Biotech Feeling Government Shutdown, AstraZeneca, Denali, Allergan, Aptinyx, Sangamo” - *Scrip*, 10 Jan, 2019.)

Sangamo also updated investors on its manufacturing capabilities, a complex and critical component of developing gene therapies. A new facility under construction in Brisbane, Calif. is expected to be operational in 2020 to deliver Phase I/II cGMP supply. The company also signed an option agreement with the gene therapy contract development organization Brammer Bio to secure access to large-scale AAV manufacturing. ▶

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## Roche Confident Spark Therapeutics Acquisition Will Complete In First Half

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Roche still expects to complete the acquisition of US biotech company **Spark Therapeutics Inc.** in the first half of 2019, despite the review of the transaction by US financial regulators taking longer than expected, and only 29.4% of Spark's shares being tendered for Roche's offer of \$114.5 per share at the end of business on April 2, 2019.

That's the day before Roche's tender offer was due to expire, but the end of the offer period has now been extended to 12.00 midnight, New York time, on Thursday, May 2, 2019, and could be extended further under the two companies' \$4.8bn purchase agreement, announced in February 2019.

Analysts at Deutsche Bank said that the deal hedged Roche's efforts in hemophilia, allowing it to grow Hemlibra “and be part of the next big thing that could be around the corner in this fast-paced environment.” The acquisition “may add extra concern on the long-term dynamics of the market for Hemlibra, but at the same time reassures that Roche could be part of this change,” they

added. (Also see “Hemophilia Seen As Good Testing Ground For Commercializing Gene Therapy” - *Scrip*, 8 Oct, 2018.)

“Our offer price is full and fair. The merger agreement has been approved unanimously by Spark Therapeutics' board of directors, and Spark Therapeutics' board of directors has unanimously agreed to recommend it to its shareholders,” Roche told *Scrip*.

The big pharma explained that the pre-merger notification and report form, required under the Hart-Scott-Rodino Antitrust Improvements Act, had been withdrawn and refiled to provide more time for the US Federal Trade Commission to complete its review of the transaction. The refiling was done in agreement with Spark and the relevant FTC stakeholders, Roche added. Currently, the waiting period will now expire at 11.59pm New York City time, on or about April 25, 2019, but may be shortened if the government grants early termination of the waiting period, or lengthened if additional information is requested from the two companies.

The closing of the tender offer is conditional upon expiry or termination of the waiting period under the HSR Act, and the tendering of the majority of Spark's outstanding shares.

The acquisition of Spark has been a high-profile affair, with the negotiating stance of Spark and Roche being put under the spotlight, and with the US biotech achieving an offer from Roche priced at a 122% premium on its closing price of \$51.56 on Feb. 22, 2019.

And the past several months has seen a flurry of big pharma companies targeting gene therapy companies for M&A as the biotechs continue to release promising news about their therapeutic programs.

**bluebird bio Inc.**'s beta-thalassemia ex vivo gene therapy, *Zynteglo* (formerly *LentiGlobin*), has just been recommended for approval by the EU's CHMP, at its March 2019 meeting, while **San-gamo Therapeutics Inc.** and partner **Pfizer Inc.** have released promising initial data on a hemophilia A gene therapy, an area in which Spark has a gene therapy, SPK-8011, being evaluated in a Phase III study.

Meanwhile, Roche's big pharma competitor, **Novartis AG**, bought the US gene therapy biotech, **AveXis Inc.**, for \$8.7bn last

Basle, the headquarters of Swiss big pharma, Roche



year. In March, 2019, **Biogen Inc.** announced the \$877m purchase of **Nightstar Therapeutics PLC**, giving it expertise in the use of gene therapies for inherited retinal diseases. ▶

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## 2018 Saw Record Launches, But No Big Splash

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The number of new drugs approved by US FDA in 2018 broke records and gave drug makers and patients a reason to be optimistic about the future of drug development. But most of the new drugs that reached the US market last year were for rare diseases or niche cancers and their commercial prospects aren't immediately apparent.

Of the 59 novel drugs and therapeutic biologics cleared by FDA's Center for Drug Evaluation and Research last year, the majority (59%) were products with orphan drug designation, a first for the industry.

As big pharma and big biotech wade deeper into rare diseases and rare cancers, it's unclear how these kinds of new products will drive pharmaceutical growth, even if there are more of them, when they deliver a fraction of the revenues generated by the blockbusters of a bygone era. The aim is that more smaller launches that address high unmet needs and can therefore get to market faster with smaller clinical trials and requiring less commercial investment will still be a compelling business proposition.

As PwC Commercial Pharmaceutical Leader Greg Rotz summed up the year's launches, "It was a great year for patients."

But was it also a great year for commercial big-sellers, for the kinds of drugs that energize investors and drive top-line growth? The answer to that question remains unclear for now, but certainly the runway for getting there will take longer.

"It has the potential to be," Rotz said. "We can't judge too strongly until we see how these drugs play out over the next few years."

### RARE DISEASE AND RARE CANCERS

Several launches last year were by small, independent biotechs and targeted to just a few thousand patients. **Alnylam Pharmaceuticals Inc.** delivered the first small interfering RNA (siRNA) therapeutic, *Onpattro* (patisiran), for the rare disease hereditary transthyretin-mediated amyloidosis, which the company believes could address a target population of 10,000-15,000 patients in the US.

**BioMarin Pharmaceutical Inc.**'s *Palynziq* (pegylisase-pqpz) is an enzyme replacement therapy to reduce phenylalanine concentrations in patients with phenylketonuria (PKU), a population of about 11,000 patients in the US. (Also see "BioMarin Gets Second PKU Approval, Anticipates Slow Ramp-Up For Palynziq" -

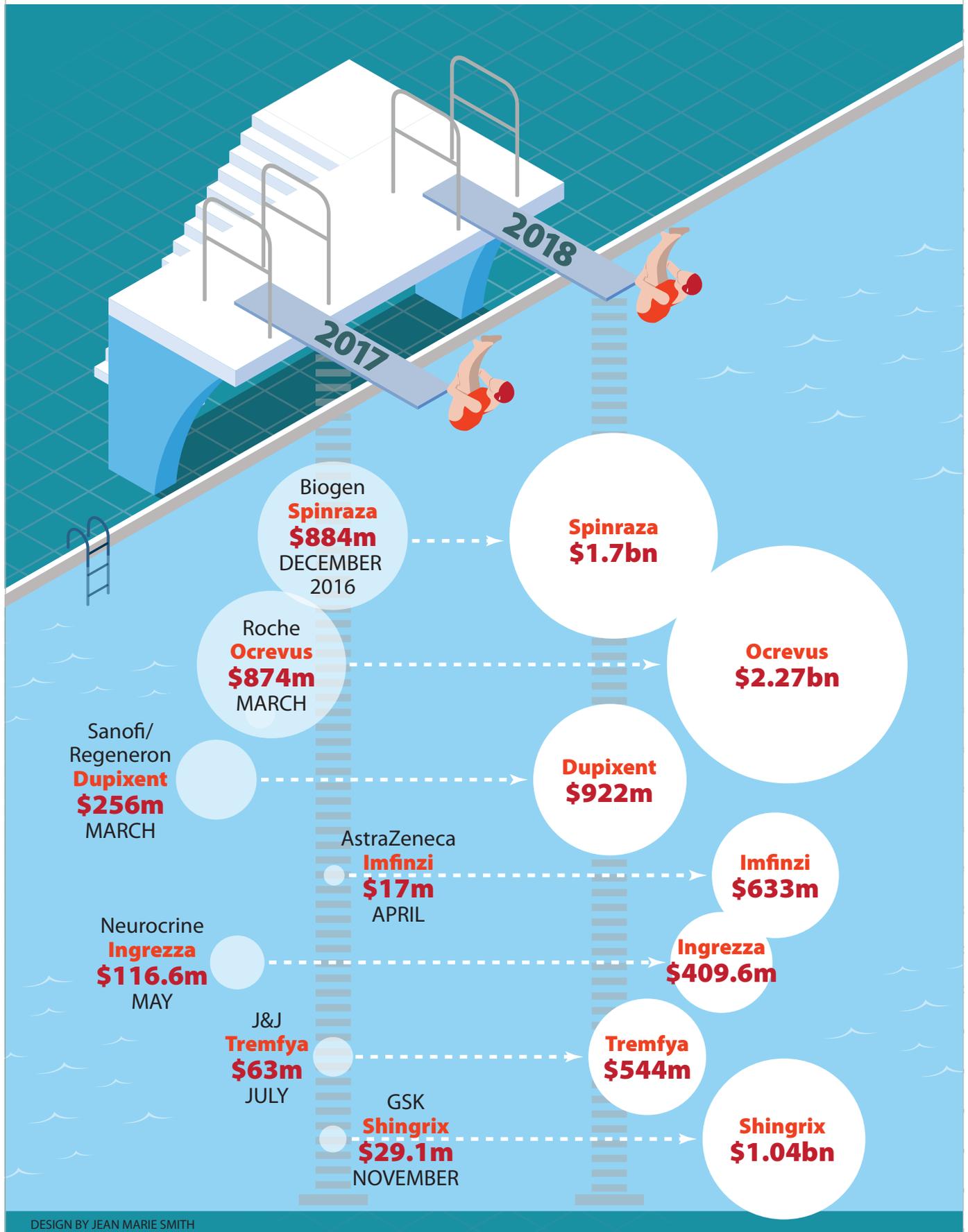
*Scrip*, 25 May, 2018.) **Ultragenyx Pharmaceutical Inc.**'s *Crysvita* (burosumab) was approved for the treatment of x-linked hypophosphatemia (XLH), a rare inherited form of rickets that is estimated to affect about 12,000 patients in the US. (Also see "Ultragenyx Gets Second Drug Approval; Crysvita With Kyowa Hakko Kirin" - *Scrip*, 18 Apr, 2018.)

On the cancer front there were promising advances, but most of the new launches were for small subsets of patients that will limit initial revenues.

**Loxo Oncology Inc.** and **Bayer AG**'s *Vittrakvi* (larotrectinib) approval in November was hailed as a milestone in precision medicine with a tissue-agnostic indication for solid tumors that have NTRK gene fusions. But there are only about 2,500 to 3,000 newly diagnosed cases of the cancer in the US each year and finding those patients will be a challenge under common cancer screening practices. (Also see "FDA Nod For Loxo/Bayer Tissue Agnostic Drug Marks Paradigm Shift In Cancer" - *Scrip*, 27 Nov, 2018.)

**Pfizer Inc.**, meanwhile, secured four cancer drug approvals in 2018 but all are for niche patient subsets like *Vizimpro* (dacomitinib), for the treatment of first-line metastatic non-small cell lung cancer

# LAUNCH SUCCESS: HOW SOME NEW DRUGS PLUNGED INTO THE MARKET



DESIGN BY JEAN MARIE SMITH

with epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 L858R substitution mutations, the hedgehog inhibitor *Daurismo* (glasedegib) for acute myeloid leukemia and the next generation ALK inhibitor *Lorbrena* (lorlatinib) for non-small cell lung cancer with ALK mutations. (Also see “Keeping Track: Three Oncologics, A New Migraine Preventive, And First LPAD Antibiotic Clear US FDA” - *Pink Sheet*, 30 Sep, 2018.) The PARP inhibitor *Talzenna* (talazoparib) was approved for BRCA-mutated breast cancer, but it is the fourth PARP inhibitor to reach the market, well behind more entrenched rivals.

All four drugs were approved by FDA in the second half of the year and Pfizer didn't break out sales of any of them in 2018.

**Sanofi/Regeneron Pharmaceuticals Inc.**'s PD-1 inhibitor *Libtayo* (cemiplimab) was the sixth PD-1/L1 inhibitor to reach the market, but the companies secured a novel indication for the drug for metastatic cutaneous squamous cell carcinoma.

The business model for new launches, especially in cancer, has evolved, ZS Associates Managing Principal Maria Whitman pointed out. “It's very important in any oncology category not to think about the single indication as equivalent to the asset value,” she said. “It is very rarely just about the one launch anymore in terms of development, but the rare disease does offer in many cases a more attractive and faster path to getting on the market.”

### SLOW OFF THE BLOCKS

The early launch trajectory for most of the drugs that debuted in 2018 has been lackluster, although it is increasingly hard to measure launch success based on initial revenues as the metrics have changed and the runway for measuring success has lengthened amid increased competition and market access hurdles.

There does appear, however, to be a contrast with the class of drugs that launched in 2017. Among the 2017 class of new drugs was **Roche's** stand-out *Ocrevus* (ocrelizumab) for multiple sclerosis, which outpaced other launches in the last decade (excluding HIV and hepatitis C) and has been Roche's best launch ever. (Also see “Roche's Ocrevus: A Rare First-Year Blockbuster” - *Scrip*, 1 Feb, 2018.) *Ocrevus* generated \$935m in 2017 revenues after launching in April

and ballooned to \$2.27bn in its second year on the market.

**Biogen Inc.'s** *Spinraza* (nusinersen) also outpaced investor expectations, partly due to the company's higher than expected pricing strategy, after launching for the rare disease spinal muscular atrophy. It generated \$884m in 2017 after being approved in December 2016, and grew to \$1.7bn in revenues in 2018. There were other noteworthy launches like Sanofi/Regeneron's *Dupixent* (dupilumab) for atopic dermatitis, which grew into a \$922m product in its second year on the market and gained a second asthma indication, and **GlaxoSmithKline PLC's** shingles vaccine *Shingrix*, which grew into a blockbuster in 2018.

The drugs debuting in 2018 have fewer early standouts along revenue-generating lines. The one class of drugs that could make a blockbuster-sized splash – the calcitonin gene-related peptide inhibitors (CGRPs) for migraine – has faced a distinctive commercial challenge. Three similar drugs all launched around the same time, with **Amgen Inc./Novartis AG's** *Aimovig* (erenumab) having a few months head start over **Teva Pharmaceutical Industries Ltd.'s** *Ajovy* (fremanezumab) and **Eli Lilly & Co.'s** *Emgality* (galcanezumab). The competitive pressure makes it harder for any one drug to take the forefront.

Given the large patient population and the unmet need in migraine, commercial expectations for the CGRP inhibitors are big, but it remains to be seen which of the new drugs will come out on top – and more competition is on the way. *Aimovig* had an early jump start, generating \$119m in 2018 revenues following its launch in May. *Ajovy* and *Emgality* both launched in the second half of the year so it's hard to draw any serious conclusions from their 2018 uptake. Free sampling was also a big part of the early launch strategy for the drugs to encourage trial and in an effort to secure early market share.

Payers, however, have shown they are willing to pit the drugs against each other through tough exclusionary contracting negotiations. (Also see “Teva Stands By Migraine Strategy After Ajovy Misses Boat On Express Scripts Deal” - *Scrip*, 17 Oct, 2018.)

Analyst consensus estimates forecast about \$600m in revenues for the class in 2019, according to Bernstein analyst Ron-

ny Gal, well below blockbuster level sales for any one product. But Gal cautioned in an April 1 research note that new prescriptions experienced a lull in February to March. “This is worrying,” he said, noting that if the trend does not improve revenues could end up closer to 60% of consensus revenues.

“It is likely we are seeing impact of the exhaustion of the first wave of unmet need coupled with market transitioning from free to paid scripts,” he said. “We believe the trend will improve, but the question is how fast will the market be growing in the durable phase.”

### BIKTARVY, SYMDEKO AMONG EARLY 2018 LEADERS

Two drugs that stood out with the strongest early starts from a revenue perspective were **Gilead Sciences Inc.'s** *Biktarvy* (bictegravir/tenofovir/emtricitabine) for HIV infection and **Vertex Pharmaceuticals Inc.'s** *Symdeko* (tezacaftor/ivacaftor) for cystic fibrosis patients with certain mutations. (Also see “Vertex Eyes Triple Glory After Hat Trick of CF Approvals” - *Scrip*, 13 Feb, 2018.) Both drugs launched in February and therefore had almost a full year on the market, but both are also somewhat unique in that they are combination pills that build off established commercial franchises. *Biktarvy* generated \$1.18bn in 2018 and *Symdeko* generated \$769m.

A smaller but nonetheless notable launch was Novartis' radiotherapeutic *Lutathera* (lutetium Lu 177 dotate) which generated \$167m in 2018 following its launch in February, a strong start for a drug with administration challenges due to radioactivity and an approval in a rare cancer indication, gastroenteropancreatic neurocrine tumors (GEP-NETs).

“Lutathera continues to exceed our expectations,” Novartis Oncology CEO Susanne Schaffert said during the company's fourth quarter sales and earnings call Jan. 30.

Novartis gained *Lutathera* with the \$3.9bn acquisition of **Advanced Accelerator Applications SA** in January 2018 and has since expanded further into radiopharmaceuticals with the \$2.1bn acquisition of **Endocyte Inc.**, citing early optimism with *Lutathera*. (Also see “Confirming Rumors, Novartis Buys AAA To Boost Oncology Business” - *Scrip*, 30 Oct,

2017.) and (Also see “Novartis Tunes Into Radiopharmaceuticals With Endocyte Buy” - *Scrip*, 18 Oct, 2018.)

Lilly and **Incyte Corp.**'s *Olumiant* (baricitinib), an oral JAK inhibitor for rheumatoid arthritis, generated a respectable \$200m in 2018, but only \$6.7m was generated in the US, where it launched in July. In the US, *Olumiant* was only approved at the lower 2 mg dose, greatly limiting its commercial prospects, since the higher 4 mg dose was the more effective one in clinical trials. (Also see “Lilly Prices *Olumiant* For JAK Battle, But Misses Approval For Higher Dose” - *Scrip*, 2 Jun, 2018.) In Europe, both doses of *Olumiant* were approved in 2017.

**AbbVie Inc.** launched *Orilissa* (elagolix) for moderate to severe endometriosis pain in August, a potentially large market opportunity given the large number of potential patients. But treatment is often managed with older, cheaper oral contraceptives and nonsteroidal anti-inflammatory drugs, plus the duration of treatment with *Orilissa* is also limited because it was associated with dose-dependent decreases in bone mineral density, both of which could limit its uptake. AbbVie didn't break out sales of the drug in its 2018 financials, but management did forecast 2019 sales of around \$200m for the product.

### METRICS CHANGE, BUT SUCCESS IS SUCCESS

Other launches brought in several millions of dollars and it's hard to draw any serious conclusions about a drug's performance too early into the launch, particularly in rare diseases. A threshold of \$200m in first-year sales as long been considered an industry benchmark for measuring a drug's eventual blockbuster potential, but the metrics for measuring success have changed as the industry has shifted more toward oncology and rare diseases.

“Because many first indication launches are smaller, you see a lot more targets for first launch in the \$50m-\$300m range,” ZS' Whitman said. “It's not the blockbuster short-term launches we are used to seeing.”

PwC's Rotz agreed. “I don't see a hard and fast rule on a number, whether it's \$200m or \$100m. What I see companies worried about is the number of patients that they are getting onto therapy,” he said.

Measuring success has evolved to focus on metrics like number of new patients and market access, and as some drugs like cell therapies and gene therapies become increasingly complicated to manufacture, on getting the product to patients effectively, Whitman added.

Certainly, that has been an issue with Novartis' launch of the CAR-T therapy *Kymriah*, which was approved in 2017 for pediatric acute lymphoblastic leukemia but has been dogged by a manufacturing issue that has limited expansion in a second indication for diffuse large B-cell lymphoma (DLBCL). (Also see “*Cosentyx Carries Novartis Sales But Kymriah Manufacturing Gives Cause For Concern*” - *Scrip*, 18 Jul, 2018.) *Kymriah* generated only \$72m in 2018 while Gilead's rival CAR-T *Yescarta* was able to generate \$264m.

“The barometer is shifting,” Whitman said. “I would shy away from saying there is a single barometer for what good looks like.”

The metrics may be shifting but drug makers, patients and investors all know what success looks like when it comes to a drug like *Ocrevus*. As for how the class of 2018 will stack up in the revenue record books, for now, it's wait and see. ▶

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<https://bit.ly/2ln5CCs>

## Genfit Hopes To Make Case For First-Line Treatment In NASH

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Heading into the European Association for the Study of the Liver meeting April 10-14, **Genfit SA** is anticipating the release of Phase III data toward year's end that it thinks may position elafibranor as the first-line drug therapy in non-alcoholic steatohepatitis (NASH) as well as a potential backbone of combination therapy in the disease.

Genfit R&D Director Dean Hum told *Scrip* that his company believes elafibranor – a peroxisome proliferator activator receptor (PPAR) alpha/delta agonist – will offer a better cardiovascular safety profile and an ability to resolve NASH in an 18-month interim look at the Phase III RESOLVE-IT study that will differentiate it from competitor **Intercept Pharmaceuticals Inc.** In February, Intercept became the first company to report successful Phase III data in NASH with its farnesoid X receptor (FXR) agonist obeticholic acid (OCA) and it plans to file the drug for approval before the end of 2019. (Also see “*Intercept Retakes The Lead In NASH*” - *Scrip*, 19 Feb, 2019.)

Intercept's success in its Phase III REGENERATE study was incomplete, however, as OCA only hit a fibrosis-reduction endpoint with the larger of two doses tested and missed a co-primary endpoint of NASH resolution. The drug, approved to treat primary biliary cholangitis (PBC) with the brand name *Ocaliva*, also has been dogged by safety concerns due to clinical trial findings of increased LDL cholesterol levels.

Meanwhile, the two other companies that have reached Phase III in NASH also have produced disappointing results, with **Gilead Sciences Inc.** failing to demonstrate a fibrosis benefit with ASK1 inhibitor selonsertib in the Phase III STELLAR-4 study earlier this year. (Also see “*In NASH, Gilead Swung For The Fences And Struck Out Again*” - *Scrip*, 12 Feb, 2019.) **Allergan PLC** also missed a fibrosis endpoint in two-year data from a Phase II study of CCR 2/5 antagonist cenicriviroc in 2017 and now has its candidate in a Phase III study expected to report out in late 2020. (Also see “*Allergan's Two-Year NASH Data Fail To Show Fibrosis Benefit*” - *Scrip*, 22 Sep, 2017.)

"If our Phase III is successful and we get on the market, at that stage elafibranor is going to be the only drug that will be able to resolve NASH without worsening of fibrosis, combined with a decrease in cardiovascular risk factors. I think that is very unique positioning that differentiates elafibranor from any of the other three programs in Phase III," Hum said in an interview. "We think elafibranor is very well positioned to be used as first-line treatment as a monotherapy but also a very strong candidate to be used as backbone in combination therapy."

### WORKING TOWARD A NON-INVASIVE NASH DIAGNOSTIC

While it won't be reporting data from the Phase III trial at EASL, which convenes in Vienna, Austria, Genfit does plan to update attendees on its progress in working toward a non-invasive method of diagnosing NASH, as well as elafibranor's progress in Phase II for PBC therapy. (Also see "In NASH Race, Bad News For Conatus, Good News For Genfit In PBC" - *Scrip*, 10 Dec, 2018.)

The Lille, France-based firm also is recruiting patients for a Phase IIb study of nitazoxanide as an anti-fibrotic drug and will soon begin recruiting for a Phase II study of elafibranor in pediatric NASH, Hum noted. If Genfit can confirm that nitazoxanide – a thiazolide previously approved for parasitic infections – can reduce fibrosis, it believes the drug could be positioned as both monotherapy and potentially combination therapy component in multiple fibrotic indications, he said.

At EASL, Genfit will present a poster assessing the ability of the NIS4 blood test to identify patients with NASH (specified as those with non-alcoholic fatty liver disease scores (NAS) of 4 or higher) and significant fibrosis (scores of F2 or greater). In January, Genfit announced a partnership with **Covance Inc.** to expand access to the test in the clinical research community. Together, the compa-

nies have a goal of getting the test approved by the US FDA as a clinical diagnostic for NASH in 2020, Hum said.

The test measures four parameters - alpha-2-macroglobulin (A2M), glycoprotein YKL-40 (aka Chitinase-3-like protein 1 (CHI3L1)), hemoglobin A1c (HbA1c), and microRNA-34a (miR-34a) – and then assesses those scores via a proprietary algorithm, the exec explained. Companies developing drug therapies for NASH have been encouraged by regulators also to work on non-invasive diagnostic tools to replace the current standard of liver biopsy.

Hum said the test may enable physicians to determine which NASH patients should be prioritized for drug therapy. "What's important is that this is a blood test so it's cost-effective, it's readily available," he said. "The idea is not to treat all NASH patients but to treat those who are at high risk for progressing to clinical events." Genfit thinks NIS4 also may offer the potential to track disease evolution in both treated patients and those who have not yet begun NASH therapy.

Genfit's Phase III NASH data could be the basis for an accelerated approval at the US FDA and a conditional approval by the European Medicines Agency, Hum said. Both regulators have advised sponsors that they can obtain approval based on surrogate endpoints – such as fibrosis reduction or NASH resolution – but they then will need to produce longer-term data on hard clinical outcomes such as progression to cirrhosis, liver cancer, liver failure and need for transplantation to obtain a full approval of their NASH medicines.

While Genfit expects to have data for the 18-month interim look by the end of 2019, the company thinks it will need roughly another two-and-a-half years to get the longer-term data on clinical outcomes, he said. The data will be based on an enrollment of 2,000 patients, which is ongoing and proceeding well, Hum added. ▶

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## After Abeta Blow, Biogen And Eisai Get BACE Boost

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**E**isai Co. Ltd. and **Biogen Inc.** should continue with their Phase III trial of elenbecestat in early Alzheimer's disease, according to the data safety and monitoring board for the program. The DSMB recommendation came after a review of safety data, including the potential for decline in cognition.



The news will be a relief for the partners, which on March 21, 2019 announced the discontinuation of their most advanced, highest-profile Phase III Alzheimer's candidate, aducanumab, a monoclonal antibody that targets the amyloid beta peptide. Aducanumab followed a string of other amyloid-targeting antibodies into clinical failure, and it has not been plain sailing for the class to which elenbecestat belongs, either.

An oral beta-site amyloid precursor protein cleaving enzyme (BACE) inhibitor, elenbecestat has continued in development where 15 similar candidates have fallen, both for efficacy and safety reasons. The most recent was **Eli Lilly & Co.** and **AstraZeneca PLC's** lanabecestat, which was stopped for futility in June 2018 on the recommendation of the data monitoring committee. (Also see "Lilly/AstraZeneca's Lanabecestat Becomes Latest BACE Inhibitor Casualty" - *Scrip*, 12 Jun, 2018.) In May 2018, **Johnson & Johnson** ended Phase II/III development of atabecestat because of liver safety concerns, something that also dogged previously discontinued BACE inhibitors. (Also see "More Alzheimer's Pain As J&J Pulls Plug On BACE Inhibitor" - *Scrip*, 18 May, 2018.) In Febru-

ary 2018, **Merck & Co. Inc.** stopped development of verubecestat after an interim safety analysis found it unlikely to establish a positive benefit/risk profile in prodromal disease (the product had already failed to show efficacy in mild-to-moderate Alzheimer's). (Also see "M&A Pressure Mounts For Merck & Co After Alzheimer's Drug Dismissed" - *Scrip*, 14 Feb, 2018.)

The specific mention of the potential for decline in cognition in the safety review was significant, since Merck & Co presented data in October 2018 at the Clinical Trials on Alzheimer's Disease conference that showed patients with prodromal Alzheimer's who took verubecestat actually had worse cognitive test outcomes than those on placebo. It raised the question of whether such effects were particular to Merck's drug, or common to the BACE inhibitor class. At the same meeting, data presented by J&J suggested something similar may have happened with atabecestat.

Nevertheless, a lack of negative effect is far from a signal of efficacy. Given the many disappointments with candidates targeting the amyloid pathway, and uncertainty over whether intervention once symptoms have become manifest can lead to an approvable therapy, today's positive news still leaves a big question mark over

the likely efficacy of elenbecestat. In the Phase II 70-patient Study 202, for which results were announced in June 2018, elenbecestat was associated with a statistically significant difference in amyloid beta levels in the brain measured by amyloid-PET, but the numerical slowing of decline in functional clinical scales was not statistically significant.

The Phase III program for elenbecestat consists of two global studies with identical protocols, MISSION AD1 and MISSION AD2, in patients with mild cognitive impairment due to Alzheimer's or mild Alzheimer's dementia, with confirmed amyloid pathology in the brain. The trials were begun in October 2016 and enrolment was due to complete in March 2019. The trial treatment period is 24 months.

Immediately following the announced discontinuation of aducanumab in early Alzheimer's, Eisai revealed that a global Phase III study of BAN2401, an anti-amyloid protofibril antibody also in joint development with Biogen, had begun in early Alzheimer's. Biogen is still assessing whether to press on with a planned study of aducanumab in Alzheimer's disease prevention. ▶

Published online 1 April 2019

## AZ Explores Orphan Diseases To Boost Fasenra Growth

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**A**straZeneca PLC's plans to expand use of its severe asthma drug Fasenra have been enhanced by successful results from a mid-stage trial in patients with hypereosinophilic syndrome (HES).

Data from a 20-patient Phase II trial, the results from which have been published in the *New England Journal of Medicine* (April 3), demonstrated that Fasenra (benralizumab) can achieve near-complete depletion of eosinophils and improve clinical outcomes in HES. The latter is a group of rare disorders in which high numbers of eosinophils, a type of white blood cell, are found in the blood and tissue which can cause progressive organ damage over time, and if left untreated, can be fatal; HES most commonly impacts the skin, heart, lungs, gastrointestinal tract and central nervous system.

In the randomized phase of the trial, which was a collaboration between AstraZeneca and the US National Institutes of Health, the primary efficacy endpoint was the percentage of patients who reduced their absolute blood eosinophil counts by 50% or more at week 12. This was achieved by 90% of patients treated with Fasenra compared with 30% of those on placebo.

In the open-label phase of the trial, 74% of patients maintained a reduction in eosinophil counts and had clinical improvements in their symptoms through week 48. Of these patients, 64% were able to taper background HES medications and in those from whom tissue biopsies were obtained (gastrointestinal tract and skin), there was near-complete depletion of eosinophils following treatment with Fasenra.

During the 48-week treatment period, the three most frequently reported adverse events attributed to Fasenra included headache, elevated lactate dehydrogenase (LDH) concentration and chills. The increases in LDH occurred after the first dose of the

drug, which was administered subcutaneously every four weeks, but they were resolved within 48 hours, AstraZeneca noted.

Mark White, global medicines lead for Fasenra at AstraZeneca, told *Scrip*, "It's an exciting set of data, not only because it's come out in the *NEJM*, but also because HES is a really devastating disease, almost the pinnacle of eosinophilic diseases [and] we were able to show a really nice clinical profile."

"The data 'reinforce what we believe about how Fasenra works and shows there's lots of opportunity for this medicine to be the first-line, first-choice biologic in a whole range of different eosinophilic diseases'."

Some of the patients had extremely high eosinophil counts – up to almost 22,000 cells per cubic millimeter – and White noted that "being able to show almost complete depletion and improve clinical outcomes in our patient population" is very encouraging. In February, the FDA granted orphan drug designation (ODD) to Fasenra for HES and AstraZeneca is now evaluating the next steps for development.

White said the data "reinforce what we believe about how Fasenra works and shows there's lots of opportunity for this medicine to be the first-line, first-choice biologic in a whole range of different eosinophilic diseases." These include eosinophilic granulomatosis with polyangiitis (EGPA) for which the

FDA granted ODD in November 2018, while a Phase III program for nasal polyps is ongoing.

He added that there was quite a long list of other related diseases, including eosinophilic esophagitis and other eosinophil-driven gastrointestinal disorders. The data to date “mesh very well with what we’ve seen in asthma,” White noted, pointing out that with the HES, the drug’s clinical benefits can be seen “not just in the lung which is where we have previously focused in the past but in a whole range of different organ systems.”

Fasenra, which binds directly to the IL-5a receptor on an eosinophil and attracts natural killer cells to induce cell death, is currently approved in around 35 countries as an add-on maintenance treatment for severe, eosinophilic asthma. White told *Scrip* that “we’re

very pleased with the first full year calendar performance in 2018 when we got very close to \$300m in sales, and about 22,000 patients on treatment in asthma.”

Fasenra led in the IL-5 class for new treatments in the US, Japan and Germany last year, where it faces stiff competition from **GlaxoSmithKline PLC’s** rival severe asthma drug *Nucala* (mepolizumab). White acknowledged that the company was disappointed by negative results from two Phase III trials of the drug last year - TERRANOVA and GALATHEA – in chronic obstructive pulmonary disease but “we’ve been continuing to work our way through that data set to really understand the eosinophilic sub-populations that sit within it.” ▶

Published online 4 April 2019

## No More Deal? Novartis, Amgen Trade Lawsuits Over Aimovig Agreements

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A quiet disagreement between **Amgen Inc.** and **Novartis AG** regarding their partnership for the first-to-market calcitonin gene-related peptide (CGRP) receptor inhibitor *Aimovig* (erenumab) has erupted into formal legal proceedings. The two companies filed lawsuits against each other on the same day and in the same court – with Novartis seeking to keep the companies’ agreements in place and Amgen seeking to terminate the migraine drug collaboration in which Novartis has invested \$870m to date.

The disagreement arose last year when Novartis informed Amgen that its sister company, the Austrian contract manufacturing organization (CMO) **Sandoz GMBH**, entered into an agreement with **Alder BioPharmaceuticals Inc.** in 2015 to manufacture a competing CGRP inhibitor eptinezumab. Amgen deemed the Sandoz-Alder contract manufacturing agreement (CMA) to be a material breach of its Aimovig deals with Novartis and began the process of terminating those contracts late last year, according to legal filings.

Without a satisfactory end to the CMA for eptinezumab, Thousand Oaks, Calif.-based Amgen sent Novartis a notice of termination of the Aimovig agreements signed in 2015 and 2017 on April 2 – and told its partner that it would seek legal recourse.

“Novartis disputes the notice vigorously,” the Swiss pharma said in a statement. That’s why Novartis filed its lawsuit against Amgen in the US District Court for the Southern District of New York on April 4 asking the court to determine that Novartis has not materially breached the companies’ contracts and declare that the agreements should not be terminated.

“The agreements will remain in force unless and until a final and binding court decision is pronounced that terminates the agreements,” Novartis said.

Amgen filed its own lawsuit seeking a jury trial to determine whether the Sandoz-Alder CMA is a material breach of the Aimovig agreements and grounds for the company’s contracts with Novartis to be terminated. But while Novartis only wants to recoup its expenses related to the litigation – and any other fees a judge may choose to award – Amgen wants to be reimbursed for its le-

gal costs and be awarded compensatory damages. “Termination of the agreements would not be effective until the litigation is resolved,” Amgen noted in a statement.

“The companies’ collaboration agreements remain firmly in place while this dispute proceeds,” the big biopharma explained. “We will take all necessary steps to ensure that patient access to Aimovig is not compromised in any way. Novartis has indicated that it will also maintain its commitment to patients while the matter is being resolved.”

### DEFINITIONS MATTER: IS SANDOZ CONTRACT A ‘DISTRACTING PROGRAM’?

One of the legal hooks on which the dispute rests is whether the Sandoz-Alder CMA for eptinezumab qualifies as a “distracting program” under the Aimovig agreements between Amgen and Novartis, and whether the Sandoz CMO is actually an affiliate of Novartis.

The first agreement related to the development and commercialization of Aimovig was signed in 2015. Amgen gave Novartis rights to Aimovig (then AMG 334) and other migraine candidates outside of the US, Canada and Japan, while committing to share global rights for Novartis’ BACE inhibitor CNP520 (AMG 520), which now is in Phase II/III for Alzheimer’s disease.

The companies amended that agreement and signed a new deal for Aimovig in 2017 under which the partners share US rights to Aimovig; Amgen books US sales and pays Novartis a royalty, while Novartis books sales in all ex-US markets except for Japan and pays Amgen a royalty. Amgen hailed the deal at the time as leveraging “Novartis’ strong and established presence in neuroscience to more effectively reach people with migraine.”

Under both deals, Amgen is responsible for all Aimovig manufacturing. Novartis notes in its complaint that there’s a firewall blocking its view of any Amgen manufacturing information.

The companies’ alliance has the potential to pay off substantially for both parties with estimates that Aimovig will be a block-

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CONTINUED FROM PAGE 16

buster drug. However, Novartis claims in its lawsuit that Amgen is using the Sandoz-Alder CMA and its allegation that the eptinezumab manufacturing deal is a material breach of contract as a ploy to end the Aimovig partnership and keep the biologic's revenue all to itself.

Novartis notes that Aimovig's future sales are the only way it can get a return on its investment in the drug – a total of \$340m in development, approval and commercialization expenses and milestone fees paid to Amgen under the 2015 agreement and \$530m in launch-related expenses and milestone fees under the 2017 deal.

Amgen says in its lawsuit that the Sandoz-Alder CMA does constitute a distracting program – i.e. a deal between Novartis or one of its affiliates and another party for a competing product – under its agreements with Novartis. A distracting program is a material breach of contract that would allow for termination of the Aimovig contracts if the breach isn't resolved.

Novartis claims in its court filing that Sandoz isn't an affiliate, but a sister company that doesn't work with the Novartis Pharma division – the business that contracted with Amgen. It also says that the Sandoz-Alder CMA for eptinezumab isn't a distracting program or a material breach of the Aimovig deals. Amgen's lawsuit notes that Novartis has described it as a "technical breach."

Regardless, Novartis argues in its complaint, Sandoz has moved to end its CMA with Alder, so any alleged breach has been resolved. Amgen's lawsuit counters that the breach isn't resolved, because Sandoz still must supply Alder with eptinezumab through 2023 or earlier if a certain production volume is reached.

### AIMOVIG FIRST TO MARKET, BUT IN A CROWDED FIELD

Amgen and Novartis won the race to bring the first CGRP inhibitor for migraine headache prevention to the market in the US in May 2018. Its first-to-market approval in the EU followed later in the year.

However, the biologic only had about four or five months as the only CGRP-targeting product in the US, as approvals for **Teva Pharmaceutical Industries Ltd.**'s *Ajovy* (fremanezumab) and **Eli Lilly & Co.**'s *Emgality* (galcanezumab) followed in September. All three products are administered by subcutaneous injections, though *Ajovy* is the only one indicated for both monthly and quarterly dosing.

Alder's eptinezumab, which was filed with the US FDA in February, will be the fourth CGRP inhibitor in the US – if approved – and the only intravenously-administered product in the class. Both **Allergan PLC** and **Biohaven Pharmaceutical Holding Co. Ltd.** have oral CGRP inhibitors for acute migraine (on-demand treatment) in development, but Allergan was the first to submit its drug to the FDA. Allergan and Biohaven have oral CGRP drugs in development for prevention as well. (Also see "J.P. Morgan Notebook Day 2: Biogen, GSK, Bluebird, Roche, Amgen, Biohaven, Lilly And FDA's Gottlieb" - *Scrip*, 9 Jan, 2019.)

Regardless of the increasingly competitive CGRP inhibitor market for migraine prevention and treatments, Mizuho Securities analyst Salim Syed said in an April 4 note that consensus pegs peak Aimovig sales at \$1.5bn in the US and \$750m ex-US.

"Termination of the agreement means here that Amgen may have to work more in the ex-US market and if that's the case, it could put some medium-term pressure on ex-US numbers until sales get to full stride in Europe," Syed noted. "At the same time, it would no longer have to pay a 'double-digit' royalty to Novartis on US sales ... and US is a bigger dollar market."

Novartis said in its lawsuit that the Aimovig launch has exceeded expectations. The company claimed that 210,000 patients in the US have benefited from Aimovig, while in ex-US territories the product has launched in 27 additional countries in which 20,000 people have been prescribed the migraine drug.

"If Amgen wins the dispute, they could get full rights on Aimovig and earn significant economics back," Jefferies analyst Michael Yee said in an April 4 note. "This would represent upside because Aimovig has high expectations and could become a multibillion-dollar blockbuster drug. To date, Aimovig has been such a surprising success that Amgen has been incentivized to get all the rights back."

Yee also pointed out that Amgen is involved in intellectual property litigation with Novartis' **Sandoz Inc.** generics unit over the anti-TNF blockbuster *Enbrel* (etanercept) and there's some dispute about whether the Aimovig dispute could help or hurt that case.

"Bulls believe that a settlement around the Enbrel IP could be more likely now because the companies want to be friendly due to the Aimovig partnership," he wrote. "However, whether or not the Aimovig situation has any impact on the ongoing dispute is unclear, as one can make the argument on both sides whether this is positive or negative for the Enbrel IP situation." ▶

*Published online 4 April 2019*

## Novartis Dives Into Inflammasome Pool With IFM Tre Purchase

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**N**ovartis AG is the latest big pharma player to enter one of the hottest areas of anti-inflammatory drug development – NLRP3 inhibition – by spending \$310m upfront to acquire IFM Tre, which was only formed last summer.

Boston, MA-headquartered IFM Tre is developing anti-inflammatories that target the NLRP3 (nucleotide-binding domain, leucine-rich repeat-containing receptor pyrin domain containing 3) pathway which plays a critical role in the

body's innate immune system. When activated, NLRP3 triggers an inflammatory response via the assembly of a multi-protein complex called the inflammasome, Novartis noted, and is associated with several metabolic, fibrotic, autoimmune and

neurological diseases. The Swiss major is acquiring IFM Tre's three NLRP3 inhibitors and the first one, IFM-2427, only went into Phase I trials last week. It is being evaluated for an array of chronic inflammatory disorders, including gout, atherosclerosis and non-alcoholic steatohepatitis (NASH); the study is being carried out in up to 90 subjects and is expected to complete in the fourth quarter of 2019.

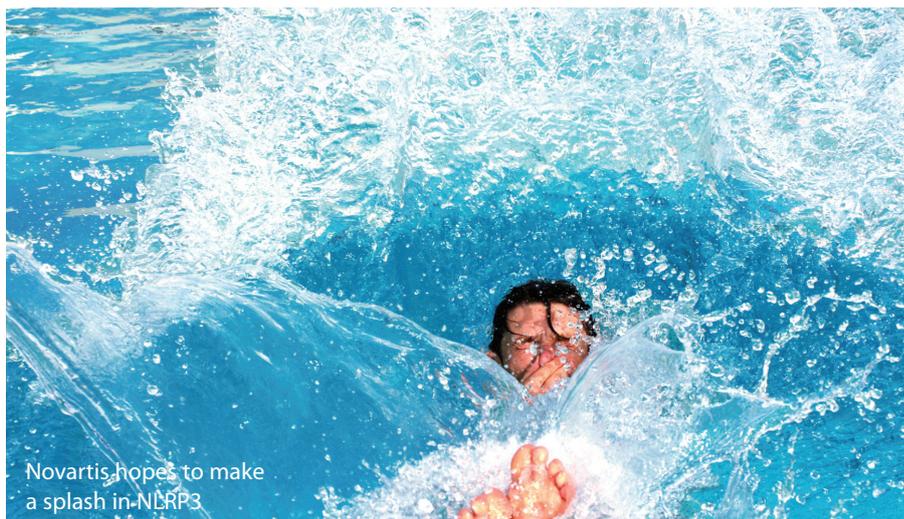
Also included in the deal, which could be worth up to \$1.58bn, is a preclinical candidate that is directed at the gastrointestinal tract with potential in inflammatory bowel disease. The third compound is a preclinical central nervous system (CNS)-penetrant molecule.

IFM Tre's compounds "have demonstrated that they can fine-tune the immune system, offering a potentially potent approach for treating a large variety of diseases associated with inflammation," said Jay Bradner, president of the Novartis Institutes for BioMedical Research, in a statement. "We look forward to applying our deep expertise in this field to advancing these medicines through the clinic," he added and Novartis sees the programs as complementing its existing pipeline of anti-inflammatory drugs.

### \$31M SERIES A

The company was only formed in July last year around the NLRP3 antagonists assets of **IFM Therapeutics** which was acquired by **Bristol-Myers Squibb Co.** in 2017. IFM Tre debuted with a \$31m series A financing that was led by Atlas Venture, Abingworth and BMS. (Also see "An Inflammatory Deal: Bristol Commits Up To \$2.3bn To Buy IFM Therapeutics" - *Scrip*, 4 Aug, 2017.)

Gary Glick, CEO and co-founder (in 2015) of IFM Therapeutics, said that "with Novartis we have identified a partner that shares our conviction in the potential of this approach, and who has deep expertise bringing inflammatory and autoimmune disease therapeutics to market." He added that the firm would continue to develop programs that target other components of the innate immune system through the broader IFM enterprise and especially through its IFM Due unit. The latter launched in February 2019 and is developing small-molecule antagonists and inhibitors tar-



geting aberrant inflammatory responses of the innate immune system triggered by the cGAS-STING pathway.

Commenting on the acquisition in a blog, Bruce Booth, an early stage venture capitalist at Atlas, wrote that "the IFM story has been breathtakingly productive and created an enormous amount of value" since it was co-founded less than four years ago by Glick and Atlas. Since then, two of IFM's therapeutic programs are in the clinic, a third is about to enter first in human studies and three more are in advanced preclinical trials.

All of these were originally *de novo* discovery programs addressing various aspects of innate biology, Booth noted, and "during this time, they've raised less than \$60m in equity capital from investors and generated \$610m in upfront payments and future milestones that could exceed \$3bn. Truly impressive delivery of value." He added that "we're all super keen on IFM's third chapter – IFM Due – [and] given their track record and demonstrated nose for drug discovery, we suspect this crew of incredible serial biotech entrepreneurs will be back with more progress soon."

The excitement surrounding NLRP3, and particularly its potential in NASH, provided the rationale behind **Roche's** acquisition in November last year of **Jecure Therapeutics Inc.** for an undisclosed sum. Founded in 2015, Jecure has been evaluating two preclinical NLRP3 blockers – JT349 and JT194 – in NASH and liver fibrosis, drugs that are based on research done by Ariel Feldstein at the University of California, San Diego.

The NLRP3 field is expanding, and one of the key players is **Inflazome Ltd.** Last week the Irish biotech announced that it had been awarded funding in excess of \$1m by the Michael J. Fox Foundation to develop an NLRP3-specific imaging tool to visualize neuroinflammation that may help investigate Parkinson's onset and progression as well as evaluate new treatments.

### CLINICAL TRIALS THIS YEAR

Last November, the Dublin-headquartered group closed a series B financing round of €40m, led by Forbion, while Longitude Capital and founding investors Novartis Venture Fund and Fountain Healthcare Partners, also participated. Inflazome is using the proceeds to advance its NLRP3 inflammasome inhibitors into multiple clinical trials this year.

Another developer of NLRP3 blockers is **NodThera Ltd.** The Cambridge, UK-based biotech closed a series A financing for £28m in June 2019 and in an interview with *Scrip* last year, chief scientific officer Alan Watt, who previously led inflammasome discovery at GSK, said: "I truly believe that important medicines are going to come out of this. It was attractive 10 years ago when I first looked at it and the science has only strengthened over the last decade. It is one of the most compelling drug discovery stories around." (Also see "Inflammasome's Time Has Come, Says Ex-GSK NodThera Chief After £28m Financing" - *Scrip*, 25 Jun, 2018.) ▶

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# Medigene Takes Center Stage In Roivant's Latest 'Vant'

KEVIN GROGAN kevin.grogan@informa.com

**M**edigene AG's place at the top table for T-cell receptor (TCR) therapies has been confirmed with a deal with **Roivant Sciences GmbH** that will see the German biotech's programs at the heart of another new spin-out – or Vant – focusing on the Asian market.

Roivant and its China subsidiary **Sinovant Sciences Ltd.** announced the launch of Cytovant Sciences on April 4, with the goal of developing and commercializing cellular therapeutics “that have the potential to transform the treatment of diseases prevalent in Asian patients.” The announcement was made at the same time as Cytovant unveiled a multi-program license and collaboration agreement with Medigene which gives it Asian rights to two of the latter's programs.

Specifically, Cytovant is getting the rights to Medigene's TCR treatment targeting the tumor antigen New York esophageal squamous cell carcinoma 1 (NY-ESO-1) and its dendritic cell (DC) vaccine against Wilms Tumor-1 (WT-1) and Preferentially expressed Antigen in Melanoma (PRAME) in greater China, South Korea and Japan. The deal also includes a partnership to develop two more TCR programs tailored for patients in east Asia.

## FINANCIAL TERMS

Medigene will receive an upfront of \$10m as well as potential development, regulatory and commercial milestone payments which could total over \$1bn for the four products across multiple indications. The Martinsried firm will also be eligible to receive low double-digit percentage royalties from the relevant countries. All its R&D costs incurred within the collaboration will be reimbursed.

In an interview with *Scrip*, Medigene CEO Dolores Schendel noted that the deal was an example of the company's strategy of licensing in other geographies while concentrating its own efforts in Europe and the US. The company is conducting a Phase I/II trial of the DC vaccine for the treatment of acute myeloid leukemia (AML). The final data will be available towards the end of 2019/beginning of 2020; to date, the results have been encourag-

ing and after a 12-month treatment period, Medigene revealed at the beginning of this year that overall survival was 89% (n=18/20) and progression-free survival was 60% (n=12/20).

Medigene also commenced patient treatment in a Phase I/II trial of its TCR therapy MDG1011 for the treatment of AML, myelodysplastic syndrome and multiple myeloma in the first quarter of this year. The Phase II portion is expected to include 80 patients.

Noting that TCRs “are the scouts of the immune system [which] help T cells recognize and destroy cancer cells,” Schendel noted that the Cytovant deal and a recently extended partnership with **bluebird bio Inc.** represent a validation of the company's screening systems to generate tailored TCR therapies for patient populations with specific genetic characteristics. The bluebird alliance was expanded last year from four to six targets, bringing in more R&D funding and increased potential milestones, plus an additional upfront payment of \$8m.

The initial bluebird deal was agreed in 2016 and Schendel said that “when they started with us it was a black box, so to speak, the question being ‘can Medigene deliver? When they wanted to have two

more targets after a year and a half working with us, that validated our approach. It's a very nice alliance with them and we anticipate the same thing happening with Cytovant,” she added, saying that the latter's strategy of getting therapies into the clinic quickly makes it an ideal partner.

Medigene's expertise in manufacturing cell therapies is a big plus and Schendel noted that it can provide advice to Cytovant in that area, although she stressed that in essence, “they have to set it up in China - you're not going to do any back and forth - and they have to configure to what their facilities look like. Manufacturing is a very tedious, extremely detailed process. However, we can teach them a lot about the biology behind these cells and what you need to do to make the cells deliver what you want them to deliver in a cellular therapeutic.”

She expects more news to be coming from Medigene this year, adding that “we like to put our European company on the map and show that we've got some great stuff.” Investors seem to think so too and the firm's shares rose over 13% to close at €10.39; in a recent note, analysts at Bryan Garnier wrote that “Medigene is well managed scientifically, clinically, financially and commercially, and we are optimistic for its future.” (Also see “*Under The Radar: Potential Small Cap Takeover Targets*” - *Scrip*, 20 Aug, 2018.)

As for Cytovant, it is the sixteenth Vant to be set up, this time with a mission to become “Asia's premier cell therapy company.” Explaining the rationale, Benjamin Zimmer, president of Roivant, said that “the complexities of end-to-end cell therapy manufacturing, development and commercialization in Asia require regional focus, specialization and knowledge. Roivant and Sinovant have built Cytovant precisely to address these scientific and logistical complexities.”

John Xu will serve as the new company's president. Prior to joining Cytovant, he was president and chief scientific officer of Mab-Legend Biotech, a Shanghai-based antibody discovery company. ▶

Published online 5 April 2019



“Cytovant is the sixteenth Vant to be set up, this time with a mission to become Asia's premier cell therapy company.”

# Japan Cell, Regenerative Therapy Environment 'Exciting' But Ongoing Dialog Needed

IAN HAYDOCK [ian.haydock@informa.com](mailto:ian.haydock@informa.com)

It is an exciting time for cell, gene and regenerative therapies in Japan, helped by a much improved and highly supportive regulatory environment. But continuing discussions with regulators are essential if industry concerns, particularly in the pricing area, are to be reflected in policy, stresses the CEO of **Athersys Inc.**

Dr Gil Van Bokkelen, chairman and CEO of the US stem cell venture, is generally optimistic on the present environment for the development and commercialization of such therapies in the country, highlighting a number of supportive policy and regulatory changes in this major market over the past few years.

"There has been good pricing for the first few products in the area, and these are being given a high priority. I'm optimistic that the environment will be continue to be positive," the executive told *Scrip* in an interview at the recent BIO Asia meeting in Tokyo.

Japan took the first decisive steps to implement a supportive regulatory framework in 2014, when it formally enacted new and revised legislation governing the development, approval and use of regenerative medicines and cell therapies.

In a *Scrip* round table earlier this year, Van Bokkelen also pointed to the wider positive developments in the pharma regulatory environment in Japan, where the main drugs and devices regulator, the PMDA, has taken multiple steps to address the former "drug lag" delay in approvals versus the US and Europe. (Also see "*J.P. Morgan Roundtable: The Regulatory Role In Accelerating Complex Therapies*" - *Scrip*, 11 Feb, 2019.) The agency now occasionally but routinely issues first approvals globally for new products.

## PRICING ISSUES

But the CEO also sounded a note of caution. Given the expected advent of some high-priced new therapies this year in Japan - which some observers already see a prompting further official debate over reimbursement - he warned that "short term decisions on pricing could be counterproductive - we must engage in productive dialog."

Following an approval late last year, **Nipro Corp.**'s stem cell therapy for spinal cord injury *Stemirac* was recently awarded a reimbursement price under Japan's national health insurance system equivalent to around \$134,000 per "dose".

In a sign of the positive regulatory support for access to such new therapies in Japan, and amid some international criticism of the *Stemirac* approval, PMDA head Dr Tatsuya Kondo strongly defended the decision at BIO Asia. (Also see "*PMDA Chief Defends Japan Spinal Cord Therapy Approval*" - *Pink Sheet*, 7 Mar, 2019.) But other recent developments are serving to focus more attention



Dr Gil Van Bokkelen

on the pricing of newer cell and regenerative therapies. **Novartis AG's** *Kymriah* (tisagenlecleucel) has just been approved in Japan at the first CAR-T therapy in Asia, and its price-setting process is being closely watched.

The Swiss company's gene therapy AVXS-101 - which is expected to have a list price of around \$4m in the US - should also be approved in Japan this year for spinal muscular atrophy.

Generally, there are still concerns in the industry in Japan that drug pricing remains a sensitive topic amid general political and budget pressures to contain the country's rising health costs amid a rapidly aging population. Reimbursement policy changes in April last year effectively raised the bar for innovation to be rewarded, and cut back a pricing premium scheme that had been awarded to all new drugs.

Van Bokkelen's view is that there is now a need to build on the achievements in Japan of the past few years, given a situation where multiple political constituencies may not always be on same plate. "This can be a year of constructive dialog. We want to work with regulators and want safe, more effective medicines and to develop these efficiently to improve outcomes for patients," he stressed.

## THE VALUE PROPOSITION

He added that the industry needs to look at more quantification of value to support their pricing and reimbursement propositions - on health outcomes and overall benefits for healthcare systems. "It needs to engage with policy-makers to show holistic benefits. Key questions include 'how do we address this as a pharma industry,' and 'how do we absorb cost of new cell therapies into the system?'"

While CAR-Ts and other therapies may have a high up-front cost, overall they may be more cost effective, Van Bokkelen observed, pointing to parallels with the newer, highly effective (but relatively expensive) antiviral drugs that offer an effective cure for hepatitis C. While there is a need to foster competition, there is a concomitant need to provide sufficient incentives to innovators.

New different ways of financing higher-priced new therapies are also emerging, such as installments, spreading of savings and costs, payments that carries through to the health outcome "dividend phase", and insurance bridging.

Turning to some specific Japan pricing policies, Van Bokkelen said the 2018 revisions to the price maintenance premium system - which had exempted new drugs from regular price cuts during their patent life - and the tougher qualifying criteria for price premiums, are disadvantageous to smaller companies.

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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.



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## PIPELINE WATCH, 29 MARCH – 4 APRIL 2019

Event Stage	Lead Company/Partner	Drug Name	Indication	Comments	Change To LOA (%)	LOA (%)
Phase III Published Results	Esperion Therapeutics, Inc.	bempedoic acid	Dyslipidemia	CLEAR-Serenity; JAMA, March 29, 2019	0	84
Phase III Updated Results	VistaGen Therapeutics, Inc.	PH-94B	Social Anxiety Disorder	Pilot Study; Positive Data	0	51
Phase III Updated Results	Liquidia Technologies, Inc.	LIQ861	Pulmonary Arterial Hypertension and Pulmonary Hypertension	INSPIRE; Positive Data	0	49
Phase II/III Updated Results	Grifols, S.A.	albutein + flebogamma DIF	Alzheimer's Disease	AMBAR; Encouraging Results	0	42
Phase II/III Updated Results	TG Therapeutics, Inc.	umbralisib (TGR-1202)	Marginal Zone Lymphoma	UNITY-NHL; Positive Interim Data	1	40
Phase III Top-Line Results	Astellas Pharma, Inc.	Xospata (gilteritinib)	Acute Myeloid Leukemia	ADMIRAL; Improved OS	0	100
Phase III Trial Initiation	PellePharm, Inc.	patidegib	Gorlin syndrome	Topical Gel	25	35
Phase III Trial Initiation	Aldeyra Therapeutics, Inc.	reproxalap	Dry Eye	RENEW; Moderate-To-Severe Disease	27	55
Phase III Trial Announcement	Johnson & Johnson/Genmab	daratumumab sc	Multiple Myeloma	AURIGA; Maintenance Therapy	0	41
Phase II/III Trial Initiation	Biohaven Pharma	BHV-3500	Acute Migraine	Intranasal Administration	42	52

Source: Biomedtracker | Informa, 2019

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“Those that have few products or have not conducted many clinical trials would effectively be excluded from the system,” he said. (Also see “‘Drastic’ Japan Price Reforms Hitting R&D Incentives, Plans - EFPIA ” - *Scrip*, 9 Nov, 2018.)

Meanwhile, the lingering preponderance in Japan’s reimbursement tariff of long-listed, older but branded products “has kept a lot of people afloat. But we don’t want a hyper-competitive environment either but a happy medium, for example a generic environment that is not purely competitive but with some incentives and rewards,” the CEO suggested.

He also warned of the potential impediment to timely access, and possible unintended consequences, from Japan’s planned expansion this year of a cost-effectiveness assessment scheme for selected products. (Also see “Japan Firms Up Cost-Effectiveness Plans As Industry Concerns Linger” - *Pink Sheet*, 13 Feb, 2019.)

### JAPAN LINKS

Cleveland, Ohio-based Athersys has a particularly close interest in this market through its partnership with the Japanese regenerative medicine venture **Healios KK**, which became its largest shareholder in March 2018 when it acquired an 8.7% stake in the Nasdaq-listed firm. (Also see “Japan’s Healios Eyes First Approvals As It Progresses Regenerative Therapies ” - *In Vivo*, 3 Oct, 2018.)

Athersys has developed an off-the-shelf platform, *MultiStem*, for cell therapies for tissue repair, which do not require tissue matching. Healios has a Japan and global license to explore the platform for organ bud therapies, ophthalmology indications, and in combination with induced pluripotent stem cells and embryonic cells in this latter area.

Healios is conducting some larger placebo-controlled trials in the space, including with HLCM051, a somatic stem cell therapy for ischemic stroke, and hopes to provide an example for other companies.

“[Healios CEO] Hardy [Kagimoto] and I believe the technology will be transformative. But there needs to be a value-centric perspective in the debate, does it provide this?” Van Bokkelen commented. (Both CEOs also took part in a Japan policy panel session at BIO Asia.)

Van Bokkelen is an active member of BIO and on issues affecting the regenerative and cell medicine sector globally. During his visit to Japan, he was also involved in a BIO delegation that visited local politicians, noting the need for “a continuous process of engagement.”

In general, he remains positive on developments in Japan. “I am very excited about the regulatory framework and the way it is being applied. At the same time, we need to give credit and latitude, and help trace other global moves in the sector back to Japan to fuel progression and momentum.” ▶

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From the editors of *PharmAsia News*.

### APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
Gianluca Corbinelli	Aerie Pharmaceuticals Inc	Chief Commercial Officer, Europe	Shire	Vice President, Global Strategy Lead	1-Apr-19
Sarah J. Spencer	Audentes Therapeutics Inc	Vice President, Corporate Communications	GlaxoSmithKline plc	Head, US Corporate Communications	1-Apr-19
Paul Sbrilli	Biohaven Pharmaceuticals Holding Co Ltd	Vice-President, Market Access, Reimbursement and Payer Relations	Biogen	Senior Director, Market Access and Reimbursement	3-Apr-19
William Jones	Biohaven Pharmaceuticals Holding Co Ltd	Chief Commercial Officer, Migraine and Common Diseases	Takeda Pharmaceuticals Inc	Vice President, Sales and Commercial Operations	3-Apr-19
Catherine Mathis	Enterome	Chief Development Officer	ElsaLys Biotech	Chief Operating Officer and Head, Regulatory Affairs	3-Apr-19
Giovanni Selvaggi	Xcovery	Chief Medical Officer	GlaxoSmithKline plc	Medical Director	28-Mar-19
Li Mao	Xcovery	Chief Executive Officer	Johnson & Johnson China Lung Cancer Center	Vice President	28-Mar-19
Emmanuel Dulac	Zealand Pharma AS	Chief Executive Officer	Alnylam Pharmaceuticals	Chief Commercial Officers	22-Apr-19

Click here for all appointments: <https://bit.ly/2oHWRyN>

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