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Novartis Blows Storm Clouds Off Sandoz US In Aurobindo Sale

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Novartis AG has acted pretty swiftly to lift the gloom that was hanging over its **Sandoz International GMBH** unit which should have a brighter future following the sale of the latter's troubled generic oral solids portfolio and US dermatology business to India's **Aurobindo Pharma Ltd.**.

In the last year, Novartis management has been frequently asked what it planned to do to stop the decline that had set in at the US division of Sandoz. While the Swiss group as a whole posted strong second quarter financials, with turnover rising 7% to $13.20bn, the performance of Sandoz in the US was again a cause for concern, with sales falling 16%.

The decline was not a great surprise as Sandoz had been struggling in the US for a while, with the company, and indeed the rest of the sector, being battered by US generic drug price erosion. At the beginning of 2018, Sandoz CEO Richard Francis told *Scrip* that for the past couple of years, the firm had been reshaping and evaluating the business in the US and the future of the generic oral solids business was an integral part of that. *(Also see "Interview: Sandoz CEO On Biosimilars And Reshaping US Business" - Scrip, 25 Jan, 2018.)*

That reshaping has culminated in the sale announced today (Sept. 6) to Aurobindo which could be worth around $1bn ($900m cash upfront and another $100m in potential performance-based premiums). It includes approximately 300 products, as well as additional development projects and the transaction is expected to close in the course of 2019 following the completion of customary conditions.

As to whether there were other offers for the assets, Francis told *Scrip* that "this was a healthy competitive bidding process and we are pleased with the outcome."While analysts were taken by surprise by the announcement, it appears negotiations had been underway for a while and the Sandoz chief noted that "these things always take a while. The important thing is not to close in a hurry; it is important to identify the right partner and finalize an agreement that adds real value."

Having done this, Sandoz hopes to move the sale along quickly. As part of the agreement, around 750 employees in Hicksville, Melville, Wilson and Princeton, New Jersey, as well as the sales reps for the PharmaDerm branded dermatology business, are expected to transfer to Aurobindo upon closing and Carol Lynch, head of Sandoz North America, said "we recognize that the transfer of ownership for a business of this size is a complex process."

She added that "we are aware that it may create some uncertainties for our associates in the US. It is thus a priority for us to make the transition as clear and quick as possible."

As to whether any other divestments are being lined up, Francis told *Scrip* that "the US is a unique market – which is why the Sandoz US strategy is unique vis-à-vis other parts of the world." Outside of the US, the company continues to grow, he stressed, saying that "we are pleased with year-on-year performance, including in our historic core business of small molecules."

Francis went on to say that "simultaneously, we are increasingly investing in future

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from the editor

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Whether there will be a viable market for your therapies is a constant concern for companies developing new therapies. You must stay abreast of the competition throughout the years of painstaking research and development, and truly understand the needs of your patient population and how your product will fit in with (and ideally improve upon) other treatment options. You must understand the entrenched assumptions, practices and constraints of the physicians who will eventually prescribe the treatment. And you must be able to sell your product at a price that payers are willing to accept.

For all the sound and fury around the drug pricing debate, truly valuable new therapies that address important unmet needs usually get to patients eventually (at least in the richest countries of the world). But even in rich countries, there are instances of failed market access, and they reflect poorly on payers and drug makers alike.

The ongoing stand-off between Vertex Pharmaceuticals and the UK government is a case in point. It is appalling that British patients desperate for Vertex's ground-breaking cystic fibrosis treatment Orkambi are left to lobby both sides in desperation as the UK Health Minister accuses the company in the national media of "trying to hold the NHS to ransom" and Vertex refuses to even submit its next-generation product *Symkevi* (aka *Symdeko*) for reimbursement appraisal. It's not easy developing life-changing treatments, and it's hard to believe that pricing negotiations are an even tougher challenge. Is the obstinacy on both sides really worth the patient harm and the reputational damage to both industry and the government?

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ITF Pharma Plans October US Roll-Out Of Liquid Riluzole Formulation For ALS
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Early engagement with US payers suggests openness to covering a liquid form of riluzole, because the tablet version is proven, but it's impossible to take for many ALS patients, says Italfarmaco subsidiary ITF Pharma.

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The UK biotech is expanding access to its unapproved lupus drug, has signed a licensing deal with Incantera and unveiled plans to divest its metabolic disorder subsidiary Ureka but fears about ImmuPharma's future remain.

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Glenmark-Celon's generic version of GlaxoSmithKline's Seretide Accuhaler dry powder inhaler (DPI) has received the go ahead in Germany, upping the competition quotient in a significant market that has generally been seen as tough to penetrate.

Tezepelumab Deemed Breakthrough But Can Phase III Reproduce Data?
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Biologic's breakthrough designation is based on Phase IIb PATHWAY data that showed tezepelumab significantly reduced asthma exacerbations compared to placebo in severe asthma.

Deal Watch: Mylan Clears Up Mystery, Acquires TOBI Cystic Fibrosis Products From Novartis
https://bit.ly/2x6hrpj
Having previously disclosed in an SEC filing that it acquired a commercial product, Mylan announces it bought TOBI Podhaler for $463m. Biohaven completes second licensing deal with AstraZeneca, while struggling United Therapeutics and MannKind team up.

Finance Watch: Three New Funds, Including Former Amgen R&D Head Harper's Next Venture
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Private Company Edition: Westlake Village BioPartners launched with $320m and Harper as a managing director; UK-based Ahren unveiled a $100m-plus "deep science" fund; and UCSD partnered with Deerfield to finance drug programs. In new financings, Allogene leads with $120m.

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Big Statement By Aurobindo As It Seals $1bn Sandoz US Deal

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Aurobindo Pharma Ltd.'s acquisition of **Sandoz International GMBH**'s US dermatology business and generic US oral solids portfolio in a deal worth around $1bn will potentially trigger a significant shift in competitive dynamics in a market already under significant pricing pressure.

The deal, which represents the largest out-bound M&A transaction by an Indian pharma company, will catapult Aurobindo to second position in the US generic market by number of prescriptions with a combined 8.6% share, zipping past generic rival **Mylan NV** (with a 6.4% share) but still well behind top-ranked **Teva Pharmaceutical Industries Ltd.** (14.3%), as per IQVIA data for the 12 months to July 2018.

The transaction, which includes about 300 Sandoz products as well as additional development projects, also gives Aurobindo a market-leading dermatology franchise, placing it in the top league in a segment that has a significant Indian presence, among other global players. Projects in development include ANDAs that have already been filed and first-to-file opportunities which have the potential to be exclusive, Aurobindo said in a presentation on the deal.

Three manufacturing facilities – in Hicksville and Melville in New York and Wilson in North Carolina – are also part of the carve-out Sandoz business being divested to the Indian firm.

SEAMLESS INTEGRATION

Aurobindo's management kept the deal narrative simple, with managing director N Govindarajan saying that the acquisition is in line with the company's strategy to grow and diversify its business in the US, and that the firm expects a "seamless integration" of the acquired businesses.

"As we have done in some of our previous acquisitions, we will be focused on leveraging our group's market-leading vertically integrated and highly efficient manufacturing base to enhance the market position and medium-term profitability of the businesses we are acquiring," Govindarajan said.

In a post-announcement investor call, the Aurobindo management refrained from getting into finer details around the prospect of transferring production of oral solid products to sites locally and improving profitability, and simply maintained that the company would evaluate all options "appropriately" and on deal closing. The acquired oral solids portfolio also includes products for autoimmune disease, anti-neoplastic agents, and a variety of hormonal agents, among others.

Net sales of the acquired business were about $1.2bn in 2017; Aurobindo anticipates estimated net sales for the first 12 months after completion of transaction to be over $900m, though this does not factor in potential divestments as per possible US Fair Trade Commission requirements.

Analysts, however, told *Scrip* that while the deal valuation seemed reasonable, much will depend on how the management can deliver on "deal promise" and how pronounced the price erosion will be on the acquired portfolio.

"There's limited room for error, given the deal size, " one analyst told *Scrip*. *(Also see "Muted Q1 For Aurobindo But Outlook Firm; Don't Expect 'Exotic' M&A" - Scrip, 10 Aug, 2017.)*

Aurobindo also didn't want to be drawn into a discussion around what swayed the deal its way, with the management only saying: "We went through the regular process, which any M&A would go through," on the investor call post Indian market hours on September 6. Private equity players were reported to be among those in the running for the Sandoz assets.

Sandoz indicated there was "a healthy competitive bidding process" and that the company is "pleased with the outcome."

The deal consideration has been structured as an upfront payment of $900m in cash and $100m as potential earn-outs, and the transaction is expected to close "in the course of" calendar year 2019 post the completion of customary conditions, including FTC clearance.

Aurobindo, which had earlier believed to have lost out to **Intas Pharmaceuticals Ltd.** in the race for Teva's assets in Europe and was also thought, at varying points, to be in the fray for **Mallinckrodt PLC**'s specialty generics business in the US, in July this year snapped up **Apotex Inc.**' businesses in Poland, the Czech Republic, the Netherlands, Spain and Belgium. *(Also see "Aurobindo Takes Pole Position In Less Genericized Portuguese Market" - Scrip, 9 Jan, 2017.)*

DERMATOLOGY PLAY

The transaction will also leap-frog Aurobindo into the dermatology space, positioning it as the second-largest player in the US for both generic and branded dermatology products, and covering a broad range of therapeutic areas including topical antibiotics, gynecological and dermatological antifungal agents, anti-acne products, local anesthetics, analgesics, anti-itching preparations, and a dermatological chemotherapeutic agent.

An Aurobindo presentation noted that the acquired generic dermatology portfolio breadth meets over 80% of dermatologist prescribing needs in the US. In the branded Rx derma segment the Indian firm touted that the wider acquired portfolio, which covers diverse therapeutic areas ranging from onychomycosis and external genital warts to fungal infections and others, has been well-known by prescribers and key opinion leaders for over 15 years.

Aurobindo also hopes to leverage the "well established" derma commercial infrastructure that the deal brings. In addition to "strong relationships" with the "Big 3" buyers in the segment, the Indian firm aims to expand its presence with mid-tier buying groups.

It also sees an opportunity to scale into a "sizeable" consumer OTC portfolio in the dermatology space, noting that the transaction provides infrastructure to facilitate future Rx-to-OTC switches.

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Is There Life Left In Laquinimod? Teva Bows Out, But Active Biotech Interested In Brain Atrophy

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There may be life in laquinimod yet. Despite the multinational **Teva Pharmaceutical Industries Ltd.** deciding it doesn't want to continue clinical development after disappointing clinical trials in multiple sclerosis and Huntington's disease, the compound's originator, **Active Biotech AB**, is vowing to "assess all opportunities for a continuation of the development of laquinimod."

Lund, Sweden-based Active Biotech is regaining the global development and commercialization rights to laquinimod from licensee Teva because of Teva's decision not to continue clinical development. All preclinical and clinical data generated on laquinimod since 2004 are to revert to Active Biotech.

The Swedish company believes there are still therapeutic avenues to explore with laquinimod: "The pronounced effect of laquinimod on brain atrophy demonstrated in both relapsing-remitting multiple sclerosis (RRMS) and Huntington's disease patients supports our belief in the potential of laquinimod as a possible treatment for neurodegenerative diseases, a disease where the medical needs remain high," said Active Biotech's CEO, Helen Tuvesson, in an announcement on Sept. 5. Investors responded by sending Active Biotech's stock down by 5% during Sept. 5, although the price, SEK3.915 price share, was still higher that a week ago, when it was SEK3.44.

"The clinical data has been pretty consistent with regard to relapse rate and brain atrophy, and laquinimod still has potential, particularly in Huntington's disease," Active Biotech's CFO Hans Kolam commented to *Scrip*. "It's a little early to talk about the path forward, but it's likely to involve finding partners who can continue development," he added.

Laquinimod was extensively evaluated by Teva as a potential replacement for its aging blockbuster-selling oral MS therapy, *Copaxone* (glatiramer acetate), and following 11 years or so spent evaluating the compound, the decision to return rights to the originator couldn't have been an easy decision for the company.

However, following three completed Phase III studies in relapsing-remitting MS, ALLEGRO, BRAVO and CONCERTO, a Phase II study in primary progressive MS, ARPEGGIO, and a Phase II study in Huntington's disease, LEGATO-HD, the compound evidently didn't live up to Teva's expectations.

As Biomedtracker analysts commented after the LEGATO-HD results were announced two months ago, "at the optimal dose of 1.0 mg daily, *Nerventra* (laquinimod) failed to improve upon placebo treatment and did not meet its primary endpoint of change from baseline after a year of treatment, as measured by the Unified Huntington's Disease Rating Scale – Total Motor Score. Nerventra met its secondary endpoint of change in caudate volume from baseline at 12 months as compared to placebo."

That said, there have been signals of potential efficacy in some clinical studies of laquinimod. In the two earlier Phase III studies in RRMS, ALLEGRO and BRAVO, laquinimod showed promising results. But the compound missed its primary endpoint in MS patients in a third RRMS Phase III study, CONCERTO, reported in May 2017. And in December 2017, Active Biotech and Teva reported that laquinimod had missed its primary endpoint in the ARPEGGIO study in patients with primary progressive multiple sclerosis. *(Also see "Pipeline Watch: Phase III Studies of CSL112 And RT-100 Imminent" - Scrip, 8 Dec, 2017.)*

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CONTINUED FROM COVER

global growth areas for Sandoz such as biosimilars, value-added medicines and complex generics." The US strategy will involve a clear focus on these differentiated products "where development and commercialization skills offer us a competitive advantage. The US offers huge potential for these medicines."

The sale has gone down well with analysts. Eric Le Berrigaud at Bryan Garnier issued a note admitting that "to state it very clearly, we were not expecting Novartis to close this chapter so quickly." He added that a successful launch of *Glatopa* (glatiramer acetate) a generic version of Teva's multiple sclerosis drug *Copaxone* developed with **Momenta Pharmaceuticals Inc.**, launching a low-cost competitor to **Mylan NV**'s blockbuster *EpiPen* licensed in from **Adamis Pharmaceuticals Corp.** and finally getting a generic version of **GlaxoSmithKline PLC**'s big asthma seller *Advair Diskus* (fluticasone/salmeterol) past US regulators, plus progressing biosimilars in the US "is priority number one for the organization but any success would have been diluted a lot by the recurring issues of this traditional business." *(Also see "Sandoz's Less Frequently Dosed Copaxone Generic Glatopa Hits Teva Two Months Early" - Scrip, 13 Feb, 2018.)(Also see "Three Strikes For Generic Advair With An FDA CRL For Sandoz" - Scrip, 8 Feb, 2018.)*

Le Berrigaud went on to say that the ratio price to sales – the soon-to-be divested businesses brought in $600m in the first half of 2018 – "is therefore not among the highest seen in the industry but it is of course worth stressing that it is declining year over year and is under deep pressure from payers." However, "the very positive aspect…is that it closes this chapter that quarter after quarter was putting a damper on Novartis's otherwise very good achievements. The double-digit decline in US Sandoz sales was the dark side of each and every quarterly release with a never-ending horizon."

The analyst concluded by saying that with the sale to Aurobindo, divesting its stake in the GSK consumer joint venture and plans for spinning off its eye care unit Alcon, "there is not long to wait now until Novartis operates as a more focused company with an improved ability to perform and to grow." *(Also see "Novartis Sees The Light And Plumps For Alcon Spin-Off " - Scrip, 29 Jun, 2018.) (Also see "What Will Novartis Do With $13bn Cash Pile From GSK?" - Scrip, 27 Mar, 2018.)*

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Ranbaxy Family Feud: Transparency And Ethics 'Continuously Negated' Says Younger Brother

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Ranbaxy Laboratories Ltd.'s founding family is once again engaged in a very public spat – this time younger scion Shivinder Singh has moved the National Company Law Tribunal (NCLT) accusing his older sibling Malvinder Singh and their close family associate Sunil Godhwani of "oppression and mismanagement" of group firms RHC Holding, Religare and Fortis Healthcare.

Godhwani is a former CEO of Religare, which ironically means 'bind together' in Latin, and the executive, was, in the past, described as "guide and mentor" to the various group businesses of the financial services firm.

Shivinder, who had generally taken a back seat over the recent past letting Malvinder steer the group and take key decisions, lamented that he could no longer be party to activities in which "transparency and ethics" are "continuously and consistently" negated.

"The collective, ongoing, actions of Malvinder and Sunil Godhwani led to a systematic undermining of the interests of the companies and their shareholders….as also the committed and loyal employees of the group," Shivinder said in a note, adding that he is "disassociating" from his sibling as a "business partner" and will pursue an "independent path" hereon.

ONE OF THE MOST DAMAGING ARBITRATION CASES

Shivinder also said that "red flags" had "crept up" in the group with "disturbing regularity." He referred to "decisions taken" in Religare's NBFC [non-banking financial company] arm and the transaction and subsequent management of the sale of the group's then flagship Ranbaxy to **Daiichi Sankyo Co. Ltd.**, which he described as culminating in "one of the most damaging arbitration cases in the history of India Inc." There were also the "unimaginable losses" accumulated in running a private charter airline business (Ligare aviation).

"All these only go to show that the malaise is systemic," Shivinder declared. It is not immediately clear if the latest developments will, in any way, impact the case with Daiichi Sankyo, where the Japanese major is pressing to enforce a INR35bn damages award by an arbitration tribunal in Singapore.

India's Supreme Court in February this year dismissed the Singh brothers' appeal against a high court verdict which upheld the international arbitral award. In July, the Delhi High Court was reported to have asked the Singh brothers to disclose their bank accounts and assets overseas in the case.

Last month the court was said to have restrained the brothers from operating their bank accounts in India and Singapore while it enforces the arbitration award. Compliance details on this front were apparently put forth, among others aspects, at the latest court hearing held Sept. 5, sources indicated to *Scrip*; a commitment to repatriate certain sums from share sales in a group company was also apparently made. An official confirmation on this was, however, not immediately available. The court, a local report suggested, however, noted that its orders to maintain status quo of assets had been disobeyed - it ordered the release of around INR93m ($1.3m) received from the sale of shares in certain listed firms by the brothers to Daiichi.The next hearing is expected in October. Daiichi had also sought to block the sale of Fortis to Malaysia's IHH and the indications are that further hearings on that are expected in November.

Daiichi Sankyo previously initiated arbitration proceedings in Singapore against the former shareholders of Ranbaxy over alleged misrepresentation of critical information concerning the US Department of Justice (DoJ) and FDA investigations against Ranbaxy at the time of the 2008 takeover by the Japanese company. In 2014, Daiichi divested Ranbaxy to **Sun Pharmaceutical Industries Ltd.**

ATTEMPTS TO PASS THE BUCK

The ongoing saga around the crumbling Singh family empire has also put the spotlight on a philosophical organisation Radha Soami Satsang Beas (RSSB), led by the guru, Gurinder Singh Dhillion, who is said to be related to the Singh brothers.

While tensions have apparently been simmering between the brothers for a while now, what may have led to a further downward spiral were recent allegations suggesting that financial linkages with Dhillion may have had some role in the group's downfall.

Shivinder's latest note doesn't refer to the guru by name, but notes that recent "planted" media articles attempting to "foist" the responsibility of "poor decisions" taken to an "elder in the family, who always stood by us as a father-figure" ever since the premature demise of the brothers' own father, Dr Parvinder Singh, had compelled him to break his silence.

"Attempts to pass the buck to an eminent figure, who has been a guiding light not only to our family but also to a large section of the public, deceives no one," Shivinder said. Dhillon, who is believed to have played a key role in assisting the Singh brothers take control of their father's business after his untimely demise, has not been accused of any wrongdoing. Both brothers, in the past, were reported to have expressed great regard for the guru and were quoted in agency reports as saying that the guru has "only ever had their best interests at heart."

RUIN OF NATIONAL HEALTHCARE ASSET

But there's little denying that companies run by the Singhs have seen a massive erosion in their fortunes and a sharp dent in their reputational capital. Fortis, for one, is being investigated by the Serious Fraud Investigations Office (SFIO,) under the ministry of corporate affairs, and by the Securities and Exchange Board of India for certain alleged irregularities.

Shivinder said that his focus and passion has always been Fortis since its inception and that it was the only company he worked for and that all his intent and resources have been in "nurturing" the company.

"I took public retirement to my spiritual home, Beas, to serve my master in 2015; leaving the thriving company I founded in trusted hands. In a period of less than two years, it has moved towards disintegration and ruin of a national healthcare asset," he said in his latest note.

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From Interchangeability To Exclusivity: US FDA Looks For Ways To Make Biologics Market More Competitive

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The US FDA has a lot of work to do to encourage both biosimilar competition and innovation in biological product development, if stakeholder comments at a recent public hearing are any indication.

The agency can help spur biosimilar development and market success by finalizing guidance on interchangeability, enhancing public education efforts about biosimilars, and taking a more forceful approach to combating misinformation about the follow-on products, speakers said.

In addition, the FDA should use its bully pulpit to help other agencies institute change in areas where the drug regulator lacks authority, such as enforcing anti-competition laws and cracking down on rebate practices that disadvantage biosimilars, stakeholders said.

On the flip side, the agency was urged to take various steps to ensure that innovation in the biologics space continues, including applying an "umbrella" exclusivity policy to protect all formulations of a licensed biologic, and clarifying the marketing protection for certain protein products whose regulatory status will change in March 2020.

HELPING A FLEDGLING MARKET GROW

The FDA convened the Sept. 4 hearing to gather input from industry, health care professional groups, patients and other stakeholders on ways to increase the availability of biosimilars and interchangeable products in the nascent US market. To date, the FDA has approved 12 biosimilars, none of which carry interchangeability determinations. Four of the 12 products have launched, with the remainder delayed largely by patent issues.

Even for those few fortunate enough to reach the market, gaining a commercial foothold has proven challenging, although data suggest the situation is improving at least for the first biosimilar, **Sandoz Inc.**'s *Zarxio* (filgrastim-sndz), which references **Amgen Inc.**'s *Neupogen* (filgrastim).

Amgen showed data indicating that Zarxio, which launched in September 2015, now holds the largest share (41%) in the US short-acting filgrastim market, which includes Neupogen and **Teva Pharmaceutical Industries Ltd.**'s *Granix* (tbo-filgrastim).

In contrast, biosimilars to **Janssen Biotech Inc.**'s *Remicade* (infliximab) – **Celltrion Inc./Pfizer Inc.**'s *Inflectra* (infliximab-dyyb), launched in November 2016, and **Samsung Bioepis Co. Ltd./Merck & Co. Inc.**'s *Renflexis* (infliximab-abda), launched in July 2017 – have struggled to gain market share.

Pfizer has sued Janssen parent **Johnson & Johnson**, alleging the company engaged in anti-competitive rebating and contracting practices aimed at blocking access to Inflectra.

At the FDA hearing, Pfizer said the current share for the two infliximab biosimilars is about 5%. The company cited a Pacific Research Institute study that found that if the US increased its use of biosimilar infliximab to just 50% of the market, the country could save about half a billion dollars in one year.

Increasing access to, and speeding up the availability of, lower-priced generic drugs and biosimilars is a key element of the Trump Administration's drug pricing blueprint and has been a priority for FDA Commissioner Scott Gottlieb since he took office in May 2017. The commissioner has been a vocal critic of rebating and contracting practices that have limited biosimilar uptake.

The agency released a Biosimilars Action Plan in July highlighting actions it is taking to encourage innovation and competition in the biologics space. The public hearing was aimed at gathering feedback on additional policy steps.

INTERCHANGEABILITY TOPS THE LIST

While Gottlieb has previously said that interchangeability designations alone will be inadequate for biosimilar developers to overcome current commercial barriers, agency officials heard a loud and clear message from innovator and biosimilar sponsors that final guidance on interchangeability is important and needed.

Draft guidance released in January 2017 drew extensive comment, with biosimilar sponsors urging the FDA to offer more flexibility on the design and endpoints of clinical switching studies and to rethink its recommendation that such studies use a US-licensed reference product as a comparator rather than a reference biologic approved in foreign markets.

While some industry representatives urged the FDA to finalize the draft guidelines without significant changes, others sought more flexibility in how such interchangeability switching studies are conducted and on the use of foreign reference products.

Amgen seeks clarification on how interchangeability determinations will be impacted by lifecycle management changes to a reference product.

For example, the Biosimilars Forum said the FDA should allow use of non-US-licensed reference products for interchangeability analytical similarity assessment if comprehensive, sensitive and specific bridging data can be provided to justify the use of such batches. In addition, the FDA should exercise flexibility regarding the structure and design of bridging studies, allowing for discussions with sponsors to determine the necessary requirements on a case-by-case basis.

However Amgen, which is a member of the Biosimilars Forum, suggested interchangeability designations may not have a substantial impact on the market because only 10% of biologics facing loss of exclusivity through 2023 are distributed via retail pharmacy, where automatic substitution of an interchangeable product can occur. "Therefore the function of pharmacy substitution likely will offer little contribution to the marketplace for 90% of these products," said Richard Markus, vice president of biosimilars global development at Amgen.

The FDA's draft guidance on interchangeability outlined appropriate science-based standards and allowed an appropriate degree of regulatory flexibility, Markus said, urging the agency to finalize the document without significant revisions.

Nevertheless, he requested that FDA clarify in the final guidance how proposed interchangeable products can address potential lifecycle management by the refer-

ence product, such as changes in formulation, concentration or delivery device, and new indications.

INTERCHANGEABILITY LIMITS

Janssen and **AbbVie Inc.** said the FDA should address the scope of its interchangeability determinations given the potential ramifications of automatic substitution.

The agency should make clear to prescribers and pharmacists – through education, labeling and the agency's "Purple Book" listing of biological products – that multiple biosimilars determined to be interchangeable to the same reference product are not interchangeable with each other, they said.

Andrew Greenspan, vice president of medical affairs at Janssen, urged the FDA to require postmarketing data on what happens when interchangeable biosimilars to the same reference product are substituted for each other. Such data are needed to instill confidence in prescribers that pharmacy-level switching between biosimilars will not result in adverse effects due to subtle differences between the biosimilars, Greenspan said.

The FDA should address biosimilar-to-biosimilar switching because "this switching is already occurring in the real world," Greenspan said, pointing to the Veterans Administration's (VA) experience with infliximab.

Prior to 2017, Remicade was the exclusive infliximab in the VA hospital system, but in September 2017 Inflectra became the preferred product. The VA changed once again in August, when Renflexis became the preferred product. "This change in the formulary has already resulted in Remicade patients switching to Inflectra and will result in switches from Inflectra to Renflexis," Greenspan said. "Prescribers have many questions regarding such switching between biosimilars, with few if any studies that evaluate the consequences of it."

Biosimilar sponsors, health care providers and patient advocates urged the FDA to step up its educational efforts around biosimilars, including developing materials that can be used at the prescriber and patient level.

The agency's educational efforts to date include explanatory information on its website, articles in professional journals, a continuing education course and webinars. The Biosimilars Forum urged the FDA to expand the educational footprint beyond its website and focus additional attention on patient and patient group educational efforts, including the development of patient-focused educational materials. **Mylan NV** said the FDA has a unique role as a trusted voice to increase confidence and trust in biosimilars.

"The FDA biosimilars education campaign is an excellent beginning," said Chrys Kokino, head of global biologics commercial at Mylan. "Amplifying these educational activities is an immediate step that FDA could take to improve acceptance of biosimilars and increase competition. Bold statements on the FDA website, or via social media, to underscore key facts could have and will have a huge impact."

"For example, an interchangeable biologic is not a better biosimilar," Kokino said. "Reinforcing this message has the effect of building confidence in biosimilars as well as removing doubt about the safety, quality and efficacy of these products."

Mylan and other biosimilar developers also urged the FDA to move more aggressively to stem misinformation about biosimilars. In an August citizen petition, Pfizer requested FDA issue guidance on truthful and non-misleading communications about biosimilars.

"FDA could also take a stronger stance in tackling misinformation about biosimilars," Kokino said. For example, he said some clinical guidelines exclude biosimilars "due to a perceived lack of sufficient data to justify use in extrapolated indications," while some formularies require patients to "fail first" on a reference product before being able to use a biosimilar.

EXCLUSIVITY CONSIDERATIONS

Turning to potential FDA actions aimed at ensuring continued innovation, several companies urged the agency to apply umbrella exclusivity so that subsequent changes to a licensed biologic would be protected by the original exclusivity. This is the same approach the FDA follows for small molecules.

"With an umbrella policy, the approval of a supplement or new application that does not receive its own period of reference product exclusivity would not compromise already earned exclusivity for the first licensed product," said David Korn, vice president of intellectual property and law at the Pharmaceutical Research and Manufacturers of America (PhRMA). "Instead the period of remaining exclusivity would cover the innovation reflected in the new application. Importantly, an umbrella policy would not extend exclusivity beyond the original period."

"An umbrella policy is essential to preserve the value of reference product exclusivity and encourage the R&D investments needed to support the development of continued improvements in biologics to meet patient needs," he said.

PhRMA and other innovator industry representatives also pushed the FDA to clarify its plans for implementing the transition provisions of the Biologics Price Competition and Innovation Act. Under the BPCIA, certain protein products, such as insulin and human growth hormone, that have traditionally been regulated as drugs will be "deemed" biologics in March 2020.

In a March 2016 draft guidance, the FDA proposed that any remaining exclusivities at the time of the transition date would be extinguished, and that existing products would not receive new exclusivity after the transition. The guidance received strong criticism across the pharmaceutical industry.

PhRMA said extinguishing unexpired Hatch-Waxman and pediatric exclusivities for transitioning products would significantly harm incentives for innovation, and the FDA should allow existing exclusivities to remain in place after the transition date.

USE THE BULLY PULPIT

Many speakers at the hearing raised issues related to drug pricing and competition that were clearly outside of the FDA's domain.

These include the types of rebate and contracting practices at the heart of Pfizer's lawsuit against J&J, formulary design, Centers for Medicare and Medicaid Services reimbursement policies, and innovators' use of "patent thickets" to protect reference products.

Biosimilar sponsors, providers and patients urged the agency to work with federal partners to establish policies that will help reduce the barriers to biosimilar entry and drive uptake. "We really encourage you to just use your bully pulpit that the commissioner has to influence other agencies because you've taken us all very far on biosimilars, but we need the assistance of your compadres in the federal government to get us across the finish line," said Christine Simmon, executive director of the Biosimilars Council.

"FDA approval is super important, obviously its critical, but it's insufficient" alone to ensure market access and commercial success, Simmon said.

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Exelixis: NCCN Change Supports Broader Use Of Cabometyx In Kidney Cancer

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Exelixis Inc. is heartened by broader inclusion in National Comprehensive Cancer Network (NCCN) clinical practice guidelines for *Cabometyx* (cabozantinib) across risk groups in first-line kidney cancer, though the tyrosine kinase inhibitor doesn't have as high of a rating as **Bristol-Myers Squibb Co.**'s immunotherapy combination of *Yervoy* and *Opdivo*.

Cabozantinib is an oral drug that works on a number of targets, including VEGFR2, MET and RET. The drug was approved by the US FDA in 2013 for treating the very rare medullary thyroid cancer and labeling was expanded in April 2016 to second-line renal cell carcinoma (RCC) in December 2017 to all lines of advanced RCC. Cabozantinib is branded as *Cometriq* in thyroid cancer and Cabometyx in RCC.

Clinical practice guidelines from NCCN were updated on Sept. 4 to recommend Cabometyx for patients with previously untreated advanced RCC and a favorable risk outlook, about 20% of the population. The drug was given a Category 2B recommendation for these patients, even though this risk group was not included in the pivotal trial supporting first-line metastatic RCC approval.

NCCN guidelines are highly influential with both prescribers and payers. Various treatments are assigned a rating – Category 1 is the highest and Category 3 means there is a lot of disagreement about whether the intervention is appropriate.

"A lot of prescribers – especially those in the community – look to the compendia for guidance on what to use, especially when there is a lot of data for many compounds," Exelixis CEO Michael Morrissey said in an interview.

Cabometyx has a Category 2A recommendation for use in patients with poor- or intermediate- risk in first-line RCC.

Whereas the last version of NCCN guidelines for RCC, released in April, presented available treatments in a long list format, the latest version presents the options in chart format, clearly showing which drugs are preferred for first-line and second-line metastatic RCC (*see tables*).

Cabometyx and Bristol's immuno-oncology (IO) combination of the PD-1 inhibitor Opdivo (nivolumab) and the CTLA4 inhibitor Yervoy (ipilimumab), which was approved for first-line use in April, are considered preferred regimens for first-line RCC in poor-to-intermediate risk patients with clear cell histology. Yervoy/Opdivo has a Category 1 rating and Cabometyx is Category 2A.

Another change in the latest version of practice guidelines is that **Pfizer Inc.**'s tyrosine kinase inhibitor *Inlyta* (axitinib) moved from 2A to a 2B recommendation for favorable risk and poor/intermediate risk patients in the first-line metastatic setting with clear cell histology. For second-line use in clear cell histology, the recommendation for **Bayer AG**/**Amgen Inc.**'s tyrosine kinase inhibitor *Nexavar* (sorafenib) was changed from 2A to 2B.

DIFFERENTIATING CABOMETYX AMONG TKIS

Exelixis pointed out in a Sept. 7 statement about the updated NCCN guidelines that Cabometyx is the only preferred tyrosine kinase inhibitor (TKI) treatment option for first-line patients in the poor- and intermediate-risk groups, with a Category 2A rating. Cabometyx also is the only preferred TKI for previously treated patients, with a Category 1 rating.

The company is looking to build the case that Cabometyx is the tyrosine kinase inhibitor of choice in kidney cancer. In the second quarter, the drug had a 28% share of total prescriptions for the class across lines of RCC therapy in the US, vs. 36% for **Novartis**' *Votrient*, 29% for Pfizer's *Sutent* and 7% for *Inlyta*, the company said, citing IMS data.

Exelixis reported product revenue of $145.8m in the second quarter, up 66% year-over-year, due to continued growth for Cabometyx in advanced RCC.

Patrick Haley, senior vice president-commercial, said during the company's second quarter call on Aug. 1, that broad labeling provides a strong foundation for the drug as the TKI of choice in kidney cancer.

The first-line approval is helping the company continue to grow, both in terms of increasing the eligible patient pool and increasing prescriber adoption as more community oncologists treat patients with first-line disease, Haley said.

Relative to the first quarter, the prescriber base for Cabometyx increased by 14% in the second quarter, driven by academic and community physicians, and due to broad utilization across lines of therapy in clinical risk categories, the company reported.

Bristol needs to see sales growth for Opdivo and Yervoy in RCC to help balance potential losses in non-small cell lung cancer, where **Merck & Co. Inc.**'s competing PD-1 inhibitor *Keytruda* (pembrolizumab) has been surging ahead. Bristol reported sales of about $1.6bn for Opdivo in the second quarter, up 36% year-over-year. The

NCCN Guidelines: Relapsed or Stage IV: First-line Therapy For Clear Cell Histology

PATIENT RISK LEVEL	PREFERRED REGIMENS	OTHER RECOMMENDED OPTIONS	USEFUL UNDER CERTAIN CIRCUMSTANCES
Favorable risk	Novartis AG's Votrient (pazopanib) and Pfizer's Sutent (sunitinib): Category 1.	Bristol's Yervoy/Opdivo / nivolumab): Category 2A. Cabometyx: Category 2B.	Roche's Avastin (bevacizumab) + interferon alfa-2b: Category 1. Active surveillance: Category 2A. High-dose IL-2: Category 2A. Pfizer's Inlyta: Category 2B.
Poor/intermediate risk	Yervoy/Opdivo: Category 1. Cabometyx: Category 2A.	Votrient and Sutent: Category 1.	Pfizer's Torisel (temsirolimus): Category 1. Avastin with interferon alfa-2b: Category 1. High-dose IL-2: Category 2A. Inlyta: Category 2B.

NCCN Guidelines: Relapsed Or Stage IV: Subsequent therapy, Clear Cell Histology

PREFERRED REGIMENS	RECOMMENDED REGIMENS	USEFUL IN SOME CIRCUMSTANCES
Cabometyx and Opdivo monotherapy: Category 1. Opdivo/Yervoy: Category 2A.	Inlyta, Eisai Co. Ltd./Merck & Co. Inc.'s Lenvima (lenvatinib) and Novartis' Afinitor (everolimus): Category 1. Afinitor, Votrient and Sutent: Category 2A.	Torisel: Category 1. High-dose IL-2: Category 2A. Avastin and Nexavar: Category 2B.

company reported that by the end of the second quarter, the combination of Opdivo with Yervoy had gained a 30% market share in first-line metastatic RCC following FDA approval in April. Approval was based on the CheckMate 214 study, in which it demonstrated better overall survival compared with Pfizer's standard-of-care Sutent.

Exelixis acknowledges that the RCC market is very competitive, but believes it will continue to be driven by the sequencing of therapeutic options and that most patients will get immunotherapy as well as cabozantinib. "The narrative has been that IO is going to be the preferred option and everything else will suffer because of that," Morrissey said.

But the reality is that very few patients are cured and the vast majority progress. "It's not an either or issue – it's really a sequence issue and how do you maintain long, durable quality of life with these new agents," Morrissey said.

Meanwhile, Bristol and Exelixis are testing Opdivo and cabozantinib in combination against Sutent in previously untreated metastatic RCC in the CheckMate 9ER study .The primary completion date is September 2019.

In addition to pursuing broad use in RCC, the company also is looking to drive sales through a label expansion in hepatocellular carcinoma (HCC), the most common form of primary liver cancer and the second leading cause of cancer death worldwide.

A supplemental new drug application (NDA) for cabozantinib in second-line HCC based on the CELESTIAL study, which was terminated early for efficacy after an interim analysis, is under FDA review with a Jan. 14 user fee date. Cabozantinib has orphan drug status with the FDA in advanced HCC.

Ahead of approval, in the latest version of its hepatobiliary cancer guidelines, released Aug. 28, the NCCN added cabozantinib as a Category 1 option for patients with HCC (Child-Pugh Class A only) who previously were treated with Sutent.

The HCC market has long been underserved, but options are growing rapidly. The FDA approved Bristol's Opdivo in September 2017 for second-line HCC regardless of PD-L1 expression, based on response rate data in the open-label Phase I/II CheckMate 040 study.

Eisai Co. Ltd.'s *Lenvima* (lenvatinib), partnered with Merck, won approval on Aug. 16 for first-line treatment of unresectable HCC, which was groundbreaking as the first new option in this setting in a decade.

Merck's Keytruda has a Nov. 9 user fee date for a supplemental NDA covering second-line HCC. *Published online 8 September 2018*

J&J Seeks A Priority Review For Esketamine

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Johnson & Johnson's depression drug esketamine could reach the US market early next year if the new drug application is granted a six-month priority review by US FDA as requested. The company announced the submission of an NDA for the glutamate receptor modulator for treatment-resistant depression Sept. 4. A marketing authorization application is on track for filing in Europe later in 2018.

The race to build new power brands in depression is expected to intensify in 2019 as several new drugs could launch that work through novel mechanisms, targeted at patients who don't respond to current therapy. Esketamine is considered one of the high-profile drugs that could launch in 2019.

Whether or not the FDA will grant a priority review remains to be seen, but the unmet need for new options remains high and the data on esketamine, though not a slam dunk, have been encouraging. About one-third of the 300m people with major depressive disorder worldwide do not respond to current treatments, J&J said.

Esketamine has been granted FDA breakthrough therapy designation, and the NDA filing is based on five pivotal Phase III studies. The Phase III efficacy data have been mixed, but encouraging. Of the first two short-term Phase III trials to read out, only one met the primary efficacy endpoint, while the other showed a "meaningful" improvement, though not statistically significant, in patients with treatment-resistant depression. That study was the first of its kind targeted to patients 65 and older.

Two long-term Phase III studies are also included in the package, including one that showed a delayed time to relapse in patients taking esketamine plus an oral antidepressant versus those taking a placebo nasal spray plus an oral antidepressant, as well as a trial that provided evidence of safety for up to one year.

Clinical studies for depression drugs are notoriously challenging and are frequently sidelined by a high placebo effect.

Several other drug makers also are working to bring novel drugs to market for various forms of depression. **Alkermes PLC**' ALKS-5461, a fixed-dose combination of the partial mu-opioid receptor agonist and kappa-opioid receptor antagonist buprenorphine with the mu-opioid receptor antagonist samidorphan, has a Jan. 31 FDA action date.

SAGE Therapeutics Inc., meanwhile, is ramping up commercialization efforts for *Zulresso* (brexanolone) in postpartum depression ahead of a Dec. 19 user fee date. Sage submitted an NDA for the GABA-A modulator in April. **Allergan PLC**'s rapastinel, an NMDA receptor partial agonist, is in Phase III development for patients with major depressive disorder who fail to respond to treatment.

The cost of the new treatments will certainly be an issue for payers. *Published online 4 September 2018*

Indication-Based Pricing Hurdle A Block For Roche's Ocrevus In UK

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NICE and **Roche** are under pressure to reach a deal after the UK health technology assessment body decided not to make Ocrevus available on the UK NHS to treat people with primary progressive multiple sclerosis (PPMS), citing price and uncertainty over the drug's efficacy. Flexibility to price the product differently for different indications is a particular sticking point.

The EU approved drug, which has been proven to slow the progression of the disease, is currently the only treatment for people with PPMS, a highly debilitating form of multiple sclerosis. PPMS affects around 10-15,000 people in the UK.

In June, the National Institute for Health and Care Excellence finally endorsed *Ocrevus* (ocrelizumab) for relapsing-remitting MS, which is the most common type of the disease.

But NICE has now rejected it for the rarer and more severe primary-progressive form of MS.

"We were unable to recommend ocrelizumab at the price agreed between the company and NHS England, because it was not considered a cost-effective use of limited NHS resources," explained Meindert Boysen, director of the centre for health technology evaluation at NICE.

"We recognize that there is a large unmet need for treatments for people with primary-progressive multiple sclerosis and we are open to discussions with the company and NHS England to address this," he added.

The HTA also said that while clinical trial results indicate that ocrelizumab can slow the worsening of disability in people with the condition, "the size and duration of this effect are uncertain."

ROCHE SEEKS INDICATION-SPECIFIC PRICE

Roche said it had wanted to offer an indication-specific price in order to make ocrelizumab cost-effective to the NHS for people with early PPMS, but that that approach had been barred.

"As the Department of Health does not allow medicines to have different confidential prices for different indications NICE had to consider the current RRMS approved price for the PPMS indication. This was not deemed cost effective in PPMS. As a result, NICE could not even consider the indication-specific price offered by Roche for PPMS," a Roche spokesperson told *Scrip*.

> 'We ask that NICE are given the flexibility to consider an indication-specific price for ocrelizumab in PPMS'

The Swiss drug maker's UK general manager Richard Erwin in a statement said: "We ask that NICE are given the flexibility to consider an indication-specific price for ocrelizumab in PPMS."

"The challenge with ocrelizumab for people with PPMS could also have huge implications for future access to innovative medicines for people in the UK ... We want to work together with NICE and NHS England to find a solution so this decision can be overturned," Evans said.

NICE OUTLINES ROCHE OPTIONS

NICE believes Roche has some options to choose from moving forward:

"They could reduce the confidential price for the RRMS indication to have one price available to the NHS and enable access for all patients," a NICE spokesperson told *Scrip*.

"Alternatively they could reduce the list price of the product to that of the RRMS price but this could not be confidential, and offer a discount specific for the PPMS indication," the spokesperson added.

Datamonitor Healthcare analyst Stephannie Yip said the parties have been through this exercise before and therefore are likely to find a compromise. "While this is a significant setback, Roche did overcome NICE's initial negative recommendation for Ocrevus for RRMS earlier this year and negotiations could still resolve outstanding pricing issues," she told *Scrip*.

Ocrevus got EU marketing authorization in January, leaving it to member states to decide whether to provide the treatment, which costs £4,790 (about $6,192) per 300 mg vial. There are no other drugs currently approved for PPMS, only treatments designed to manage symptoms.

There are other therapies coming on stream for the PPMS indication. They include MediciNova Inc.'s ibudilast. Other pipeline products being developed for PPMS include **AB Science**'s masitinib which is in Phase III trials, and **Mylan NV**'s glatiramer acetate depot, currently in Phase II studies.

Datamonitor Healthcare's Yip noted "Ocrevus is differentiated in the MS space by its broad efficacy amenable to RRMS and PPMS patients. Its superior clinical profile compared to other available disease-modifying therapies is forecast to propel its sales to a peak of $6.2bn across the US and five major EU markets, those being France, Germany, Italy, Spain, and the UK, with $1.7bn attributed to PPMS sales."

ROCHE HOPES FOR SOLUTION

Roche for its part intends to keep the conversation going between itself and NICE, but it will keep pushing for an indication-specific price.

"We are actively seeking ways to work with NICE to ensure it is made available to people with early PPMS," the Roche spokesperson said.

"Roche is confident that given the flexibility to offer an indication-specific price, we will be able to offer a price that is deemed cost-effective for PPMS."

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UK's NICE Okays Crysvita For XLH In Kids After Partners Cut Price To NHS: https://bit.ly/2MjLJKE

Manchester United With Big Pharma On Improving Outcomes

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The leading players in the pharmaceutical industry are beating a path to Manchester, seeing the English city's devolved health and social care system as an ideal place to demonstrate the real world value of their medicines.

One fan of Manchester is Erik Nordkamp, managing director of **Pfizer Inc.** UK, who last month became the new president of the Association of the British Pharmaceutical Industry. Attending the NHS Expo conference in the city this week to speak about the importance of collaboration between industry and the UK health service, he said that the Greater Manchester area, with its 2.8m citizens, represents an ideal size to test initiatives aimed at transforming the way health care will be delivered both locally and, if successful, globally.

Nordkamp noted that the industry is on "a wave of innovation that we haven't seen for decades" with a pile of "shiny new toys in the shop." However, the advances made in clinical research, combined with the rise of digitalization, artificial intelligence and medtech, has led to the need for better operating models to improve uptake of innovation and he said that pharma has found a partner in Manchester that is willing to collaborate.

Two years ago, Greater Manchester became the first local authority in England to take control of its £6bn health and social care budget in an experiment that some observers at the time believed would be doomed to failure for being too complicated. However, something needed to be done, and speaking at NHS Expo, Ben Bridgewater, chief executive of Health Innovation Manchester, noted that "we were at the top of the tables you don't want to be top of," ie poor cancer survival rates and a high prevalence of cardiovascular and respiratory disease.

With a growing number of people with long-term illnesses that are devouring the region's health and social care budgets, Greater Manchester has been using data and digital technology to tackle some of the big health problems in the region, with an emphasis on prevention and early intervention to help control costs. A big point in Greater Manchester's favor is that unlike other areas in the UK, and indeed the rest of Europe, it can now boast single commissioning and provider boards for the region and this, plus the city's world-renowned academia centers, makes it very attractive to pharma.

Drug makers have been keen to contribute to a number of projects being run in Manchester that are moving away from the straightforward transactional relationships they had in the past, Nordkamp said. He argued that in times of increasing patient power, social media and more corporate social responsibility, "we are increasingly being asked what we are doing as an industry and are we offering value for money."

The industry is hoping that some of the initiatives underway in Manchester will help answer those questions. One of them is a chronic obstructive pulmonary disease project which sees **GlaxoSmithKline PLC**, Pfizer and **Chiesi Farmaceutici SPA** provide training and other resources to GPs and the community at large to develop personalized treatment plans that will hopefully reduce exacerbations and hospital admissions, and increase the use of cost-effective therapies, whether pharmacological or otherwise.

Another eye-catching project involves **Johnson & Johnson**'s Janssen unit, which has developed an outcomes payment scheme which involves tracking schizophrenia patients prescribed the company's antipsychotic *Xeplion/Trevicta* (paliperidone). Jennifer Lee, director of health economics, market access, reimbursement and advocacy at Janssen, told *Scrip* that the scheme reimburses the provider in full if the treatment does not work as planned, demonstrating the company's belief that paliperidone can play a role in preventing relapse and the substantial cost – between £12-25,000 – that goes with it.

Janssen is also a member of the Dementia Industry Group, along with the likes of **Merck Sharp & Dohme Ltd.**, **Biogen Inc.**, **Eisai Co. Ltd.**, **Otsuka Pharmaceutical Co. Ltd.** and Alzheimer's Research UK, which has recently linked up with Health Innovation Manchester and the Greater Manchester Health and Social Care Partnership. They are developing the Early Dementia Diagnostic Framework so that when disease-modifying treatments finally become available, people who may benefit can be rapidly identified and treated in time.

The list of collaborations between pharma and Manchester is a long one. **Novartis AG** and **Celgene Corp.** are running a psoriasis rapid access clinic in Salford, while **AbbVie Inc.**, MSD and **Gilead Sciences Inc.** are participating in a program which has the objective of eliminating hepatitis C in Greater Manchester by 2025 – Health Innovation Manchester estimates that 17,450 people in the area are infected and 7,000 are undiagnosed but just 28% are engaged with specialist services.

One challenge for the pharma industry with these projects is that they involve operating models which the drug makers do not entirely control. Nordkamp told *Scrip* that the highly regulated area in which companies work means "we are struggling, we don't renew ourselves" and a culture of multi-layered internal procedures that is embedded in big pharma makes change difficult and agility a problem.

As such, "people get frustrated" and projects in newer areas such as the digital space can often stall, he added. The industry needs to take more risks in its partnerships, Nordkamp stated, and work with partners to create data which it can genuinely trust.

Some of the programs being trialled in Manchester may not work, Bridgewater acknowledged, "but that doesn't matter, not everything will succeed." However, the pacts between Manchester and pharma are already driving better outcomes for patients and "we are working collaboratively to move towards best value not just best price."

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Gazyva, Imfinzi Launched Following Japan Listing, Entyvio In The Wings

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The anticancer antibodies *Gazyva* and *Imfinzi* have been launched in Japan following the granting of reimbursement prices under Japan's national health insurance scheme on August 29, both at levels that suggest the country is continuing to support the availability of such new therapies despite their relatively high prices.

Meanwhile, global blockbuster gastrointestinal drug *Entyvio* has also been granted a price but has yet to be launched in the country, where official forecasts suggest its sales may be relatively limited.

All three products were priced along with other new products, plus and additional indications, that were given approval in early July, in some cases only a matter of months after the first approvals globally, indicating the more parallel development tracks and faster approvals not common in Japan.

Chugai Pharmaceutical Co. Ltd. and partner **Nippon Shinyaku Co. Ltd.** said the anti-CD20 antibody Gazyva (obinutuzumab; originated by **GlycArt Biotechnology AG**, now part of **Roche**) was now available in Japan after receiving its first approval in the country, for CD20-positive, B-cell follicular lymphoma.

The product is reimbursed at JPY450,457 ($4,058) per 1,000mg/45mL vial for single intravenous infusion and is being co-marketed by Nippon Shinyaku, in a follicular lymphoma market estimated by Chugai to account for around 7-15% of the approximately 24,000 non-Hodgkin's lymphoma cases in the country.

Gazyva was first approved in the US in 2013 in combination with chemotherapy for chronic lymphocytic leukemia, and for untreated follicular lymphoma in November 2017.

Standard current therapy for the lymphoma indication in Japan is a combination of Chugai/Roche's *Rituxan* (rituximab) and CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) or Rituxan plus this combination minus doxorubicin.

In the Phase III GALLIUM study, described as "practice-changing" by one oncologist for the first-line treatment of follicular lymphoma, Gazyva reduced the risk of disease progression or death by 34% compared with Rituxan.

In the maintenance setting, Gazyva also has the advantage of relatively infrequent dosing, being given as a monotherapy only once every two months for up to two years.

In its price calculations for the product, the Central Social Insurance Medical Council (Chuikyo), the body which sets drug prices in Japan, forecast peak annual sales of JPY20.5bn for Gazyva.

IMFINZI EARLY ACCESS SCHEME

Also in oncology, **AstraZeneca PLC**'s Imfinzi (durvalumab) has been launched following price listing as a maintenance therapy following definitive chemoradiation therapy in locally advanced (Stage III), unresectable non-small cell lung cancer (NSCLC).

The UK-based company's Japanese subsidiary disclosed that the PD-L1-targeting antibody had been provided free of charge to selected patients in Japan following the July 2 approval and ahead of its formal launch under the NHI scheme.

Such early access is provided for under the country's so-called mixed medical care scheme, which allows the concurrent use of reimbursed and non-reimbursed medicines under certain high-need circumstances.

A total of 153 patients at 45 facilities had been provided with Imfinzi in this way ahead of the launch, AstraZeneca in Japan commented.

It pointed out that unmet need in the NSCLC sector "remains strong, with few new therapies approved for use at Stage III" over the past years, meaning few options for patients.

So far, Imfinzi is the only immuno-oncology drug to be approved in Japan for curative use in the Stage III setting, helped by data from the global Phase III PACIFIC trial, which showed an improvement in median progression-free survival of 11.2 months versus placebo.

Globally, this form of the disease – the majority of cases of which are unresectable - accounts for around a third of all NSCLC patients, and about 17% in Japan, AstraZeneca Japan noted. Some 89% of Stage III patients have recurrent disease within five years, even following standard chemotherapy.

Imfinzi was granted a reimbursement price of JPY112,938 (around $1,017) per 120mg vial and JPY458,750 per 500mg vial, with peak annual sales of JPY37.4bn forecast by Chuikyo.

ENTYVIO PRICED BUT NOT YET LAUNCHED

Meanwhile, **Takeda Pharmaceutical Co. Ltd.**'s international big-seller Entyvio (vedolizumab) has also been given a price under the NHI scheme following its July 2 approval as a treatment and maintenance therapy for moderate to severe ulcerative colitis unresponsive to standard anti-TNF-alpha therapy.

The alpha 4 integrin 7 blocker's launch reimbursement price will be JPY274,490 per 300mg vial, roughly on a par with its UK list price of £2,050.

However, in line with predictions from some analysts that its sales may be relatively limited in Japan, Chuikyo is forecasting peak annual sales of a modest JPY21.2bn (around $190m). Datamonitor Healthcare expects sales in the ulcerative colitis and Crohn's diseases uses combined to be even lower at around $66m in 2025.

The main constraining factors are seen by Datamonitor to be competition from newer oral therapies such as **Pfizer Inc.**'s JAK inhibitor *Xeljanz* (tofacitinb), a wide range of existing anti-TNF products, and Entyvio's later line use.

Furthermore, all forms of ulcerative colitis are said by Takeda itself to affect only around 220,000 people in Japan, and some studies have shown that the incidence of inflammatory bowel disease in general tends to be lower in Asian populations than in other major racial groups. Takeda in Japan told *Scrip* that it was now preparing for a launch following the listing (the final regulatory process that allows commercial roll out), but that it could not provide a specific date.

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From the editors of PharmAsia News.

Dermira Leans On Patient Experience With Hyperhidrosis As It Readies For Qbrexza Launch

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Dermira Inc. Chief Commercial Officer Lori Lyons-Williams said the company has been pursuing reimbursement since January for *Qbrexza* (glycopyrronium), approved in the US for primary axillary hyperhidrosis (excessive underarm sweating) at the end of June, and found that having patients share their experiences with skeptical payers has been the most effective strategy for obtaining coverage.

The topical drug administered once-daily via cloth wipes inhibits the interaction between acetylcholine and the cholinergic receptors that activate sweat glands in hyperhidrosis, a disease with an estimated 15m US patients, including 10m with axillary hyperhidrosis.

Dermira gave its first FDA-approved product – set to launch on Oct. 1 – a list price of $550 per month and revealed on Sept. 5 that it has negotiated reimbursement from payers and pharmacy benefit managers (PBMs), including **Express Scripts Holding Co.** and **OptumRx Inc.**, representing 34% of patients covered by commercial health plans in the US. The company's goal is 50% by Jan. 1.

In the name of patient access, Dermira also said that it will not raise the list price for Qbrexza this year or in 2019, and it will assist patients with out-of-pocket costs via its DermiraConnect program. The program will provide various patient support services, including a savings cards that will limit insured patients' monthly co-pays to $35; uninsured and underinsured patients will pay no more than $70 per month.

However, Lyons-Williams told *Scrip* in an interview, some payers to date have agreed to formulary placement at tier 2, which will keep covered patients' co-pays in the $25 range. Tier 3 coverage may mean $50-$70 co-pays, but that's where DermiraConnect will come in to cut out-of-pocket costs for patients under those plans to $35.

Dermira had to begin discussions with payers and PBMs with an introduction to hyperhidrosis and its impact on patients, while also talking about giving people access to Qbrexza at an affordable out-of-pocket cost.

Access, Lyons-Williams noted, was the company's top concern a year or so ago when it first approached payers, because reimbursement negotiations always are difficult, drug pricing is a sensitive issue and Qbrexza's indication is not well understood. But while there have been skeptics that questioned whether hyperhidrosis was just a cosmetic issue, since everyone sweats, many have been convinced that the condition needs better prescription therapies after hearing directly from patients.

"We've done a lot of things to get them down that path," Lyons-Williams said. "If I had to point to one thing that was probably the single biggest point of transition for the payers and PBMs, it was that we actually invited patients to come in with us for some of the appointments. There were large PBMs sitting across the table from people who actually live with hyperhidrosis. And as much as we tried to talk about the burden of the condition, they really didn't kind of get it until the patient was sitting across from them saying, 'This is really what it's like to live with this condition. This is how it impacts my life physically and emotionally and professionally and socially.'"

After talking with a patient who opened up his suit coat to reveal that he'd sweat through multiple layers of clothing during the course of a 30-minute meeting, she said, "it's kind of hard not to find that compelling."

Lyons-Williams noted that Qbrexza's list price "is one that allows us to derive access with them" and said negotiated rebates have been in line with normal discounts for new prescription drugs. She also pointed out that "the lengthy payer discussions weren't driven by rebates, but by the payers' recognition that hyperhidrosis is a serious condition and Qbrexza is a therapy that warrants a place on their formulary."

Many payers who've agreed to cover Qbrexza are not requiring onerous prior authorization or step-through therapy with topical agents, such as prescription aluminum chloride-based antiperspirants. The Dermira product also doesn't require prior treatment with **Allergan PLC**'s *Botox* (onabotulinumtoxinA), which may require up to 100 injections per treatment and has not been widely covered by payers for hyperhidrosis. Botox is indicated in hyperhidrosis for patients who haven't benefited from topical treatments.

Lyons-Williams, as a sales executive at Allergan before moving to Dermira in 2016, worked on commercialization of Botox in hyperhidrosis, so she is familiar with patient needs, prescriber concerns and payer limitations in this indication.

ACTIVATING PATIENTS

Dermira kicked off an online disease awareness campaign in December with a website – checkyoursweat.com – that does not promote the company or its product, but does allow patients to join a database for future outreach by Dermira.

The website also offers a tool similar to the proprietary patient-reported outcome in Dermira's Phase III program to help people assess whether they may have hyperhidrosis and should contact a dermatologist for treatment. A television advertising campaign in June increased traffic on that website by five to six times the pre-TV level.

"To date, we actually have had more than 850,000 people complete that online assessment, which – to be transparent – is just exceeding anything that we expected based on our experience," Lyons-Williams said. "And we're frankly on track to see that number reach 1m before we get to the October launch."

So far, about 93,000 people have entered their name in Dermira's patient database and the company's goal is to reach 100,000 by the time Qbrexza hits the market in October.

EXPERIENCED SALES TEAM

"The single largest tactic that we'll have to raise awareness with physicians is the sales force and as of two weeks ago we have hired and started to on-board 112 sales representatives," Lyons-Williams said. "We were pleasantly surprised at the massive response we got in the marketplace to our announcement that we were hiring – for those 112 positions, we actually received and processed more than 15,000 applications."

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CRISPR Therapeutics, Vertex Initiate First Industry-Sponsored Trial – What's Next?

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CRISPR gene editing has been a hot area of biotechnology for the past few years despite the absence of data in humans, but the field finally crossed a new threshold with initiation of the first industry-sponsored clinical trial, from **CRISPR Therapeutics AG** and partner **Vertex Pharmaceuticals Inc.** And, with aggressive investment in gene-editing technologies across the industry, this should be the start of a wave of clinical trials.

CRISPR Therapeutics and Vertex kicked off a 30-patient Phase I/II trial for CTX001 in transfusion-dependent beta-thalassemia, according to an Aug. 31 clinicaltrials.gov listing. The autologous therapy involves editing CD34-positive hematopoietic stem and progenitor cells outside of the body, so that when infused back into the patient they produce red blood cells containing fetal hemoglobin, which may provide a protective effect in beta-thalassemia or – in a future trial – in sickle cell disease.

However, while CTX001 is the first company-sponsored clustered regularly interspaced short palindromic repeats (CRISPR) candidate to be tested in humans, CRISPR is not the first gene-editing technology to reach patients.

CTX001 isn't even the first CRISPR-based gene-editing therapy to go into clinical testing; oncologists at Huaxi Hospital in China's eastern Sichuan province beat CRISPR Therapeutics and Vertex to the punch in 2016 with the first investigator-sponsored trial of this type of technology. The Phase I trial in China is testing a treatment using CRISPR to knock out the programmed cell death-1 (PD-1) gene in peripheral blood lymphocytes as a treatment for lung cancer.

But given the massive amounts of cash that have flowed into biopharmaceutical firms developing therapeutics with CRISPR technology, it's momentous to see a company and its partner take a program from preclinical testing into human studies, especially after the US FDA placed a clinical hold on the investigational new drug (IND) application for CTX001 in the treatment of sickle cell disease in May, a month after the IND was submitted to the agency. CRISPR Therapeutics said in its second quarter earnings report on Aug. 7 that it is working with the FDA and has identified a clear path to resolving the clinical hold on the sickle cell program.

The company's recently initiated single-arm, open-label Phase I/II trial for CTX001 in beta-thalassemia will be conducted at a hospital in Regensburg, Germany. The study's primary endpoint is the proportion of patients with a reduction in transfusions for at least six months and the 15 secondary endpoints include the proportion of patients achieving transfusion independence; the primary completion date is February 2021 and study completion date is May 2022.

PARTNERSHIPS POWER PROGRESS IN CRISPR PUSH

CRISPR Therapeutics and Vertex entered into a collaboration in October 2015 for the development of CRISPR gene-editing therapeutics to treat multiple diseases, including the initial indications of cystic fibrosis and sickle cell disease. The agreement gave CRISPR Therapeutics $105m up front in a deal worth up to $2.65bn to the then-private firm. Vertex has option rights for up to six drug candidates and licensed CTX001 in December.

CRISPR Therapeutics also entered into a novel agreement with **Bayer AG** in December 2015 to form a joint venture focused on gene-editing for the treatment of hemophilia, blindness and congenital heart disease. The JV, called **Casebia Therapeutics**, is operating from locations in San Francisco and Cambridge, Mass.

But ahead of these first two human trials for CRISPR therapies, the field has seen a lot of controversy, including ongoing patent disputes involving the technology's academic discoverers and the companies they founded, such as CRISPR Therapeutics. There also have been various concerns about side effects and technical challenges, but CRISPR Therapeutics CEO Sam Kulkarni shrugged off a controversy about resistance to CRISPR/Cas9 gene-editing in an interview with *Scrip* in January.

Investors remain entranced by CRISPR's promise despite the technology's potential challenges. CRISPR Therapeutics went public at $14 per share in October 2016 and closed at $49.88 on Sept. 6. Its stock rose 6% to $56.67 on Aug. 31 in response to the clinicaltrials.gov listing for the Phase I/II beta-thalassemia study with Vertex for CTX001.

The table below lists key CRISPR-based programs in development and plans for Phase I studies.

Other CRISPR companies include:

- **Exonics Therapeutics Inc.**, which launched in February 2017 with a focus on Duchenne muscular dystrophy *(Also see "Exonics Using CRISPR To Develop One-Time Treatment for Duchenne" - Pink Sheet, 27 Feb, 2017.)*;
- **KSQ Therapeutics**, which launched in October 2017 with $76m and plans to use CRISPR in drug discovery *(Also see "KSQ Comes Out Of Stealth Mode With $76m And Meeker As CEO" - Scrip, 2 Oct, 2017.)*; and
- **Agenovir Corp.**, a viral disease-focused firm acquired in May by Vir Biotechnology Inc. *(Also see "Agenovir: Using Gene Editing To Kill Viral DNA" - Scrip, 15 Aug, 2017.)*.

CRISPR Clinical Trial Plans

COMPANY	PHASE I PLANS	OTHER PROGRAMS
CRISPR Therapeutics	CTX001 is in Phase I/II for beta-thalassemia; planning is under way to lift an FDA clinical hold on the candidate in sickle cell disease.	An IND filing is expected in the US by year-end 2018 for CTX110, an allogeneic anti-CD19 CAR-T therapy for cancer; IND-enabling studies are ongoing for the BCMA-targeting CAR-T CTX120; and seven additional candidates are in the research stage, including a cystic fibrosis program that Vertex has an option to license. CRISPR had $319.7m in cash as of June 30.
Editas Medicine Inc.	EDIT-101 could be the first *in vivo* CRISPR gene-editing therapy in the clinic (CTX001 is an *ex vivo* CRISPR therapy); an IND filing is expected in October. **Allergan PLC** paid $15m to exercise its option to license the candidate for the treatment of Leber's congenital amaurosis (LCA) and will pay a $25m milestone fee once the IND is cleared by the FDA.	Editas lists all of its development programs as being in the discovery stage, including partnered programs. The company, which had $344.1m in cash as of June 30, entered into a partnership with **Juno Therapeutics Inc.** (now part of **Celgene Corp.**) in May 2015 to use CRISPR technology in the development of novel CAR-T and T-cell receptor (TCR) therapies.
Intellia Therapeutics Inc.	An IND filing is expected by the end of 2019 for a transthyretin amyloidosis program under an April 2016 partnership with **Regeneron Pharmaceuticals Inc.**	All of the company's programs are in preclinical development, but it lists the amyloidosis candidate partnered with Regeneron and a candidate to treat sickle cell disease under a collaboration with **Novartis AG** as being in late preclinical development. Intellia had $306m in cash as of June 30 and the company said its collaboration revenue through the second quarter of this year totals $114.1m.
Excision BioTherapeutics Inc.	Excision – unlike CRISPR Therapeutics, Editas and Intellia, which lean towards genetic diseases – is focused on the treatment of viral diseases. The company intends to take EBT 101 for the treatment of HIV-1 into the clinic in 2019.	The private company also plans to take EBT 103 for JC virus into the clinic in 2020, while 2021 is the target for trials testing EBT 104 for HSV-1 and EBT 105 for HSV-2 in humans. The clinical trial plan for EBT 106 for hepatitis B is to be determined. Excision raised $10m in seed funding in 2017. It licensed intellectual property from the **University of California, Berkeley** in November.

Merck KGAA also has developed what it views as next-generation CRISPR technology, but it primarily will be used for research rather than in gene-editing therapies. *(Also see "Merck Develops 'New And Improved' CRISPR" - Scrip, 18 May, 2017.)*

MaxCyte Inc. has developed CRISPR, TALEN and zinc finger nuclease (ZFN) gene-editing technologies for non-therapeutic and therapeutic uses. The company said in June that it entered into a Cooperative Research and Development Agreement (CRADA) with the National Institutes of Health (NIH), under which MaxCyte and the National Heart, Lung and Blood Institute (NHLBI) will work on preclinical development of treatments for sickle cell disease using CRISPR/Cas9-based single-nucleotide correction enabled by the company's cell engineering platform.

MaxCyte previously revealed a CRADA in June 2017 with the NIH's National Institute of Allergy and Infectious Diseases (NIAID) to develop treatments for X-linked chronic granulomatous disease using the company's CRISPR/Cas9 and Flow Electroporation Platform technologies.

BEYOND CRISPR: OTHER GENE-EDITING PROGRAMS

Sangamo Therapeutics Inc. revealed the first data from a human study for a gene-editing therapy on Sept. 5 for SB-913, which uses the company's ZFN gene-editing technology. However, results from the Phase I/II study of SB-913 in the treatment of mucopolysaccharidosis Type II (MPS II), otherwise known as Hunter syndrome, were mixed. *(Also see "Sangamo Data Is A Moment For Gene Editing, But Leaves Questions " - Scrip, 5 Sep, 2018.)*

Sangamo's stock fell 24% based on the data to $14.55 per share, while companies using CRISPR for gene editing also slipped on Sept. 5 – CRISPR Therapeutics fell 3.7% to $53.45, Editas dipped 2.4% to $32 and Intellia declined 2.2% to $30.06.

CRISPR and other gene-editing technologies are being used in next-generation chimeric antigen receptor T-cell (CAR-T) and other T-cell therapies for the treatment of cancer. The first two CAR-T therapies approved in the US last year and in the EU last month were Novartis' *Kymriah* (tisagenlecleucel) and **Gilead Sciences Inc.**'s *Yescarta* (axicabtagene ciloleucel) – autologous therapies that involve genetically engineering patients' own T-cells to target CD19 on lymphoma and leukemia cells.

TALEN GENE EDITING

Cellectis SA has three allogeneic gene-edited CAR-T therapies in or near the clinic, including two that use the company's TALEN gene-editing technology to edit donor T-cells – UCART19 in Phase I for relapsed or refractory acute lymphoblastic leukemia (ALL) and UCART22, which will be tested in B-cell ALL in a Phase I study starting in the second half of 2018.

Servier SA had global rights to UCART19 that were out-licensed to **Pfizer Inc.**, which recently spun out its allogeneic CAR-T programs in a well-funded start-up called **Allogene Therapeutics Inc.**

Precision BioSciences Inc. partnered with **Baxalta Inc.** for the development of gene-edited CAR-T therapies in March 2016 using Precision's proprietary ARCUS gene-editing technology. Baxalta subsequently was acquired by **Shire PLC**, which sold its oncology assets to Servier in April ahead of Shire's integration into its acquirer **Takeda Pharmaceutical Co. Ltd.**

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Sangamo Data Is A Moment For Gene Editing, But Leaves Questions

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Sangamo Therapeutics Inc. crossed an important milestone Sept. 5, becoming the first drug company to release efficacy data on a gene editing therapy in human patients. The data were early and in only four patients, but Sangamo was able to show a benefit on a key biomarker of the disease being studied.

The data also raised questions, however, because it didn't show the medicine helped patients produce a critical missing enzyme, and it remains unclear what regulators would require for approving such a treatment.

The big takeaway from the landmark data is that gene editing technology has a long way to go before new medicines reach the market. Gene editing works differently from traditional gene therapy; gene therapy involves delivering a new gene into cells to fix a defective gene, while gene editing technology works to correct defective DNA at the native location. Gene editing has the potential to modify the genome to address a wide range of genetic diseases, but it is further behind in development than gene therapy, the first of which has already reached the market.

Sangamo's management declared the Phase I/II data encouraging, saying it suggests early signs of success. Investors had concerns, however. The company's stock closed 24% lowerat $14.55.

The company is developing SB-913, a zinc finger nuclease (ZFN) gene editing product, for mucopolysaccharidosis Type II (MPS II), also known as Hunter syndrome. MPS II is a lysosomal storage disorder caused by deficient iduronate-2-sulfatase (IDS) enzyme, which breaks down glycosaminoglycans (GAGs), dermatan sulfate and heparan sulfate. Without IDS enzyme, the GAGs accumulate in organs and tissues, causing serious damage.

SB-913 is designed to insert a new copy of the IDS gene into the precise location in the DNA of liver cells, to enable the patient's liver to produce a supply of the missing IDS enzyme. The hope is that it could be a single intravenous infusion that would replace current treatment with weekly enzyme replacement therapy.

UNDETECTABLE PLASMA IDS RAISES QUESTIONS

The challenge for Sangamo is that while the company was able to show reductions in the important biomarker of MPS II – GAGs – in the four patients, the patients did not show a notable increase in the level of plasma IDS activity versus baseline.

Sangamo said that could be because the activity level may be below the level that can be measured by the current assay.

> The big takeaway is that gene editing technology has a long way to go

"The absence of detectable levels of IDS doesn't mean IDS isn't being produced by SB-913 and the liver cells," CEO Sandy Macrae told investors on a same-day call. "Cells of patients with MPS II are starving for IDS, and we believe that continuous exposure of cells to low levels of circulating IDS may be sufficient to drive enzyme uptake into cells and reduce or maintain suppression of GAGs."

Sangamo is working to develop an assay that can detect lower levels of the enzyme, but Macrae said he believes the editing has occurred.

"The GAG levels are convincingly reduced and the only way that could have happened is if IDS is produced, and the only way that could have happened is if the editing took place," he said.

Data from the Phase I/II trial, called CHAMPIONS, was released at the annual Symposium of the Society for the Study of Inborn Errors of Metabolism (SSIEM) in Athens, Greece. The data involved two patients in two separate cohorts, a low-dose and mid-dose cohort. Enrollment and dosing of two additional patients in a third high-dose cohort that is five times the mid-dose was recently completed. All patients are also being treated with weekly ERT.

In the mid-dose cohort 2, mean reductions in urinary GAGs, dermatan sulfate and heparin sulfate of 51%, 32% and 61%, respectively, were observed at 16 weeks post dosing. No serious adverse events were reported in any of the five patients included in the safety results.

ERT WITHDRAWAL COMES NEXT

The next steps for Sangamo are collecting the data from all three cohorts and then working toward withdrawing the patients from enzyme replacement therapy (ERT). Sangamo will work with site investigators to determine when withdrawal of ERT is appropriate for individual patients. That data will be critical to determining if SB-913 is helping to produce the needed IDS enzyme, and thus, its therapeutic potential.

"We want to see GAGs are reduced and remain reduced when the patient withdraws enzyme replacement therapy," Macrae said. "That is the target product profile for this technology."

"I think if the patient has to take our medicine and take ERT on top of it, it's a less attractive proposition," he added.

PROVISIONAL APPROVAL?

The CEO said there is a lot still to be worked out about the requirements for getting SB-913 over the finish line at FDA. GAGs could be an endpoint FDA would accept, he speculated, but noted the company would also need to measure the clinical benefit. "You might be able to get provisional approval with a biomarker and follow-up later," he added.

Sangamo signed a potentially lucrative licensing deal with **Gilead Sciences Inc.** earlier this year, securing $150m upfront and up to $3bn in milestones and fees for an exclusive license to the ZFN technology for oncology indications. Sangamo was one of the early pioneers working in gene editing, while newer players like **Editas Medicine Inc.** and **CRISPR Therapeutics AG** have gotten attention over the last five years.

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CEO Interview: Ulcerative Colitis Trial Shows Abivax's HIV Candidate Has Broader Potential

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Abivax will start trialing its novel lead compound in other anti-inflammation conditions after a Phase IIa trial showed ABX464 to be safe and effective in ulcerative colitis patients who are refractive to current therapies, including anti-TNF treatment, the French biotech's CEO told *Scrip*.

Orally administered ABX464 had already shown good results in a recently completed Phase II clinical trial to demonstrate it can deplete HIV reservoirs with a lasting effect of up to 60 days with little or no side effects, offering the prospect of a major advance over current HIV antiviral treatments.

> 'There are other inflammatory indications that we are going to tackle now, including Crohn's and rheumatoid arthritis, and that changes the profile of Abivax dramatically'

Now, a relatively small Phase IIa clinical trial has validated the biotech's claim that the compound delivers impressive anti-inflammatory effects by triggering an increased expression of miR124, which is a potent anti-inflammatory microRNA.

TOP-LINE DATA

That placebo-controlled clinical trial was conducted in 32 patients for induction treatment of moderate-to-severe ulcerative colitis (UC) refractory to anti-TNF monoclonal antibodies or corticosteroids.

Its topline data showed ABX464 was safe, well-tolerated, and demonstrated statistically significant efficacy based on both clinical and endoscopic endpoints in this study.

Also, the onset of the therapeutic effect of ABX464 was fast, with a difference of the reduction of the partial Mayo score between ABX464 and placebo being observed at the first assessment following treatment for two weeks, which became significant ($p<0.02$) at eight weeks. Similarly, the difference of the reduction of the total Mayo score after eight weeks was statistically significant ($p<0.03$), according to Abivax.

The Mayo score and a non-invasive 9-point partial Mayo score are used as outcome measures for clinical trials assessing therapy for ulcerative colitis. The higher the score, the more severe the case of ulcerative colitis. The highest score possible is a 12. Scores should be compared with previous scores taken for a patient.

GIVES NEW VALIDATION

Abivax now has validation in a completely different therapeutic area where a novel therapeutic approach could do extremely well, its CEO Hartmut Ehrlich said in an interview.

"We cannot over-estimate the value of this data to Abivax. It opens up ulcerative colitis with an orally administered drug that has a brand new mechanism of action. And there are other inflammatory indications that we are going to tackle now, including Crohn's and rheumatoid arthritis, and that changes the profile of Abivax dramatically," he said.

Based on the trial data, Abivax will now accelerate its trialing of ABX464 in ulcerative colitis.

"We will now move it into a Phase IIb trial in approximately 180 patients with moderate to severe ulcerative colitis," the CEO said.

He added that the latest clinical data data could be extrapolated beyond that indication.

"You can define this as ulcerative colitis but also as inflammatory bowel disease and by inference Crohn's disease, and we will soon initiate a Phase IIa clinical trial in Crohn's with ABX464. But you can go more broadly and identify the potential as the whole anti-inflammatory space," he said, adding that "the global sales of these products are exceeding $30bn by now and that speaks to the potential of drugs in that space that are safe and efficacious."

PHARMA PARTNER SOUGHT

To be successful though, Abivax will need to find a big pharma to partner its lead ABX464.

"We are too small a biotech to market ABX464 in either of these important but competitive therapeutic indications, those being HIV or ulcerative colitis. We want to have a partner for the Phase III program where we would certainly seek a partial funding by a third party and the market expertise offered from a larger pharma company."

He said the ideal situation would be for Abivax to have just one partner.

"That said, I could also see the possibility of Abivax partnering with two companies involving either a global split of the rights to ABX464, or the rights being distributed by indication. We'd be open to that idea as well," Ehrlich said.

REGULATORY PATHWAYS

The regulatory pathway for the drug would differ depending on the indication, he noted.

"There is a wide gap in available guidance from the regulatory agencies regarding regulatory pathways for therapies to treat HIV and ulcerative colitis – in HIV there is very little definition so far, while in ulcerative colitis there is very clear guidance from the FDA and in Europe as to what is required if you want to eventually file your NDA in a successful way," the CEO explained.

"An advantage of the inflammatory indications is that many aspects of the process are set in stone, and it is up to us the company to bring the data being requested.

"On the HIV side, however, it's still more of a back-and-forth exercise with regulatory authorities in order to get the desired label for the product," Ehrlich said.

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Gilead/Galapagos' Trailing JAK1 Filgotinib Boosted By AS Trial

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Gilead Sciences Inc. and **Galapagos NV** now have promising mid-stage clinical data for their investigational JAK1 inhibitor filgotinib in another inflammatory disease, ankylosing spondylitis.

The topline TORTUGA Phase II study results give a further boost to the drug as the companies await the data from the Phase III FINCH 2 study in rheumatoid arthritis later this year. They also reinforce filgotinib's safety profile, which is expected to be a vital differentiator for a product that is trailing its competitors slightly in a well-served market.

In the TORTUGA trial in 116 patients with moderately to severely active ankylosing spondylitis, 200 mg once daily of filgotinib brought significantly greater improvements in AS Disease Activity Score (ASDAS), the primary endpoint, at week 12 than placebo, with a mean change from baseline of -1.5 versus -0.6 ($p<0.0001$). ASDAS is a standard composite index for assessing the disease and incorporates five disease activity variables.

The companies added that more patients receiving filgotinib also achieved an ASAS20 response than placebo patients (76% versus 40%, $p<0.0001$). Further details will be presented at a future scientific meeting.

Analysts say that at first glance, and bearing in mind the problems with comparing across trials, the data position filgotinib well against its rivals.

Bryan Garnier analysts said: "Although these results need to be confirmed in a Phase III trial and in over a longer period of time, we note that the placebo adjusted ASAS20 responder rate of 36% appears very competitive to the c.30% placebo adjusted responder rate shown by secukinumab in the MEASURE 1 trial over a slightly longer period of time (i.e., 16 weeks)."

Pfizer Inc.'s JAK inhibitor *Xeljanz* (tofacitinib) Phase II ASAS20 at week 12 were 81% with a 5 mg *bid* dose ($p<0.001$) and 56% with a 10 mg *bid* dose (not significant) compared with 41% for placebo, noted Jefferies analysts, "at best comparable to filgotinib," they said in a Sept. 6 research note.

Safety data were also reassuring, despite one case of non-serious deep vein thrombosis (DVT) seen in a patient with an inherited risk of thrombosis.

Gilead and Galapagos said that overall adverse events were generally mild or moderate and no new safety signals were seen. There was one treatment-emergent serious adverse event reported for a patient receiving filgotinib who experienced pneumonia and recovered after hospital-based antibiotic treatment.

The Jefferies analysts said the DVT case would likely initially raise widespread concern, given that DVT is a well-documented risk for **Eli Lilly & Co./Incyte Corp.**'s competing JAK inhibitor, *Olumiant* (baricitinib), and has been scrutinized for **AbbVie Inc.**'s upadacitinib. *(Also see "AbbVie's New Generation JAK inhibitor Looks Good But CV Specter Looms" - Scrip, 12 Sep, 2017.)* "Importantly we understand this patient had an inherited risk of thrombosis (Factor V Leiden gene mutation) and the DVT occurred in the follow-up period post-treatment, hence was later assessed to not be treatment-related." They added that the pneumonia case was "not unexpected as for all immuno-modulating drugs."

The next test for filgotinib, for both its efficacy and safety profile, is the Phase III FINCH-2 study in the lead indication of rheumatoid arthritis. Again, its thrombotic profile will be of huge interest. Jefferies analysts say they are optimistic that filgotinib's high selectivity for JAK1 could make it best in class as it does not increase platelets (making DVTs less likely) and does not decrease hemoglobin or lymphocytes (making anemia and infections less likely). "Since filgotinib is likely to be the fourth JAK1 to market, a clean safety profile could help drive use."

Data from FINCH-2 are expected by year end, to be followed by FINCH-1 and -3 results in 2019, and a possible launch in 2020, if all goes well and assuming no problems with the Phase II MANTA testicular toxicity study (expected in H2 2019).

Success should open up a large market for filgotinib, although one that could be curtailed by the loss of patent protection for Xeljanz in 2025. Peak sales have been forecast in the regions of $6bn, half of which are expected to come from rheumatoid arthritis. Ankylosing spondylitis should contribute round 10% of sales.

TORTUGA is one of several Phase II trials of filgotinib in inflammatory diseases. In addition, there is the ongoing FINCH Phase III program in rheumatoid arthritis, the DIVERSITY Phase III trial in Crohn's disease (also small bowel and fistulizing Crohn's disease Phase II studies) and the Phase III SELECTION trial in ulcerative colitis. A Phase III trial in ankylosing spondylitis is expected to follow next year.

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

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

Selected clinical trial developments for the week 31 August–6 September 2018

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
PHASE III RESULTS PUBLISHED			
Shionogi & Co. Ltd./ Roche	*Xofluza* (baloxavir marboxil)	flu	CAPSTONE 1; *NEJM*, Sept. 6, 2018.
Bausch Health Companies Inc.	loteprednol etabonate ophthalmic gel	pain after cataract surgery	Study 842; *Journal of Cataract and Refractive Surgery*, Sept. 2018.
PHASE III INTERIM/TOP-LINE RESULTS			
AstraZeneca plc	anifrolumab	systemic lupus erythematosus	TULIP 1: missed primary endpoint.
EyeGate Pharmaceuticals Inc.	EGP-437	anterior uveitis	Not non-inferior to standard of care.
Histogenics Corp.	*NeoCort* cell therapy	knee cartilage injury	Some clinically meaningful outcomes.
Recro Pharma	N1539 (meloxicam iv)	post-surgery pain	Pain relieved and well tolerated.
UPDATED PHASE III RESULTS			
bluebird bio	*Lenti-D* gene therapy	adrenoleukodystrophy	Starbeam; reduced disease progression.
Biohaven Pharma Holding Co. Ltd.	rimegepant	migraine	Well tolerated, rapid and sustained pain relief.
PHASE III INITIATED			
Biogen Inc.	*Cirara* (iv glibenclamide)	ischemic stroke, severe	CHARM; for treatment and prevention.
argenx NV	efgartigimod	myasthenia gravis	In patients with generalized disease.
NeuroRx Inc.	NRX-101 (D-cyclo-serine/ lurasidone)	bipolar disorder with acute suicidal ideation and behavior	SBD-ASIB; a fixed dose oral combination.
PHASE III ANNOUNCED			
AstraZeneca	AZD3759	non-small cell lung cancer (NSCLC)	Asia (EGFR Mut+); as first-line therapy.
ProQR Therapeutics NV	QR-110	Leber's congenital amaurosis	ILLUMINATE; a double blind 12-month study.
Xenon Pharmaceuticals Inc.	XEN496 (ezogabine)	KCNQ2 epileptic encephalopathy	A rare pediatric disorder.
PHASE II INTERIM/TOP-LINE RESULTS			
Gilead Sciences Inc./ Galapagos NV	filgotinib	ankylosing spondylitis	TORTUGA; met primary endpoint.
BioCryst Pharmaceuticals Inc.	BCX7353	hereditary angioedema	ZENITH-1; signs of efficacy, well tolerated.
Tesaro Inc.	*Zejula* (niraparib) plus TSR-042	NSCLC, first-line	JASPER; objective responses seen.
Synlogic Inc.	SYNB1618	phenylketonuria	Well tolerated, signs of efficacy.
NeuroRx Inc.	NRX-101 (D-cyclo-serine/ lurasidone)	bipolar disorder with acute suicidal ideation and behavior	STABIL-B; encouraging efficacy data, well tolerated.
Abivax SA	ABX464, oral	ulcerative colitis	101EU; effective and well tolerated.
iXBiopharma Ltd.	*Wafermine* (ketamine) sublingual wafer	acute pain post bunionectomy	Pain relief observed, well tolerated.
Checkpoint Therapeutics Inc.	CK-101	NSCLC	Encouraging safety and efficacy data.
Arrowhead Pharmaceuticals Inc.	ARO-HBV	hepatitis B	Signs of efficacy, well tolerated.

Source: Biomedtracker | Informa, 2018

Novo Nordisk Grabs Shark Antibody-Based CNS Delivery Technology From Ossianix

JOHN DAVIS john.davis@informa.com

Novo Nordisk AS has followed in the footsteps of another European mid-sized pharmaceutical company and entered into a research collaboration with Philadelphia, PA-based **Ossianix Inc.** on the development of technology based on shark antibodies which allows therapeutic proteins to be smuggled across the blood-brain barrier (BBB).

Getting therapeutic antibodies to cross the BBB efficiently and effectively has been the aim of much drug delivery research, and Ossianix, a privately held US company set up in 2012 by ex-**Wyeth** and ex-**Pfizer Inc.** researchers, has been exploring the use of the single-domain variable part of a subset of heavy chain-only antibodies made by sharks, called VNAR (variable new antigen receptor) antibodies, to facilitate the entry of therapeutic agents into the CNS.

Single-domain VNAR antibodies are small and stable and can be used to ferry a therapeutic antibody inside the CNS, by linking the antibody to a VNAR which binds to the BBB transferrin receptor, a Trojan horse approach to transporting biologics into the nervous system. The process delivers therapeutic doses of MAbs with long-lasting pharmacokinetic properties, Ossianix says, which has been supported by Denmark's **Lundbeck Inc.** and the US seed investor, BioAdvance, which provides early-stage capital for companies in the mid-Atlantic region.

Novo Nordisk is not straying far from its core expertise in metabolic diseases; the research and option agreement with Ossianix involves the potential delivery of therapeutic molecules for diabetes and other metabolic diseases across the BBB. Ossianix will use its patented single-domain VNAR antibodies to deliver a pre-defined number of therapeutic agents to Novo Nordisk, and the Danish company will be responsible for the development and commercialization of those agents.

Financial terms were not disclosed, although the companies said in their announcement on Sept. 4, 2018 that Ossianix would receive up-front, preclinical, clinical and commercial milestone payments, R&D funding and product royalties, while Novo Nordisk would have a buyout option on each product on pre-agreed financial terms.

The arrangement is the latest in a long line of agreements entered with biotech companies by Novo Nordisk this year, particularly in the area of drug discovery, as the Danish company battles with intense competitive and pricing pressures on its best-selling insulin franchise.

In late August 2018, the Danish company entered into a research collaboration with **Evotec AG** for metabolic diseases including non-alcoholic steatohepatitis, cardiovascular disease and diabetic kidney disease.

Published online 4 September 2018

APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
Julie Feder	Aura Biosciences Inc	Chief Financial Officer	Verastem	Chief Financial Officer	4-Sep-18
Benjamin Hickey	Halozyme Therapeutics Inc	Chief Commercial Officer	Bristol-Myers Squibb	General Manager, UK and Ireland	10-Sep-18
Charles Morris	Radius Health	Chief Medical Officer	PsiOxus Therapeutics Limited	Chief Development Officer	4-Sep-18
Sanjay Keswani	Rheos Medicines	Chief Executive Officer	Roche	Senior Vice President and Global Head, Neuroscience, Ophthalmology and Rare Diseases	6-Sep-18
John Hunter	SiteOne Therapeutics Inc	Chief Scientific Officer	Merck & Co. Inc	Vice-President of Research Science and Head of Discovery Research for the Cardio-Renal Therapeutic Area	6-Sep-18
Ginna G. Laporte	Tempest Therapeutics	Chief Medical Officer	Corvus Pharmaceuticals Inc	Vice President, Clinical Development	4-Sep-18
Karima Boubekeur	Tillotts Pharma AG	Global Head, Innovation	AstraZeneca	Vice President Emerging Portfolio and Search & Evaluation	1-Sep-18

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

Source: Medtrack | Informa, 2018

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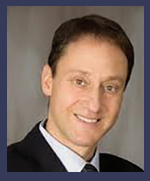

Professor Kenneth Getz, Director and Associate Professor at **CSDD**, **Tufts University School of Medicine**, *USA*

Inma Martinez, Venture Partner, Data Sciences & Product Innovation at **Deep Science Ventures**, *UK*

Daniel Prieto-Alhambra, Associate Professor & NIHR Clinician Scientist at **Oxford University**, *UK*

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