Pfizer Wants FDA To Stop Sponsor Promos From Implying Biosimilars Are Inferior

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Seeking to boost biosimilar uptake, Pfizer Inc. is asking the FDA to issue guidance to deter innovator companies from suggesting that biosimilars are not as safe and effective as reference biologics.

In an Aug. 22 citizen petition, Pfizer requests that the agency publish a guidance document that describes the types of sponsor communications about reference products and biosimilars – including interchangeable biologics – that would be false or misleading. It contends inappropriate messages include those that suggest there is a clinical difference between reference products and biosimilars or that a patient should not be switched to a biosimilar.

The company also asks that the guidance clarify that biosimilar sponsors may communicate clinical trial data about their products even if it is not in labeling.

“For the few biosimilars that have both obtained marketing approval and achieved commercial launch, market acceptance, in general, has been much slower than anticipated,” the petition states. “We believe that a major factor contributing to this slow uptake is a lack of market confidence in biosimilars resulting from the efforts of certain reference product sponsors to disseminate false and misleading information that casts doubt about the safety and efficacy of biosimilars in the minds of patients and prescribers.”

The FDA has approved 12 biosimilars, four of which have launched to date. Pfizer has three approved biosimilars and has launched one in partnership with Celltrion Inc., Inflectra (infliximab-dyyb), a biosimilar to Remicade.

Inflectra has had a hard time gaining acceptance on the market, however, and Pfizer has taken a lead in trying to take down barriers brand companies have put up to protect their blockbuster biologics. It has called out J&J’s use of exclusory contracts with payers to block biosimilars. In a suit filed last year, Pfizer claimed J&J required insurers to sign contracts explicitly agreeing not to cover Inflectra, either at all or only in rare circumstances when patients fail treatment with Remicade first. It also alleges that J&J is bundling rebates on different products in its portfolio along with Remicade, so that payers who don’t accept exclusive contracts will lose out on other portfolio rebates. Earlier this month, a district court denied J&J’s motion to dismiss the complaint.

FDA Commissioner Scott Gottlieb has also been a vocal critic of practices that drug manufacturers, insurers and pharmacy benefit managers have used to limit the biosimilar market.

With the citizen petition, Pfizer is trying to spur the FDA to concrete action on promotional practices and company communications around brands and biosimilars.

“FDA needs to proactively remind people that a biosimilar has no clinically meaningful differences and will have the same safety and efficacy as the reference product,” Juliana Reed, Pfizer’s corporate affairs global biosimilar lead, said in an interview. “That key message needs to be included in...
News that the Chinese FDA has approved Chi-Med’s Elunate (fruquintinib) capsules for previously treated colorectal cancer in China is a further indication of how China, the world’s second largest pharmaceuticals market, is rapidly embracing innovative drugs. This approval represents the first for a homegrown innovative medicine but, in recent years, the CFDA has been transformed so that innovative drugs developed elsewhere in the world have been made accessible to Chinese patients more quickly than before.

Indeed, AstraZeneca’s Targinos (osimertinib) was approved in China at about the same time regulators in the US and EU granted full approval, while Roche’s Alecensa (allectinib) was approved within nine months of US and EU approvals. While the prices companies can charge for innovative drugs are lower in China than in Western markets, the sheer size of the market is already delivering substantial growth opportunities for multinationals who are seeing revenues squeezed in traditional markets. According to Deutsche Bank, the top 20 pharma companies are seeing 18% year-on-year growth in Chinese revenues.

While these milestones will cheer the industry, the one cloud on the horizon is the potential fallout from the vaccines scandal, which saw hundreds of thousands of Chinese children given ineffective treatments, that forced the resignation last month of China’s top regulator Bi Jingquan. Since he took office in 2015, Mr Bi has been a major driver in the CFDA’s transformation. It is not yet clear whether his departure might put the brakes on the rate of change in the Chinese regulatory landscape.
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Genomics CEO Says Vertex R&D Pact, £25m Series B Secure Its Viability
https://bit.ly/2Pn4iG1
The Oxford biotech raised £25m from investors and inked a collaboration with Vertex that’s probably worth tens of millions of pounds, maybe much more. The founder and CEO of Genomics PLC tells Scrip the four-year-old company will also seek other pharma alliances.

Art Of War: Why Pharma Must Do Digital Dance In China
"Winning the war without fighting. Using five types of fire attacks." Sounds familiar? Sun Tzu’s 2,000 year-old wisdom on the art of war is echoing down the ages, and winning in China today means that pharma needs to embrace a digital strategy more than ever before.

BeyondSpring CEO On Plinabulin’s Dual Regulatory Pathway For US and China
https://bit.ly/2MPgX1C
BeyondSpring’s lead clinical asset, plinabulin, is currently in late-stage global registrational studies for the prevention of chemotherapy-induced neutropenia and treatment of lung cancer, with read-outs expected soon. CEO Lan Huang discussed coming catalysts and their potential with Scrip.

CAMELLIA Adds To Belviq’s CV Confidence But ‘Caution’ Still Needed
Full results from a large cardiovascular outcomes study with Belviq show the Eisai/Arena obesity drug was not associated with higher such risk versus placebo, but neither did it show benefits in reducing major CV events, leaving uncertainty over its increased uptake amid lingering issues around diabetes and valvulopathy risks.

Deal Watch: Emergent Strikes Again, Acquiring Adapt
https://bit.ly/2MIg1Hg
Following its purchase of PaxVax earlier this month, Emergent is taking on Narcan nasal spray for opioid overdose as part of its acquisition of Adapt. Also-busy Evotec teams up with Centogene in rare genetic disease and Novo in diabetes/obesity.

IPO Update: August Had A Slow Start, But New US Filings Hint At Busy September
https://bit.ly/2wHHJ0L
There were only two biopharma IPOs in the US during August, bringing the year’s total to 47. But with eight new filings in August, launches in September could rival July’s total of nine first-time offerings, especially since this average return on this year’s IPOs remains in positive territory.

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Bluebird Casts Wide Partnering Net To Keep Advancing Cell Therapy

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With the exception of one small acquisition in 2014 to bring translational technology in house, bluebird bio Inc. has looked to collaborations to expand its capabilities in developing CAR-T and TCR therapies for what it hopes will be a wide range of solid and hematologic cancers.

“We’ve had a philosophy which [CEO] Nick [Leschly] refers to as the anti-pure play, where we’ve been willing to do collaborations around different technologies that we believe give us an advantage in the complex biological problems of cell and gene therapy and the targets you can engage with those technologies,” bluebird Chief Scientific Officer Philip Gregory said in an interview. “We’ve taken a fairly humble approach in the sense that we recognize that not everything that’s the best possible solution is going to be invented within the four walls of bluebird.”

This strategy centers on three areas of focus: 1) the right targets combined with antibody and TCR technology to facilitate the recognition of tumor cells by bluebird’s chimeric antigen receptor T-cell (CAR-T) and T-cell receptor (TCR) therapeutics; 2) tools for product optimization, including gene editing, manufacturing enhancements and synthetic biology; and 3) synergistic collaboration with academic and private-sector partners.

The Cambridge, Mass.-based firm unveiled a cancer cell therapy collaboration on Aug. 23 with Gritstone Oncology, under which the partners will combine their technologies and know-how to identify novel tumor-specific targets and possible TCR therapy candidates directed at those targets. The better targeting and specificity could help bluebird advance CAR-Ts from hematologic to solid tumors, a common goal across the field.

The company told Scrip that its strategy for building upon its B-cell maturation antigen (BCMA) program in multiple cancers means that “we need the right tools and technology to drive transformative outcomes across all tumor types, including solid tumors.”

The Gritstone collaboration is the 7th cancer-focused deal in five years as bluebird looks toward leadership in the next generation of adoptive cell therapy. The biotech also licensed rights to its lentiviral vector technology patents to GlaxoSmithKline PLC in 2017, which the pharma will use in developing gene therapies for a pair of rare autoimmune disorders.

Bluebird started out focused on developing gene therapies for disorders such as childhood cerebral adrenoleukodystrophy, before switching its focus to cancer. Previously known as Genetix Therapeutics until 2010, it used stem-cell harvesting to develop gene therapies for rare diseases such as childhood cerebral adrenoleukodystrophy (CALD) and beta-thalassemia/sickle-cell anemia.

**Partnering for Capabilities**

In September 2014, bluebird acquired gene-editing biotech Precision Genome Engineering Inc. in a stock transaction valued at $19.2m to enable more specifically engineered CAR-T and TCR therapies. But the remaining deals bluebird has signed since 2013 have been structured as partnerships, although Gregory said M&A activity is not off the table if such a deal offers “the right fit and the right weight.”

“The are tremendous skill sets that exist outside of bluebird that can be applied to the problems we’re trying to solve; in our case, targeting moieties for T cells for CARs and TCRs,” the exec said. “Sure, we could try to organically build that ourselves, but the right sorts of collaborations solve for that and bring in very bright people with lots of great ideas in addition to the technologies that they’ve already become experts at.”

“We have a pretty aggressive approach to partnerships [and] I don’t think we’re done,” Gregory added. “As we continue to develop and understand these technologies, we’ll understand different holes that we need to fill. Some we’ll fill internally through R&D efforts and others we’ll feel are best solved by collaboration with the brightest and best that’s external to the company.”

While bluebird doesn’t rule out M&A activity of its own, the biotech is seen by some as a takeover target in its own right, especially after January’s $9bn acquisition of Juno Therapeutics Inc. by Celgene Corp. BTG analyst Dane Leone said in a March 8 note that bluebird saw “continuous” offers after the Juno takeout.

“Bluebird now stands as the leading independent company with integrated genetic and cell therapy capabilities,” he wrote. “This all said, we truly do not think that the management team has any interest in selling the company within the near term.”

Bluebird is paying $20m in upfront cash to Gritstone while making a $10m Series C preferred equity investment in the Emeryville, Calif.-based biotech. Gritstone also may earn development, regulatory and commercial milestone fees for therapeutic candidates resulting from the partnership, as well as tiered royalties on any resulting products that reach the market.

About two weeks before announcing the Gritstone tie-up, bluebird inked a joint venture-like collaboration with Regeneron Pharmaceuticals Inc., under which Regeneron made a $100m equity investment in bluebird. The two firms said Aug. 6 that they will split costs evenly under a collaboration pairing bluebird’s lentiviral vector-based T-cell modification technology, gene transfer capabilities and cell therapy development expertise with Regeneron’s VelociSuite antibody and TCR discovery and characterization platform.

Gregory said the work being done with Gritstone may be applied to the Regeneron collaboration and a prior TCR-focused partnership signed with MediGene AG in 2016. The deal was amended in May to increase the number of targets to six, with MediGene getting $8m in additional cash, R&D funding and potential earn-outs up to $500m.

Gritstone’s part of the puzzle is helping bluebird identify and validate novel therapeutic target proteins that are not expressed on the surface of the tumor cell. While proteins such as BCMA and CD19 are found on the tumor cell surface, about 70%
of the proteins that could be targeted therapeutically with TCRs are located internally, Gregory explained.

Gritstone’s EDGE technology platform employs artificial intelligence and computational algorithms to predict which peptides will be loaded into a tumor cell and expressed on the cell’s surface. In addition, Gregory noted, the company offers a large dataset of mass spectrum-identified peptides.

“They’re eluting the very peptides that are present in the MHC [major histocompatibility complex] away from tumor samples and asking exactly what are the peptides that are expressed on that cell,” he said. This could enable bluebird to predict the right peptide to target with a therapy and then see it in the majority of tumor isolates of a particular type.

“This is about target discovery, about picking the best possible targets. We could give a target discovered by our collaboration with Gritstone to Medigene and ask them to develop a TCR for that,” Gregory pointed out. Likewise for Regeneron, he added.

“In addition, as part of this deal, Gritstone will also make TCRs against a subset of these targets,” he said. “So, it really gives us three different methods to create TCRs against what hopefully are both novel but well-validated targets that should take some of the unknowns out of TCR-based cellular therapies.”

Gritstone’s technologies also might be useful to select patients for clinical trials, by helping to clarify the frequency with which a peptide is presented by tumors of different origins. That could lead to a TCR therapy that would be likely to work in most patients with a certain type of cancer, Gregory explained. “Then, we can also take on targets that are less universally expressed, but confirm that a specific patient is expressing the precise peptide that the TCR is designed against,” he said.

Bluebird has been signing partnerships and acquiring technological capabilities since its 2013 collaboration with Celgene.

“Gritstone’s EDGE technology platform in India now can take on targets that should take some of the unknowns out of TCR-based cellular therapies. That collaboration produced two clinical CAR-T candidates to date – BB2121, in Phase II for relapsed/refractory multiple myeloma and Phase I for brain cancer; and BB21217 in Phase I for multiple myeloma.

The Celgene tie-up has been amended several times, including in 2015 to focus specifically on B-cell-targeted therapies and in March, when bluebird opted in on its right to co-develop and co-commercialize BB2121 in the US.

Bluebird enjoys a strong balance sheet, having raised $125m over three venture rounds from 2010 to 2012, netting $108m via its 2013 initial public offering and then bringing in more than $2.6bn in seven follow-on public offerings.

Following an attention-grabbing $120m Series A financing in 2015, Gritstone pulled in a $92.7m Series B last September to further fund its work on personalized neoantigen-targeting vaccines. On Aug. 24, Gritstone filed for an IPO to raise up to $80m. Published online 28 August 2018

GSK Puts Tail End Brands On The Block In India
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GlaxoSmithKline PLC appears on course to pruning its product portfolio in India and is believed to be looking for potential buyers for a basket of “trademarks” spanning various therapy groups including cardiology, anti-infectives, dermatology and pain.

The sale plans are part of portfolio rationalization measures underway in the country as the British multinational tweaks its emerging markets business model with an eye on driving sustained profitable growth.

Once the top-ranked company in India, GSK is currently at ninth position in India as per July 2018 MAT (moving annual total) sales data from AIOCD AWACS, a market research agency that tracks retail sales.

Industry analysts told Scrip that the trademarks proposed for divestment could potentially include products like Espazine (trifluoperazine), Dapsone (dapsone) and Zemternil (cefprozil), among others, though there is no official word on this.

Analysts indicate that the tail-end divestitures account for a small percentage – estimated at just 1-2% – of GSK India’s overall sales. Manufacturing facilities and sales personnel, they claimed, are unlikely to be part of the proposed transaction, and some of the products in any case may be manufactured by third parties.

GSK India declined to comment on potential portfolio divestment plans.

GSK’s rationalization efforts in India are essentially geared towards ensuring that the company can focus resources on a basket of key brands to bolster growth, alongside bringing in innovative products from its global pipeline.

GSK’s Indian arm, GlaxoSmithKline Pharmaceuticals Ltd., which has been “evolving” its commercial operating model in India, expects to focus on around 20 key brands in selected therapy areas over the next 18 months or so, down from around 70 brands currently.

The company recently told Scrip that it is focusing on key brands to drive growth in identified therapy fields where there is “significant” unmet patient need. “We are also increasing our field force by a third, and are committed to India and its patients for the long-term,” GSK said at the time.

Last year, CEO Emma Walmsley had underscoring the need to drive growth with “competitive products and competitive commercial execution” as among a string of priorities to improve globally the company’s performance and returns for the long term.

GSK had, at the time, outlined its intent to simplify its portfolio, as a key enabler of improving its network efficiency. It indicated that it expects to divest or exit over 130 non-core tail brands within pharma alone — brands that could create complexity for its supply chain. “Overall, we are looking for a 22% reduction in the number of pharma brands. We are also looking to reduce our overheads in manufacturing across the whole group with a simpler network and improved productivity,” Walmsley stated at an investor event in July 2017.

RECENT DIVESTITURES
Portfolio tucks are not really uncommon in competitive emerging markets like India, against a backdrop of multiple commercial pressures including sustained official efforts to cap prices of essential medicines. The country has also seen a push towards generic name prescriptions.

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Ferring Pharmaceuticals AS has turned to the US women’s health genomics company Celmatix to help generate new insights into ovarian biology that could speed up personalized care in reproductive medicine and women’s health.

Speaking to Scrip, Ferring’s chief medical officer Klaus Dugi said the aim of the collaboration is to use Celmatix’s large-scale datasets to explore whether women’s responses to ovarian stimulation during in vitro fertilization (IVF) are linked to individual characteristics of their genome. “We already know that women have different responses to fertility treatments, depending on factors such as age, weight and anti-Müllerian hormone levels,” he said, “but we are convinced that there are many more factors and Celmatix will help us to uncover some of them.”

Dugi noted that Ferring was planning a number of clinical trials that will analyze genomics data using Celmatix tools which could increase the success rate for couples trying to have children that go down the IVF route. He added that the insights gleaned from the collaboration could help to reduce adverse and life-threatening outcomes such as ovarian hyper-stimulation syndrome and lower the rates of IVF cycle cancellation due to poor treatment response.

The CMO went on to say that working with Celmatix is also a perfect opportunity to look at data from past trials that Ferring has conducted, as well as those being run at the moment and in the future. By studying the relationship between genes and starting a family, the aim is to tailor treatment to an individual couple, he said, adding that the pact is “just the start of a long journey to make IVF a better experience.”

Founded in 2009, Celmatix’ products include Fertilome, the world’s first multigene panel test that reveals what a woman’s DNA says about her reproductive health. It has also developed Polaris, a real-time predictive analytics platform in use at leading fertility clinics across the US.

Piraye Yurttas Beim, CEO of the New York City-based firm, told Scrip that as well as creating products for the fertility market, Celmatix was focused on “addressing the gaps in knowledge which will move the field forward.” She added that there was a “black box” of issues that needs to be investigated, including unexplained treatment failure or over-response to drugs.

Beim said that “the demographic trends are undeniable” that people were increasingly waiting until later in life to become parents. Advanced fertility technologies like egg freezing and IVF are on the rise in the US and globally, she stated, adding that it is more important than ever to understand how a woman’s unique biology may impact her response to the treatments used for these procedures.

It is also vital to address a situation where diseases affecting only women have seen less innovative research, Beim noted, pointing to the “huge disparities in public funding for research into ovarian biology which is fundamental to understanding responses.” She also expressed concern about publicly-financed biomedical research in the US, most of which comes from the National Institutes of Health. (Also see “True Innovation In Women’s Health Hindered Because Conditions Are Not Fatal” - In Vivo, 13 Aug, 2018.)

The latter, Beim told Scrip, has “a low funding priority” when it comes to ovarian biology or women’s health in anything outside oncology. No financial terms have been disclosed but linking up with Ferring, Celmatix’ first partner from the pharmaceutical industry, will help on the funding front and she praised the Saint-Prex-headquartered firm for the importance it has attached to understanding the needs of women; at a time when women are under-represented in clinical trials, Beim added that “it is great to see Ferring step up to the plate.”

The companies also noted that findings from the collaboration could potentially have an even bigger long-term impact on women’s health. In addition to fertility and reproduction, a woman’s ovarian function underlies other aspects, from age of menopause to cardiovascular health, cognitive function, and risk for diseases such as cancer.

Big data is a buzzword around pharma and Dugi noted that he has been around long enough to see through the hype, pointing out that despite much talk about gene therapy in the 1990s, it was only last year when the first gene therapy actually got to market in the US. It may take a long time for the advances in artificial intelligence, machine learning and big data to significantly affect patient outcomes but he believes that the new tools available “offer a lot of opportunities to really go beyond the pill, optimize therapies and prevent diseases.”

2018 has been a busy year for Ferring. It began with the signing of a collaboration with the Chinese Academy of Sciences to develop reproductive medicines and the company has also acquired the USA’s Rebi-otix, moving into the microbiome drug development space. It is also targeting gene therapy through a late-stage licensing deal for a novel bladder cancer treatment from Finland’s FKD Therapies OY.

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Roche Pact Is Affirmation Of Affimed Technology

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Affimed NV has inked a deal with Roche’s Genentech unit which could be worth billions of dollars and make the German biotech a major player in the next wave of immuno-oncology.

Roche is paying $96m through an initial upfront fee and other near-term funding to kickstart a collaboration which will see the partners develop and commercialize novel natural killer (NK) cell engager-based immunotherapeutics to treat multiple cancers. At the heart of the deal is Affimed’s Redirected Optimized Cell Killing (ROCK) platform, which enables the generation of both NK cell and T cell-engaging antibodies – the collaboration includes candidate products already generated from ROCK and multiple undisclosed solid and hematologic tumor targets.

An eye-catching element of the partnership is the amount of cash being mentioned, even taking into account the hype that surrounds biobucks deals. Affimed could get $5.0bn if all goes well in total milestone payments, comprising $250m relating to development activities, $1.1bn for regulatory approvals and $3.6bn depending on the achievement of specified thresholds of worldwide net sales. The Heidelberg-headquartered group is also eligible to receive tiered royalties.

The sums are hypothetical but the size of them shows that Roche clearly sees the potential of ROCK. James Sabry, former head of partnering at Genentech who earlier this month took over the same role for the whole of the Roche group, said the deal “provides an opportunity to enhance our existing efforts to understand how the immune system can be activated to help people living with cancer.”

Another thing the deal provides, according to Do Kim at BMO Capital Markets, is “big pharma validation and pipeline value for Affimed’s platform.” The analyst issued a note saying that the company’s novel bispecific, tetravalent ‘TandAb’ drug platform “could be at the forefront of the next stage of immuno-oncology with targeting of the innate immune system and NK-cell.”

The collaboration comes at a time when Affimed is expecting a number of significant clinical readouts, notably its lead candidates, AFM13 and AFM11. Neither of these is covered by the Roche pact, the company confirmed to Scrip.

AFM13 is a tetravalent, bispecific NK cell engager that specifically binds to CD30 on tumor cells and to CD16A on NK cells. The company reported interim data from its Phase Ib combination study of the drug with Merck & Co. Inc.’s blockbuster anti-PD-1 immunotherapy Keytruda (pembrolizumab) in patients with relapsed/refractory (r/r) Hodgkin’s lymphoma at the European Hematology Association meeting in Stockholm in June, which showed that the combo was well tolerated and showed encouraging response rates versus Keytruda monotherapy.

Affimed plans to provide updated three- and six-month results at a scientific conference in the fourth quarter of 2018, possibly at the American Society of Hematology meeting in San Diego in December. The data could include information about progression-free survival and in a second-quarter update issued earlier this month, Affimed said it intended to initiate discussions with the FDA on potential expedited development paths for AFM13; it also noted that patient recruitment of a Phase Ib/I study evaluating AFM13 in r/r CD30+ lymphoma with cutaneous manifestation had been completed, with readout also scheduled in Q4.

In June, Affimed entered into a preclinical collaboration with Nektar Therapeutics to investigate the approach of NK cell engagers with Nektar’s cytokine-based products NKTR-214 and NKTR-255 “to potentially achieve deeper clinical responses.” NKTR-214 forms the basis of Nektar’s $1.85bn collaboration with Bristol-Myers Squibb Co., looking at combinations with the latter’s PD-1 inhibitor Opdivo (nivolumab) across a number of tumor types.

As for AFM11, a CD19/CD3-targeting tetravalent bispecific T-cell engager, two Phase I trials in patients with r/r acute lymphocytic leukemia and with r/r non-Hodgkin’s lymphoma are actively recruiting. Affimed plans to provide an update again at a medical conference in the fourth quarter.

In terms of cash, and ahead of the injection of funds coming in from Roche, Affimed had €47.4m as of June 30, primarily attributable to net proceeds of €19.7m from a public offering in February 2018. The company, which listed on the Nasdaq in September 2014, saw its shares leap nearly 160% Aug. 27 when the Roche deal was unveiled.

As for the Swiss giant, PharmaVitae analyst Oliver Spray told Scrip the agreement “highlights Roche’s ambition to lead the next generation of cancer therapy.” He added that the firm was “looking to reignite its dominance in oncology on the back of imminent biosimilar pressure” on its blockbuster drugs such as Rituxan (rituximab), Herceptin (trastuzumab) and Avastin (bevacizumab) “and failing to take up a dominant position in the current wave of immunotherapies”, as its PD-L1 inhibitor Tecentriq (atezolizumab) is struggling to compete with Keytruda and Opdivo.

Spray went on to note that as Affimed’s ROCK engages both NK and T-cells, targeting the innate and adaptive immune system, it could produce therapies for a wide range of cancer types and settings “and is highly customizable to different patients.” He concluded by saying, “Roche’s substantial funding commitment reflects the increasing commercial demand for personalized therapies within the cancer setting and the value of Affimed’s deep understanding of the immune system.”

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all communications regarding biosimilars. The omission by originator companies of these key words in biosimilar materials is significant.”

“We strongly believe that FDA has an important role in shaping the view of physicians, patients and payers to instill confidence in biosimilars and needs to make sure misleading information does not continue to be disseminated,” she said.

**PROMOTIONS CITED**

The petition cites examples of communications it regards as misleading, including a Genentech Inc. “Examine Biosimilars” website, an Amgen Inc. tweet and YouTube video, and a Janssen Biotech Inc. patient brochure for Remicade (infliximab).

Janssen’s brochure, titled “Finely Tuned – Your Treatment. Your Choice,” says, “You may be asked to switch to a biosimilar that works in a similar way to Remicade.” Pfizer notes that the Biologics Price Competition and Innovation Act ‘explicitly states that a biosimilar is highly similar to the reference product but has the same mechanism of action, meaning that a biosimilar works in the same way as the reference product. Janssen’s materials confuse this distinction by stating that infliximab biosimilars work in a ‘similar’ way to Remicade.”

The brochure also states in bold that no infliximab biosimilar has been proven to be interchangeable with Remicade. It adds: “Switching or alternating back and forth between the interchangeable biologic and Remicade would not cause any changes in safety or how well the treatment works — no infliximab biosimilar has yet proven this.”

Pfizer maintains that while Inflectra is not designated as interchangeable, it has, in fact, demonstrated that a single switch does not result in different safety or efficacy. “By emphasizing that the Inflectra product is not interchangeable, the manufacturer is clearly attempting to mislead patients into believing that they cannot safely be switched from Remicade to Inflectra by their physicians, and that a non-interchangeable product will not have the same results, neither of which are true.”

The petition says Amgen includes a similar message in a YouTube video, “The Arrival of Biosimilars — what’s in a name?” The video states that a switch “carries risks, given that no two biologic medicines are identical, and thus can behave differently in the body. Switching drugs is not a good idea if your medicine is working for you.”

Pfizer also cites an April 13 tweet by Amgen Biosimilars, which says: “Biologics or biosimilars? It’s not just apples to apples. While biosimilars may be highly similar to their biologic reference products, there’s still a chance that patients may react differently.”

The petition also points to Genentech’s “Examine Biosimilars” website, which says FDA requires a biosimilar to be highly similar, but not identical to the reference product. The petition says the website fails to state that an approved biosimilar must have no clinically meaningful differences from the reference product.

**MISBRANDING VIOLATION?**

It is unclear whether FDA would find these messages to be problematic. The agency’s Office of Prescription Drug Promotion has yet to issue a letter criticizing a promotion for a biosimilar product. It typically targets material that excludes risk information or makes claims that go beyond the approved indication.

Pfizer suggests that an FDA enforcement action could be taken against companies for misleading communications about biosimilars.

Communications by reference product sponsors that represent or suggest that biosimilars, including interchangeable biologics, are not or may not be safe or effective misbrand the product or reference product under the Food, Drug & Cosmetic Act, the petition states. In addition, it says a promotional communication that makes an unsubstantiated comparison representing or suggesting that a drug is safer or more effective than another drug is considered false and misleading.

“Any such false and misleading statements would misbrand the reference product and cause its distribution to be prohibited under the FD&C Act,” the petition states.

Biosimilar sponsors have voiced concerns that brand company sales representatives may be encouraging providers to use only interchangeable products, which have yet to be approved by FDA. At an Association for Accessible Medicines’ conference last year, Hillel Cohen, executive director of scientific affairs for Sandoz’s biopharmaceuticals unit, said he had heard about a ‘whisper campaign’ by certain sales reps advising providers to wait to prescribe an interchangeable product because it is better than a biosimilar.

In addition to concerns about discouraging competition, Pfizer’s petition asserts that while biosimilar reimbursement policies are not directly within FDA’s purview, dissemination of false or misleading information about the safety or efficacy of biosimilars has the potential to affect payer decisions about reimbursement.

Gottlieb has specifically called out reimbursement models, including contracting and rebating practices, as holding back the biosimilars market (see sidebar).

**OBJECTIONABLE**

Pfizer says FDA’s guidance should provide examples of communications that would be considered false or misleading, such as statements that directly or implicitly communicate that biosimilar products are not as clinically safe or effective as the corresponding reference product.

For example, the petition says, FDA should explain that if a reference product sponsor says a biosimilar is “highly similar” to but not “identical” to the reference product, it should also prominently disclose that there are no clinically meaningful differences between the biosimilar and reference product.

In addition, the petition says FDA should specify that suggestions that biosimilar products are inferior to interchangeable biologics in terms of quality or similarity to the reference product would be misleading, as would be suggestions that a patient should not be switched to a biosimilar product without a showing of interchangeability, or that biosimilar products are limited to use in treatment-naïve patients.

Pfizer also asks that the guidance clarify that a biosimilar sponsor may discuss clinical and other data on a biosimilar product, whether or not it is included in the labeling.

“Such data may be consistent with the FDA-approved labeling for the product, and the ability of a biosimilar product sponsor to discuss clinical data with physicians and in promotional materials is key to educating physicians and combating ‘scare tactics’ from certain reference product sponsors,” the petition states.

Pfizer is confident FDA will be a willing partner in taking on anti-competitive practices around the fledgling biosimilars market. The petition cites actions FDA has taken to encourage biosimilar competition, including its Biosimilars Action Plan released last month. Published online 28 August 2018
Pay Day For Reata As Bardoxolone Progresses

Reata Pharmaceuticals Inc. has received a $30m milestone payment from partner Kyowa Hakko Kirin Co. Ltd. following the Japanese firm’s initiation of a Phase III clinical trial program in Japan for bardoxolone (RTA 402) for the treatment of diabetic kidney disease.

The pivotal AYAME trial, which began enrolment in May, will assess the oral, once-daily NrF2 activator in around 700 patients with a planned completion date of March 2022, and follows on from the positive Phase II TSUBAKI trial in patients with chronic kidney disease and type 2 diabetes reported last year.

The new placebo-controlled study will be conducted in patients with stage G3 or G4 diabetic kidney disease, against a primary endpoint of time to onset for a ≥30% decrease in eGFR (estimated glomerular filtration rate) from baseline or end-stage renal disease (ESRD). Secondary endpoints include a time to onset of ≥40% decrease in eGFR from baseline of ESRD.

The ongoing Phase III CARDINAL trial in Japan is assessing bardoxolone for the indication of Alport syndrome.

Under the two companies’ agreement, Kyowa Kirin has exclusive development and commercialization rights to bardoxolone in renal disease and certain other indications in Japan, China, South Korea and a number of other Asian territories.

Reata is eligible for up to $272m in upfront and milestone payments, in addition to double-digit royalties on sales, as part of the alliance.

In Japan, bardoxolone was awarded “sakigake” designation this March by the Ministry of Health, Labour and Welfare for the treatment of diabetic kidney disease, a status that grants priority regulatory consultations and priority expedited reviews for pioneering breakthrough therapies.

In the US, the drug has already received orphan status for the treatment of Alport syndrome and pulmonary arterial hypertension, while in the EU it has an orphan designation for Alport’s.

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Investors Sweet On KaNDy Menopause Treatment

KaNDy Therapeutics is pushing its breakthrough non-hormonal treatment for symptoms of the menopause into Phase II trials, boosted by a fresh cash injection and a new high-profile US backer on board.

The UK company has successfully closed a Series C financing round, raising £25m from new investor Longitude Capital, and existing supporters Advent Life Sciences, Fountain Healthcare Partners, Forbion Capital Partners and OrbiMed. In an interview with Scrip, KaNDy CEO Mary Kerr said that the company had a very strong syndicate already but was looking for a US crossover investor, ie, one which is active in both public and private markets, “and Longitude is a very good fit.”

Since 2006, Longitude has raised over $1.2bn across three funds. Its current portfolio includes investments in the NASDAQ-listed food allergy firm Aimmune Therapeutics Inc. and Kala Pharmaceuticals, which last week won FDA approval for Inveltys (lopteprednol etabonate), developed to treat pain and inflammation following eye surgery.

She added that a shortlist of potential backers was drawn up and there was a lot of interest, but at this stage, “we only wanted to bring one in” and Longitude won the day. Kerr noted that KaNDy could have raised much more than £25m but decided to limit the raising to meet the needs for getting NT-814, which could provide a viable alternative to hormone replacement therapy (HRT), into late-stage trials.

A Phase Ib study of the oral, once-daily antagonist of both the neurokinin-1 and 3 receptors is ready to start. Kerr noted that the clinical sites are lined up, the contract research organization has been hired and all the protocols have been finalized, so the first patients will be recruited in the not too distant future. Headline results are expected by end of 2019.

In June, the company announced positive data from a Phase Ib/IIa trial which showed that women who were treated with NT-814 once-daily for two weeks at the most effective doses evaluated, experienced a rapid and profound reduction in two key symptoms of the menopause, namely frequency and severity of hot flashes and the number of night time awakenings. Kerr believes the drug has “the potential to be a transformational treatment for the millions of women worldwide who suffer debilitating symptoms of the menopause.”

KaNDy will not have the field to itself with the principle competition expected to come from Astellas Pharma Inc., which is evaluating the neurokinin-3 receptor antagonist fezolinetant, which is in Phase II studies for the treatment of menopause-related vasomotor symptoms. The Japanese company got hold of the drug through its €800m acquisition in 2017 of Belgian biotech Ogeda.

However Kerr welcomes competition in a field which she told Scrip has “through a lack of focus and innovation been ignored slightly.” Referring to fezolinetant, she said that “in a multibillion dollar market, there is more than enough room for two drugs, and more.”

She believes that the dual mechanism of NT-814 will have a broader profile than the offering from Astellas and it also shows promise for other menopause symptoms, including mood and sleep. It may also have the edge of being taken once a day rather than twice in the case of fezolinetant. However, Kerr insisted that “at this stage, it is not about head-to-head but about building a class.”

As to how far KaNDy will take NT-814, the CEO said that there is a lot of commitment from the company’s investors and more funding would be available if necessary to go it alone into Phase III. “We will take it as far as we have to,” Kerr said, noting that late-stage trials would be “relatively easy and inexpensive, so going into Phase III is a real option.”

She also acknowledged the possibility of a partnership with a more established player – KaNDy was spun out of NetRe Therapeutics Ltd., itself a spin out from GlaxoSmithKline PLC, in 2017 – saying that there is interest from potential partners in something as “potentially special and transformative as NT-814.”

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From the editors of PharmAsia News.
TetraPhase Pharmaceuticals Inc. is set to launch Xerava – a broad-spectrum antibiotic just approved by the US FDA for complicated intra-abdominal infections – at the competitive price of $175-to-$250 a day in a bid to smooth the drug’s path on to formularies.

Xerava (eravacycline) is given intravenously as a one-hour infusion, typically for a course of four to 14 days, to high-risk patients in the hospital setting. The FDA approved Xerava on Aug. 27 for use in treating complicated intra-abdominal infections (cIAI) in adults 18 years of age and older. There are a range of these infections, including intra-abdominal abscess and peritonitis, with a range of causes, including Gram-negative aerobic bacteria, Gram-positive bacteria and anaerobic bacteria.

This marks the first new approval for intra-abdominal infections since Merck & Co. Inc.’s Zerbaxa (cefrozolame/tazobactam) and Allergan PLC’s Avycaz (ceftazidime/avibactam) in 2014 and 2015, respectively. But while Zerbaxa and Avycaz were both based on beta lactam antibiotics, Xerava is a new tetracycline derivative, which means it can be given to patients allergic to beta lactams as well patients with impaired liver function, Biomedtracker analyst David Dahan commented.

**LAUNCH IN OCTOBER**

Xerava will be TetraPhase’s first launch. It had already hired a US sales force of 35 account managers contingent upon the approval and will now be training them in preparation for a launch in the second half of October. Regarding pricing, CEO Guy McDonald explained to Scrip that the company provided a range instead of an exact figure because it is still conducting some research in this area.

WBB Securities analyst Steve Brozak described the $175-to-$250 range as “competitive” in an Aug. 27 note.

The company sees this range as appropriate based on its target population.

A patient with a cIAI may get an empiric treatment, meaning it is given without a culture-confirmed pathogen, so therapy must be effective for all likely pathogens, including resistant ones, which limits therapeutic options, Chief Medical Officer Larry Tsai explained during an Aug. 27 investor call about the approval.

Carbapenems are traditional treatment options but have been so commonly used over the decades that increased resistance has developed, he said.

Tetraphase is stressing that Xerava has a broad approval for use in hospital patients at high risk of being infected with resistant pathogens, including patients previously hospitalized and/or treated with antibiotics.

“We’re especially pleased to receive a label which allows Xerava to be used for patients with empiric and confirmed infections. While some antibiotics are indicated only for patients with limited or no alternative options because of limited clinical safety and efficacy data, Xerava has no such restrictions,” McDonald told the call.

Consistent with such broad use, Tetraphase’s $175-$250 a day pricing compares favorably with Zerbaxa ($300/day) and Avycaz ($1,000/day), Biomedtracker’s Dahan commented.

“Xerava will still face competition from generic meropenem (~$30-150/day). However, Xerava is an option for doctors wishing to avoid overuse of meropenem, for patients intolerant of beta lactams due to allergy or impaired liver function, for patients with a history of Clostridium difficile infections or for patients where meropenem has failed,’ Dahan said.

The proposed range of pricing will “help us get on to formularies much quicker than other companies have seen,” Chief Operating Officer Larry Edwards told the call.

Tetraphase will be working within the hospital diagnosis related group (DRG) reimbursement system, which provides bundled payments for treatment of conditions, including surgery and drug therapy.

Feedback from thought leaders in hospitals, Pharmacy and Therapeutic (P&T) committee members and directors of pharmacy suggest that if the drug is priced right for the category, there won’t be a roadblock for use, Edwards said.

“I’m sure, like every antibiotic, there’s always challenges. You have to educate people on the appropriate way to use the drug. But we feel that the pricing strategy is the right way not only for the company to succeed but also for the patient,” Edwards said.

**FOCUSBING ON HIGH-PRESCRIBING HOSPITALS**

The company has hired highly tenured sales people, with over 20 years’ experience selling with hospital-specific product launches, which it says will secure a successful, focused launch.
The 35 reps will cover five regional areas, focused mainly on large metropolitan areas, but also including some “fly-by states,” Edwards said.

The plan in the US is to target 700 “tier 1” accounts including top hospitals accounting for 60% of the Gram-negative market prescribing volume during the first quarter of the drug’s launch. The second phase of launch will include an additional 1,200 “tier 2” accounts, covering an additional 30% of the Gram-negative market.

“This targeted approach allows us to maximize revenue potential while minimizing SG&A [selling, general and administrative] burn,” Edwards said.

Medical science liaisons have already been out in the targeted hospital market with a voluntary testing program testing for susceptibility of eravacycline.

The company said that specialty distributors will be fully stocked and waiting for hospital orders a week before launch.

Tetraphase also plans to commercialize the drug itself in Europe. Eravacycline received a positive opinion for approval from the European Medicines Agency’s Committee for Medicinal Products for Human Use in late July. A decision is expected by Oct. 1.

“**A NEW WEAPON** IN BATTLE AGAINST RESISTANCE**

Tetraphase’s filing was supported by studies in the IGNITE development program, in which an I.V. formulation given twice daily demonstrated noninferiority to ertapenem and meropenem and high cure rates in patients with Gram-negative pathogens. The drug was well-tolerated with no serious adverse events and no need for a dose adjustment, which the company said has advantages for seriously ill patients with impaired kidney function. (Also see “Another Antibiotic Success Story as Tetraphase’s Eravacycline Meets Goal” - Scrip, 26 Jul, 2017.)

The company originally also tested an oral formulation but focused on I.V. following a Phase III failure. (Also see “Tetraphase Bets On I.V. Eravacycline Renun As Antibiotic Market Influx Looms” - Scrip, 17 May, 2017.)

“With Xerava, doctors now have an empiric therapeutic option that can take the selective pressures off the carbapenem class. Not only can Xerava be substituted for a carbapenem to help decrease resistance to this class, it can also be used in patients that cannot tolerate carbapenems, those with penicillin allergies or those patients that have an increased risk of seizures,” Edwards said.

The drug was developed with support of the Biomedical Advanced Research and Development Authority (BARDA). In Tetraphase’s statement on the approval, BARDA director Rick Bright was quoted as saying that the FDA approval provides “a new weapon in the battle against antibiotic resistance and addresses an unmet medical need for patients suffering from multi-drug resistant infections and other serious infections.”

WBB Securities analyst Brozak noted that the drug is “effective against a wide range of Gram-positive and Gram-negative bacteria” and the “potential to become the drug of choice for long-term care patients who suffer from recurrent infections.”

HIGH UNMET NEED DRIVES MARKET OPPORTUNITY

The company sees high unmet need in the cIAI market.

“Complicated intra-abdominal infections are the second leading cause of infectious mortality in intensive care unit patients. They are also the second most prevalent type of infection in the ICU, with one out of every five ICU infections being a complicated intra-abdominal infection. Thus, these infections are not only deadly, they are very prevalent,” Tsai said.

In the US and five major European Union markets, there are 40m patient days of therapy, of which 90% is I.V. treatment, Edwards said. And of the 40m about one quarter – 10m – include patients getting broader-spectrum antibiotics or a combination of Gram-negative, Gram-positive and anaerobic antibiotics.

“We then take a conservative approach and estimate that we can penetrate up to 20% of the market or 2m patient days of therapy. Given a price range of $175 to $250 per day of treatment, we believe this will present an attractive market opportunity,” Edwards said.

The company aims to penetrate three distinct segments of the cIAI market, first-line empiric, second-line empiric and confirmed infections.

“In 90% of the cases, when a patient presents with a complicated intra-abdominal infection, they are treated empirically. We believe we’ll be able to target the empiric market versus focusing on niche last-line markets. This will differentiate Xerava as well as our launch,” Edwards said.

“We believe approximately 60% of Xerava’s usage as well as the focus of our marketing and sales team will be focused on first-line empiric segment, which includes patients who have high risk of having an infection with a resistant pathogen or those deemed to be higher-risk patients,” the exec added.

The remaining 40% of the market is divided between secondary empiric and confirmed diagnosis, he said. There are some 2m confirmed infections caused by resistant organisms every year, according to the World Health Organization, and Xerava offers a clear advantage because it covers a significant portion of resistant pathogens, Edwards said.

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Over the last number of years the use of mHealth technologies has been increasingly embraced by patients, healthcare providers and payers. Connected health ecosystems have been evolving at a rapid pace and it is now believed that the IoHT (Internet of Healthcare Things) market will be worth $163bn by 2020. It has been estimated that over 7.1m patients worldwide benefit from remote monitoring and the use of connected medical devices as part of their care regimen, to better inform and educate themselves about their disease and to share their knowledge with each other. This patient empowerment is reflected by the estimate that 1 in 20 Google searches is healthcare related. mHealth device technology has evolved to the point where it is now possible to collect a vast array of physiological data including vital-signs such as heart rate, respiration rate, oxygen saturation, continuous glucose monitoring, sleep and activity data, and using advanced analytics to monitor patients in their own home outside the hospital environment. There is a growing awareness in the healthcare sector of the benefit and value of a mHealth approach to healthcare. As early as 2013 as a way of maximising healthcare spending, sleep apnoea patients in France have been monitored remotely to ensure they are compliant in the use of their CPAP (continuous positive airway pressure) devices. This has led to new care models in mobile health, for example, University of California, Los Angeles actively promote their remote patient monitoring program as having positive values for patients and their primary healthcare teams to manage their health “from the comfort of your own home” and to reduce hospital admissions and emergency room visits. However the penetration and use of wearables and devices in the pharmaceutical industry is still limited. But interest in mHealth/digital technology is apparent with nearly 3000 articles published in peer reviewed journals in 2017 (PubMed), an almost 100% increase on the number published five years earlier. The value of the technology is clear—in a recent industry survey for the ICON whitepaper ‘Improving Pharma R&D Efficiency’ respondents cited big data, predictive analytics, smartphones and wearables & sensors as amongst the top disruptive technology trends which will have the greatest impact on clinical trial operations.

So the question remains, in the context of drug development studies, why has the use of this technology been limited to a relatively small number of pilots? It is clear that concerns still remain about implementation of this technology in a clinical trial. These concerns focus on a number of key areas: Patient Acceptance, Device Suitability, Data Complexity and Insight Generation, Operationalisation, Privacy and Security Issues, and Regulatory Acceptance.

**How To Implement Successful Digital Clinical Trials**

**Patient Acceptance.** Patient recruitment and retention are key issues for clinical trials. While it is generally accepted that the use of devices and sensors can help create more patient centric studies, if not carefully managed digital technology can add additional burden for the patient. This is a critical factor when integrating devices and sensors into a study; ensuring your study design has a ‘maximum passiveness’ approach is key. Data collection should be as seamless as possible with minimal
actions required from the patient. Selection of a low-burden device that is simple to use with an attractive form-factor is another important aspect for increasing patient engagement. The device should, where possible, support both iOS and Android operating systems to allow for a BYOD (bring your own device) model. A single study app, that acts as the interface between the individual and the trial and includes features to support the patient in his/her day-to-day life, must also reflect the disease specific characteristics. These apps need to be designed with the user experience in mind and should add value to the patient experience while part of the study. Lastly, compliance monitoring has proven to be a significant contributor to the success of digital trials. Proactively flagging non-compliance and utilising a multi-faceted approach to engage with patients; from app to SMS notifications to direct contacts contacting patients, can help drive greater compliance and ensure optimal data generation and capture.

# Device Selection. New devices are launched almost every day and selecting the right device is a challenging task and poses a number of critical questions; so how to choose? Should we use single or multiple devices? Medical grade devices or consumer technology? Unfortunately there are no simple answers, and certainly there is no one device that can be used in all studies. There are some publications that provide guidelines and can support the selection process. Of primary importance is the selection of a device that can generate the data required to meet the study needs. The device itself must be fit for purpose: have high usability such as long battery life, be form factor appropriate for the study population, and facilitate the collection and transfer of the required data. The trial design will guide the device(s) selection process, if a device is being selected to support an endpoint, ensuring there is sufficient scientific evidence to support the use of that device is critical. If a device is being used to track trending and changes, or is used in late phase studies, greater choice exists in terms of the devices being selected for use.

# Data Complexity and Insight Generation. Existing clinical studies rely to a large extent on results from monthly outcome assessments carried out in a clinic. The potential to generate new insights from continuous measures captured as patients go about their lives is significant. If we take as an example a typical Phase II clinical trial in CNS: a few dozen patients, participating in a trial for a few months to a year. Let’s assume we would like to capture objective insights and provide patients with a wrist-worn device equipped with a 50Hz accelerometer and gyroscope sensors. The use of such a device will generate nearly 1 billion data points per day. Combining these data with ePRO (electronic patient-reported outcomes) methods, along with other physiological data such as heart and respiration rates can create a big, complex dataset that is beyond the capacity of standard electronic data capture (EDC). Therefore, when selecting a digital platform, the ability to scale and ingest high frequency datasets is important. In order to generate insights and digital biomarkers, skilled experts in advanced analytics, data scientists, are needed. The platform should enable the data scientists’ work by exposing the appropriate tools to process the data and run machine learning algorithms.

While it is generally accepted that the use of devices and sensors can help create more patient centric studies, if not carefully managed the use of digital technology can add additional burden for the patient.
Bayer To Ship Long-Acting Hemophilia Infusion Jivi In A Jiffy

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There will be little Labor Day relaxing in parts of Bayer AG, as the company says it will be working through the three-day weekend to get its just-approved long-acting recombinant Factor VIII replacement hemophilia A product Jivi (BAY94-9027) ready to ship in the US.

The US FDA approved intravenously-delivered Jivi on Aug. 29, for the routine prophylactic treatment of hemophilia A in previously treated adults and adolescents 12 years of age or older.

The product has a long half-life of 17.9 hours, owing to its engineering – it consists of a polyethylene glycol polymer attached to recombinant Factor VIII. This allows sustained high levels of Factor VIII and longer coagulation. Traditional products have a half-life of 12 hours.

Bayer’s filing was supported by the Phase II/III PROTECT VIII open-label study of three dosing regimens tested over 36 weeks in 126 patients. The company also ran an extension study evaluating the drug over at least 100 accumulated exposure days, which Bayer reported demonstrated good safety up to a median of 1.9 years. The drug also is under review in the EU and Japan.

STEPWISE DOSE-ADJUSTMENT

Jivi was approved for dosing twice weekly at a dose of 30-40 international units (IU)/kg, with the ability to dose every five days at 45-60 IU/kg, and further individually adjust to less or more frequent dosing based on bleeding episodes. It may also be used for on-demand treatment and perioperative management of bleeding in the same population.

A Bayer spokesperson told Scrip that the company will be working through Labor Day weekend in preparation for a launch in the middle of the first week of September and plans to speak with clinicians right after the US holiday.

Pricing was not disclosed, but the company said this will be on par with other Factor VIII replacement products on the market. On average, these cost $1.50 per IU for standard products and $2 per IU for longer-acting products, but pricing is not directly comparable, because with the extended versions, fewer units may be used overall on an annual basis.

“What is really important for Jivi is the flexibility of the prophylactic dosing regimen … that allows physicians to tailor the dosing regimens for prophylaxis to the needs of the patients, based on their characteristics, bleeding patterns, age and activity level,” Aleksandra Vlajnic, VP of medical affairs, said in an interview.

What is really important for Jivi is the flexibility of the prophylactic dosing regimen

Hemophilia treatment has advanced in recent years, giving patients an almost normal lifespan, which increases the importance of addressing other needs, like the burden of treatment and balancing quality of life with the demands of the disease, Vlajnic said.

However, Jivi is a bit late to the market, as long-acting recombinant hemophilia A products go. Sanofi/Bioverativ Inc.’s Elocetate was approved in 2014 and has a half life of 19.7 hours.

WILL BAYER SHIFT PATIENTS TO JIVI?

Datamonitor Healthcare noted in a May 2018 product report that BAY94-9027 clearly would not have an early-to-market advantage, but said the company would be able to encourage uptake among patients receiving its other hemophilia A Factor VIII recombinant products – Kogenate and its successor Kovaltry – and “actively support switching” to the long-acting recombinant product, now known as Jivi.

Bayer reported €967m ($1.1bn) in sales for its Kogenate/Kovaltry franchise in 2017, down 17.1% from 2016, explaining that lower order volumes were made by a distribution partner ahead of the termination of a contract. Sales also were down in the first quarter of 2018 at €224m ($261m), which was 22.2% lower than the year-ago period.

Vlajnic told Scrip that Jivi is not a replacement for Kogenate/Kovaltry, but rather it is an addition that brings flexible dosing and an extended half-life option to the table. Some patients are more active and require more frequent dosing, while others are less active and a longer-acting product is a better match, she noted.

“This is something the physicians and patients have to decide … it’s nice to have options,” Vlajnic said.

The treatment landscape has been shifting toward longer-acting injectables to allow long-term prophylaxis, but hemophilia patients are known to be slow to change and some clinicians say that patients actually are switching back to older products, because they do not feel sufficiently protected on the new therapies.

The market also is fitting in new types of therapies, like Roche’s Hemlibra (emicizumab), a bispecific monoclonal antibody that is given by a once-weekly subcutaneous injection rather than an infusion like legacy hemophilia products. Hemlibra was approved in November for hemophilia A patients with inhibitors and is in place to advance to patients without inhibitors.

Gene therapies from BioMarin Pharmaceutical Inc. and Spark Therapeutics Inc. also are in development and have been positioned as potentially curative.

Bayer also is investigating gene therapy for hemophilia, working with Ultragenyx Pharmaceutical Inc. on the development of a treatment for hemophilia A, per a 2015 deal. The German big pharma also has a joint venture with CRISPR Therapeutics AG.

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Merck To Build Case For Doravirine-Based HIV Products

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A n ahead-of-schedule approval is always good news, but it’s unclear how much Merck & Co. Inc. will benefit from the US FDA nods for two news HIV therapies, novel non-nucleoside reverse transcriptase inhibitor (NNRTI) Pifeltro (doravirine) on its own and as part of the three-drug combination pill Delstrigo.

The two products obtained US FDA approval for treatment-naive HIV-1-infected patients on Aug. 30, nearly two months ahead of their Oct. 23 user fee date. In an interview, Merck Senior VP-Infectious Diseases & Vaccine Clinical Research Nicholas Kartsonis said the company had to do “some additional engineering behind the scenes” to respond to the early approval, but anticipates making both products available to wholesalers before the end of September.

Delstrigo, which combines doravirine with the nucleoside reverse transcriptase inhibitor lamivudine (Johnson & Johnson’s Epivir) and Gilead Sciences Inc.’s tenofovir disoproxil fumarate (TDF, Viread and generics), will have a list price of $70 per day, putting it toward the lower end of pricing for HIV combination regimens. Pifeltro, approved to be used in combination with antiretroviral drugs, will be listed at $46 a day, Kartsonis said.

In the 728-patient, Phase III DRIVE-AHEAD trial, Delstrigo was tested head-to-head against Gilead’s Atripla (efavirenz/emtricitabine/TDF) and demonstrated non-inferiority on an endpoint of viral suppression of HIV-1 RNA of less than 50 copies/mL. Eighty-four percent of patients receiving Delstrigo achieved viral suppression at 48 weeks, compared to 81% in the control arm.

Single-agent Pifeltro demonstrated non-inferiority on the same endpoint versus a control arm of J&J’s protease inhibitor Prezista (darunavir) boosted with ritonavir. In the 766-patient DRIVE-FORWARD Phase III study, 84% of patients receiving study drug achieved viral suppression compared to 80% of control-arm participants.

BOLSTERING FLAT SALES OF ISENTRESS

Merck hopes the two products will bring new life to its HIV portfolio, whose top-selling integrase inhibitor Isentress (raltegravir) posts blockbuster sales annually but has stagnated of late. Isentress annual sales declined from 2016 to 2017, and through the first six months of 2018 stood at $586m, virtually level with the $587m brought in during the first half of 2017.

Kartsonis said the two doravirine-based drugs should make a valuable addition to the armamentarium for treating HIV and would offer safety advantages over competing products.

“We actually think this fits in very nicely because when you think about HIV overall, this is a disease that people often acquire early, often in the second, third or fourth decade of their lives, and they’re going to need to be on medication daily for the reminder of their lives,” he told Scrip. “Over time, it’s not surprising that people will need to have different treatment options.”

Datamonitor Healthcare analyst Michael Haydock doesn’t quite concur with Merck’s rosy view, in part because the Delstrigo combo includes TDF, rather than the second-generation tenofovir alafenamide (TAF), which Gilead is using to replace maturing TDF-backed combos with TAF-containing regimens on the promise of better renal and bone safety.

Delstrigo “is expected to achieve very limited uptake in the US market because of its inclusion of TDF, which is being rapidly replaced by Gilead’s successor product, TAF,” he told Scrip. “Additionally, TAF-based regimens have achieved strong market penetration in France, Germany, Italy and Spain, due to their potential to reduce the real-world incidence of renal dysfunction and bone fractures compared to TDF-based regimens, which is another barrier for [Delstrigo’s] uptake, as physicians are expected to be unwilling to swap or initiate new patients on a backbone with inferior safety.”

TDF SAFETY ISSUE ‘MAY BE OVERSTATED’

Both Delstrigo and Pifeltro are under review by the European Medicines Agency, but Kartsonis could not offer an estimate on when a decision might be made. He pushed back, however, on the concept that TAF-based regimens will prove safer than Delstrigo, noting that labeling for TAF-including products still includes warning language on renal and bone safety and asserting that some combination products including TDF that have been connected to safety issues may be due to the boosting agents used to enhance the potency of other components.

In Gilead’s HIV combos Genvoya (elvitegravir/cobicistat/emtricitabine/TAF) and Stibild (elvitegravir/cobicistat/emtricitabine/TDF), the integrase inhibitor elvitegravir is boosted with cobicistat.

“The boosting actually raises the level of tenofovir in the blood. You’re not going to get those situations with Delstrigo, because we don’t have a boosted component,” Kartsonis said. “This also is exactly the reason we created Pifeltro. We wanted to give people options so that if they really wanted to be on a TAF-based regimen, they could use TAF with Pifeltro and create a regimen that suits their individual needs.”

The new Merck products’ potential may be limited, however, Datamonitor’s Haydock said, because NNRTIs have been downgraded in US HIV treatment guidelines to alternative first-line agent status, with integrase inhibitors preferred because of their better resistance profiles. For Pifeltro, its head-to-head non-inferiority to Prezista may not be greatly influential with clinicians, because Prezista also was de-emphasized in the most recent guidelines, he added.

Cost, however, may provide a fruitful area on which the Merck products can compete, Haydock said. Delstrigo’s low cost “is expected to make it a more attractive option in cost-conservative EU markets, such as the UK, where NNRTIs remain ‘recommended’ options, and the conversion to TAF-based regimens has been hindered by the availability of generic TDF,” he pointed out. Kartsonis argued that Delstrigo might be viewed as safer than Atripla – it’s head-to-head comparator in Phase III – because efavirenz, a component of Atripla, has been associated with neurological complications such as dizziness, sleep disorders and altered sensorium (an inability to concentrate) as well as rash.

On efficacy, Delstrigo and Pifeltro should compete well against rilpivirine-based regimens, such as ViIV Healthcare’s Juluca (rilpivirine/dolutegravir), because rilpivirine (J&J’s Edwards) is not recommended for use in patients with high viral loads at baseline, Kartsonis added. (Delstrigo, however, has not been tested head-to-head against rilpivirine-containing regimens, Merck said.) Meanwhile, doravirine has shown efficacy in patients with high viral loads, Kartsonis said.

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Gilead And Novartis Unveil EU Marketing Plans For CAR-T Therapies, But Hurdles Remain

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The two just-approved CAR-T therapies in Europe may find it tough going to maximize their market opportunity. One of the novel products, Novartis AG’s Yescarta (axicabtagene ciloleucel), will only be launched initially in one of its indications. The other, Gilead Sciences Inc.’s Yescarta (axicabtagene ciloleucel), has been rejected by the continent’s leading health technology assessment body, the UK’s National Institute for health and Care Excellence (NICE), in draft guidance released on Aug. 28.

Kymriah is indicated in the EU for the treatment of pediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse, as well as for adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy. Yescarta is indicated in the EU for the treatment of adult patients with relapsed or refractory DLBCL and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy. Approval of both therapies by the EU Commission were announced Aug. 27, following positive opinions granted by the CHMP in June 2018. (Also see “First CAR T-Cell Therapies OK’d In EU: Novartis’s Kymriah And Kite’s Yescarta” – Pink Sheet, 29 Jun, 2018.)

PRICING WILL BE KEY

According to analysts at Informa Pharma’s PharmaVitae, the simultaneous approval of Kymriah and Yescarta creates a problem for their manufacturers, which are looking to differentiate their product and dominate the market. “Both products have shown comparable clinical profiles although Yescarta will benefit from a marginally superior overall response rate shown across a range of clinical trials,” the analysts said.

“PharmaVitae believes that the two companies will look to differentiate their products in terms of price. It may be that negotiations result in a settlement that states payment will only be made for those patients that get cured. Other forms of discounting, such as rebates may also be negotiated,” the analysts continued. But EU markets are likely to pay the high prices we have seen for both products in the US, meaning the overall market opportunity will be substantially smaller in the EU than the US, they added.

In the US, Yescarta had sales of $68m in the second quarter of 2018, compared with around $16m in sales for Kymriah. (Also see “As Gilead Seeks New CEO, Second Quarter Shows Stability” – Scrip, 25 Jul, 2018.)

Novartis has previously indicated that there have been issues in terms of cell variability when used in DLBCL. PharmaVitae noted that such issues might be expected with such a complex product, and sales are expected to pick up as those issues are addressed. (Also see “Cosentyx Carries Novartis Sales But Kymriah Manufacturing Gives Cause For Concern” – Scrip, 18 Jul, 2018.)

FIRST DOSES

Gilead said it expected the first patients in Germany to undergo treatment soon with Yescarta, and in France, the first patients have been prescribed the therapy as part of the new Temporary Authorisation for Use (ATU) scheme. (Also see “France To Speed Up Patient Access To Unapproved Drugs” – Pink Sheet, 22 Aug, 2018.)

“The first centers to administer Yescarta have already been qualified and we are in the process of bringing additional specialist centers through our rigorous training and qualification process,” Gilead told Scrip. The first qualified centers are in France, Germany and the UK, and other countries will have qualified centers shortly.

Yescarta will initially be produced for Europe at the company’s manufacturing facility in El Segundo, California, while a new facility in the Netherlands is expected to be fully operational in 2020. In an interview with Scrip last month, Gilead’s Michael Elliott, vice-president for medical affairs, indicated that the company would take a measured approach to initial EU marketing.

For its CAR-T therapy, Novartis revealed it would limit its initial EU launch efforts to the Kymriah indication not also granted to Yescarta – refractory/relapsed ALL – because of a lack of manufacturing capacity for Kymriah. The company will “launch initially in the pediatric ALL indication, as we continue to ramp up capacity,” it said in its EU approval announcement on Aug. 27.

Novartis said the timing of Kymriah’s availability will also depend on getting qualified treatment centers on board for the appropriate indications, and the completion of national reimbursement procedures. Training is already underway in certain centers, the company said. Options to expand Kymriah’s manufacturing facilities beyond its current facility in Morris Plains, New Jersey, are also being pursued by Novartis. The company confirmed it is to invest CHF90m in a cell and gene therapy manufacturing facility, to be built in Switzerland.

An agreement on Kymriah manufacturing has also been signed with the French company, CELLforCure, one of the largest cell and gene therapy contract manufacturers in Europe, and an alliance expanded with Germany’s Fraunhofer Institute, which is supporting the manufacture of Kymriah for global clinical trials and for post-approval manufacturing.

“Novartis will continue to build a global infrastructure for delivering CAR-T cell therapies where none existed before, remaining steadfast in our goal of re-imagining cancer,” said Liz Barrett, CEO of Novar-
Alnylam Switches Attention to Access After Onpattro EU Okay

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Having secured approval for Onpattro (patisiran) in Europe, the spotlight is moving from clinical to commercial strategy for Alnylam Pharmaceuticals Inc, as it prepares to market the first-ever RNA interference (RNAi) therapeutic to get the green light in the EU.

Three weeks after securing approval in the US, Alnylam has been granted marketing authorization for Onpattro for the treatment of hereditary transthyretin-mediated (hATTR) amyloidosis in adults with stage 1 or stage 2 polyneuropathy. The drug received a positive opinion from the European Medicines Agency’s Committee for Medicinal Products for Human Use (CHIMP) on July 27, reviewing Onpattro under the accelerated assessment procedure granted to medicines judged to be of major interest for public health and therapeutic innovation. (Also see “Alnylam Set for Transformation As Patisiran Nears Market With Data Upgrade” - Scrip, 25 Apr, 2018.)

The thumbs-up was based on the Phase III APOLLO study of 225 patients comparing Onpattro with placebo. The drug improved measures of polyneuropathy – reversing it in most patients – and enhanced quality of life based on patient-reported assessments. (Also see “Alnylam’s Onpattro Carries Narrower hATTR Indication Without Cardiac Data” - Pink Sheet, 13 Aug, 2018.)

Theresa Heggie, Alnylam’s head of Europe, noted in a statement that the approval “is the result of many years of dedicated effort [and] is the start of a new chapter in the treatment of this rare, rapidly progressive, fatal disease.” hATTR amyloidosis affects approximately 50,000 people worldwide and the median survival is 4.7 years following diagnosis, Alnylam stated, with a reduced survival (3.4 years) for patients presenting with cardiomyopathy.

There is an unmet need and the question now is whether payers in Europe believe that Onpattro is a cost-effective option to meet that need. Alnylam has not revealed its timeline for launches across the continent but in an interview with Scrip at the end of 2017, the company’s president Barry Greene would not be drawn on specific pricing plans but was hopeful that the “extreme value” that he believes Onpattro provides will be recognized.

“We have to look at the system in totality,” he claimed, and innovative companies “should be rewarded for the value we add.” Greene added that “we’ve spent 15 years and a couple of billion dollars to get here, we have taken tremendous risks, we’ve failed and now we’ve succeeded. The world needs to reward innovators or innovation stops and that’s no good for anyone.”

In that interview, Greene said it was vital to engage early with payers, so they “understand our philosophy as a company. Disease education is something we do ahead of the curve so that when we come with data on a specific product, it’s not the first time we’ve meet, they know who we are, they know where we are coming from.” He added that the industry had learnt from predecessors that “if you launch a drug and you surprise everybody, it is not a good thing for any of us; people want to plan ahead.”
CONTINUED FROM PAGE 17

Greene also said that Alnylam was not worried about risk-sharing projects that payers may propose, saying that the company was open to innovative pricing schemes.

This is the approach that the company has taken in the US since getting approval on Aug. 10. It is offering value- or outcomes-based contracts to payers across the Atlantic to ensure that payment is linked to improvements in outcomes after treatment with Onpattro.

Alnylam set a list price at $450,000 per year with an effective net price expected to be in the region $345,000, following rebates and discounts, with money-back clauses. There will be varying levels of discounts, because the level of improvement varies, Greene explained when the US approval was announced.

Nevertheless, Alnylam’s pricing strategy has fallen foul of the US independent drug pricing body, the Institute for Clinical and Economic Review (ICER). In a statement issued earlier this week, the latter’s chief scientific officer Dan Ollendorf said of Onpattro and the antisense drug Tegsedi (inotersen) from Ionis Pharmaceuticals Inc., which is approved in Europe but not the US, that “available data on clinical effectiveness suggest that these therapies offer important advancements for patients with hATTR amyloidosis. However, the announced price of patisiran, even taking into account expected discounts, far exceeds commonly cited cost-effectiveness thresholds.”

ICER CALLS FOR 90% DISCOUNT

ICER concluded that, at a net price of $345,000, Onpattro goes well past “commonly accepted thresholds of $50,000-$150,000 per quality-adjusted life year (QALY) at $850,000 per QALY gained.” It claimed that to align costs with the added benefits for patients, the list price would need to be discounted by 90%-95%.

The institute said that while a list price had not yet been announced for Tegsedi in the US, “ICER’s analyses suggest that the therapy would align with the benefit to patients if priced between $15,300 and $25,400 per year.” Ionis affiliate Akcea got European approval for Tegsedi in July and is currently negotiating reimbursement with individual EU member states. (Also see “Armoving And Tegsedi In Raft Of Products To Get EMA Thumbs up” - Pink Sheet, 1 Jun, 2018.)

Pfizer Inc.’s Vyndaqel (tafamidis), a once-daily oral meglumine salt, has been available in some European countries and Japan since the beginning of this decade for transthyretin familial amyloid polyneuropathy and costs around $75,000 a year. This week, the pharma giant presented data at the European Society of Cardiology congress in Munich showing that the drug cut the risk of death by 30% in ATTR cardiomyopathy, a sub-indication of hATTR. (Also see “Pfizer Has Tafamidis Data In Hand, But Market Development Still A Challenge” - Scrip, 27 Aug, 2018.)

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Celltrion Plans EU Filing For Remsima SC

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Celltrion Inc. is gearing up to file a marketing authorization with the European Medicines Agency for Remsima SC, a subcutaneous (SC) version of its autoimmune disease therapeutic antibody infliximab, a biosimilar version of Johnson & Johnson’s Remicade, following the completion of a Phase III clinical trial.

Celltrion said it is set to complete the clinical analysis for the trial soon and to submit the approval application in the second half of this year.

The company is aiming to diversify its product offering through Remsima SC and its adalimumab biosimilar CT-P17 in a high-concentration formulation to boost its competitiveness in the crowded TNF-alpha inhibitor market. Celltrion aims to lead this sector through the commercialization of the two products, in a global market for SC formulations of TNF-a inhibitors it estimates is valued at KRW30tn ($27.1bn).

The company’s already launched standard intravenous formulation of Remsima held 52% of the European market for the molecule in the fourth quarter of 2017.

It has been conducting both Phase I and III clinical trials on the safety, pharmacokinetics and efficacy assessment of Remsima SC since May 2016. The main advantage of the new subcutaneous formulation is that it allows patients to conveniently inject the drug by themselves according to the administration cycle, unlike the intravenous formulation, which requires patients to visit a hospital or clinic for supervised infusion dosing.

Celltrion expects that the potential demand base will include those patients who are satisfied with the therapeutic effects of infliximab yet prefer SC dosing, and those administered AbbVie Inc’s Humira (adalimumab) and Amgen Inc.’s Enbrel (etanercept), which are global blockbusters TNF-alpha inhibitors available in SC formulations.

REGULATORY UNCERTAINTIES

However, it is not yet clear what approach regulators in Europe (and elsewhere) might take to a biosimilar with a changed formulation, and Celltrion’s product would present the first such case.

The company said that “there are no clear regulations on this in each country, so Celltrion is discussing this [the SC approval] with regulators in each country,” it expects to be able to unveil the regulatory pathway of the SC formulation when it files for marketing authorization.

At the European League Against Rheumatology (EULAR 2018) meeting in June in the Netherlands, Celltrion showcased that its SC formulation of CT-P13 (biosimilar infliximab) is comparable in terms of efficacy and safety with the IV formulation of CT-P13, for the treatment of patients with rheumatoid arthritis up to week 30.

The positive preliminary results indicated that CT-P13 SC could become a future alternative, easier to use version of infliximab, giving patients more independence, the South Korean company’s marketing and distribution arm Celltrion Healthcare said at the time.

Professor Rene Westhovens, rheumatologist at the University Hospitals KU Leuven, Belgium observed: “These preliminary results are encouraging as they show that CT-P13 SC is safe and has comparable efficacy to the well-established intravenous version. This new injection formulation of infliximab would give patients the opportunity to self-inject, saving their time and giving them more autonomy.”

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Pfizer’s Domagrozumab DMD Setback Shifts Focus

JOSEPH HAAS

Pfizer Inc.'s R&D strategy in Duchenne muscular dystrophy now will focus primarily on gene therapy candidates, as the pharma announced Aug. 30 that it is shelving domagrozumab due to its failure to meet the primary endpoint in a Phase II trial.

The myostatin/growth differentiation factor 8 (GDF-8)-targeted antibody also did not show a significant treatment effect on any of the trial’s secondary endpoints.

Pfizer is terminating both the Phase II safety and efficacy study (B5161002) of domagrozumab (PF-06252616) as well as an open-label extension study (B5161004). Noting that neither study was discontinued due to safety concerns, the company reported that domagrozumab, an intravenous, monthly therapy given to 121 DMD patients, did not demonstrate a difference compared to placebo in mean change from baseline on the timed four stair climb after one year.

The news made for the second high-profile failure of a DMD candidate this summer. Summit Therapeutics PLC ended development of its utrophin modulator ezutromid in June after it failed to hit either the primary or any secondary endpoints in its 40-patient, Phase II PhaseOut DMD trial. Like Pfizer, Summit noted that its drug did not fail for safety reasons, but wasn’t able to replicate in a longer study promising data it showed in muscle damage and inflammation after 24 weeks of treatment.

Pfizer said its decision is based on a thorough review of the data available at the time of the primary analysis – when all study participants had completed one year on therapy – including data from patients who had been taking domagrozumab for longer than a year. However, the company plans to continue analyzing the data to see if the antibody offers potential in other muscular diseases, added Seng Cheng, the senior VP of Pfizer’s Rare Disease Research Unit.

Datamonitor Healthcare Principal Analyst Rare Diseases Zara Fulton told Scrip that Pfizer’s termination of domagrozumab is hardly a surprise, given its increasing efforts in gene therapy.

Pfizer is continuing to investigate DMD and other rare neuromuscular diseases, including continued development of PF-06939926, a Phase I gene therapy candidate the company acquired in its $150m acquisition of Bamboo Therapeutics Inc. in 2016. A recombinant AAV9 capsid that carries mini-dystrophin – a truncated version of the human gene implicated in DMD – under control of a human muscle-specific promoter is in Phase IIb with data expected during the first half of 2019, the company said.

The 12-patient study saw its first patient dosed in March and will evaluate safety and tolerability of the candidate as well as measuring dystrophin function and distribution and assessments of muscle strength, quality and function. Pfizer will share data after patients complete the one-year endpoint.

PFIZER SWITCHES LANES

Around the same time it initiated the PF-06939926 study, Pfizer revised its gene therapy R&D direction, divesting allogeneic chimeric antigen receptor T-cell (CAR-T) therapy technology it obtained from Cellectis SA and Servier SA to Allogene Therapeutics Inc. While the pharma is keeping a hand in those programs with a 25% equity stake in Allogene, Pfizer pointed out that its DMD candidate is the first recombinant adeno-associated virus vector serotype 9-based capsid candidate it has advanced into clinical development.

Pfizer also has made significant investments to enhance its gene therapy capabili-ties, including expansion of a manufacturing facility in North Carolina. The firm’s rare diseases unit also is working on therapies for hematologic, neuroscience and inherited metabolic disorders.

It believes PF-06939926 may be differenti-ated from other DMD drugs and candidates by addressing the disease’s underlying cause broadly by providing a correct copy of the mini-dystrophin gene.

To date, the DMD indication has seen a host of clinical development setbacks by drug sponsors studying a variety of targets and mechanisms of action. Two drugs have been approved in the US to date – Sarepta Therapeutics Inc.’sExondys 51(eteplirsen), which addresses a mutation present in an estimated 13% of DMD patients, andPTC Therapeutics Inc.’sEmflaza(deflazacort), a repurposed, once-generic corticosteroid. PTC also has the oxadiazole Translarna (ataluren) in Phase III in the US; it received a complete response letter (CRL) from the US FDA in October indicating that another study demonstrating efficacy will be needed for approval, at minimum. The FDA denied the company’s appeal of the CRL in February; Translarna was conditionally approved in Europe to treat nonsense mutation DMD in 2014, but an effort to develop the drug for cystic fibrosis in the EU was abandoned in 2017.

IS PFIZER LOOMING?

Datamonitor’s Fulton said Sarepta holds a clear edge on Pfizer and others working in the DMD space with multiple development efforts, including gene therapy candidates. She suggested that Sarepta might become a takeover target for Pfizer.

“Sarepta has a significant head-start in DMD with Exondys-51 and has also been making impressive progress with its pipeline, aiming to maintain its market edge as competition is set to heat up in ultra-rare DMD,” she told Scrip. “Sarepta will file an NDA with the FDA by the end of 2018 seeking accelerated approval of its second antisense therapy to treat DMD in golodirsen, which is designed to treat patients whose DMD is caused by an error in exon 53, representing 8% of the 5,000 DMD patients in the US.”

Fulton added that Exondys 51’s first quarter 2018 sales performance disappointed some analysts and investors, which caused Sarepta’s share price to slump and potentially enhanced the company’s appeal to a buyer. The drug produced sales of $64.6m during the first quarter, roughly four times what the product brought in during the first quarter of 2017, and then grew to $73.5m during the second quarter of 2018.

While Pfizer is giving up on its myostatin/GDF-8 approach in DMD, two candidates for DMD addressing that target remain in clinical development, according to Biomedtracker – Roche’sRG6206, which is in Phase II/III, and Milo Biotechnology LLC’s AAV1-FS344, a Phase II candidate.Scholar Rock Holding Corp. also has a myostatin inhibitor, SRK-015, in Phase I with data expected by year’s end.

Pfizer de-emphasized neuroscience R&D after a series of disappointments in January, in a decision that cut 300 jobs.
TULIP Fever: AstraZeneca Catches Cold With Disappointing Lupus Data

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T he first of two Phase III TULIP trials of AstraZeneca PLC/MedImmune LLC’s investigational lupus therapy, anifrolumab, has missed its primary endpoint, casting the program in doubt.

Top-line data from the 52-week TULIP 1 study in adult patients with moderate-to-severe systemic lupus erythematosus (SLE) show the drug did not significantly reduce disease activity as measured by the SLE Responder Index 4 (SRI4) at 12 months.

Anifrolumab falls outside AstraZeneca’s core therapy areas but, together with its Alzheimer’s therapy lanabecestat (with Eli Lilly), the drug was touted by chief medical officer Sean Bohen during a pipeline update late last year as one of the company’s over-looked late-stage pipeline opportunities. (Also see “AstraZeneca’s Pipeline Reaps Rewards Of Return To Science” - Scrip, 21 Dec, 2017.)

Sadly, both have now stumbled in pivotal trials. (Also see “Lilly/As-traZeneca’s Lanabecestat Becomes Latest BACE Inhibitor Casualty” - Scrip, 12 Jun, 2018.)

Like Alzheimer’s, lupus is known for its high unmet medical need and raft of late-stage failures. The only drug to be licensed for around 60 years was GlaxoSmithKline PLC’s Benlysta (belimumab), but this has been slow to produce significant commercial rewards, hampered by its inconvenience and modest efficacy.

(Also see “Benlysta Is Niche, But Growing, So GSK’s Not Giving Up On Lupus” - Scrip, 7 Aug, 2017.)

In this difficult field, anifrolumab had looked different. Promising Phase II data for the product presented in 2015 had sparked great optimism for anifrolumab and it also held hope for a personalized approach to treatment. (Also see “Real Hope For Lupus As AZ’s Anifro-lumab Impresses In Phase II” - Scrip, 10 Nov, 2015.)

Formerly known as MEDI-546, the product is a fully human monoclonal antibody that binds to subunit 1 of the type I interferon receptor, blocking the activity of all type I interferons including IFN-α, IFN-β and IFN-ω. Type I interferons are involved in the inflammatory pathways, and 60%-80% of adult lupus patients have an increased type I interferon gene signature, which has been shown to correlate with disease activity.

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

Datamonitor Healthcare analyst Karolina Kujawa noted that the major challenge for companies with drugs in the pipeline for SLE is a trial design that can demonstrate the efficacy of an active drug despite the heterogeneity of the patient population, and she suggested that could have been the issue with anifrolumab.

“Looking at the inclusion criteria for the trial, it seems like they were targeting the SLE population with disease activity and severity as the main criteria. KOLs did note that people with high interferon alpha message will be more likely to respond to the drug.” One question now is whether there were any subgroup analyses looking at response by alpha interferon message.

“Depending on whether AstraZeneca decides to do a subgroup analysis, they could potentially try to get a restrictive label specifically for patients with high alpha interferon message. Having said that, testing for alpha interferon signal in patients would add to the cost, so the drug would need to show really impressive results in that sub-population,” Kujawa added. The full TULIP 1 results will be presented at a future medical meeting.

Anifrolumab’s future now awaits data from the second TULIP study, due later this year. Analysts at Deutsche Bank are doubtful that TULIP 2 will help its case. “This trial is a carbon copy of TULIP-1, and given the wording of the release, there do not seem to have been any meaningful trends that would warrant continued optimism over the remaining trial readout,” they said in an August 31 research note.

But, for AstraZeneca as whole, the news is more disappointing than devastating. “The programme was broadly seen as risky and of uncertain market potential by most investors, given prior failures in lupus and the commercial disappointment of the only approved novel drug Benlysta,” the analysts added. “We had held more optimism over upside potential from the programme supported by recent expert feedback. However, the news does not meaningfully change our expectations for a return to strong earnings growth.”

For analysts at Bryan Garnier, the failure’s main consequence is the likely loss of a potentially significant source of externalization revenues, both short and long term, as CEO Pascal Soriot had recently confirmed that anifrolumab would most probably have been partnered with another firm with more expertise in inflammatory diseases.

Jefferies analysts had modeled peak sales of $1.5bn for anifrolu-mab in the SLE setting.

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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.

### Selected clinical trial developments for the week 24–30 August 2018

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*Source: Biomedtracker | Informa, 2018*
Sunovion Must Regroup After Dasotraline Setback

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Sunovion Pharmaceuticals Inc, the US subsidiary of Sumitomo Dainippon Pharma Co. Ltd. in Japan, had forged ahead with a new drug application (NDA) for its novel non-stimulant attention deficit/hyperactivity disorder (ADHD) drug dasotraline after having mixed clinical results, but the effort has failed with the Aug. 31 announcement of a complete response letter from the US FDA.

Sunovion reported that the US FDA “determined that they cannot approve the dasotraline NDA for the treatment of ADHD in its current form.”

“The agency indicated that additional clinical data are needed to further evaluate the efficacy and tolerability of dasotraline for the treatment of ADHD. Sunovion plans to meet with the FDA to discuss their comments and determine next steps,” the company said.

Dasotraline has been evaluated in about 2,500 children and adults with ADHD in multiple placebo-controlled safety and efficacy studies and two long-term safety studies.

But the drug failed the primary endpoint in the first Phase III study in adult ADHD patients, SEP360-301. In the Phase III Study 202 in pediatric patients, the 4 mg dose demonstrated significant efficacy, though a 2 mg failed to do so.

Nevertheless, the company decided to submit for regulatory approval after the drug succeeded in the Phase III SEP360-305 study in adolescents, in which a 4 mg dose of the drug improved the mean score using the SKAMP-combined rating scale, a functional measure. Sunovion is also running a Phase III study of a 2 mg dose of the drug in children aged 6 to 12 years, which is due to complete in November.

The additional data could support a re-submission. Sunovion was seeking approval for all three age groups, based on the totality of its data, but that remains a risky approach, especially in a field with established therapeutic options.

“Depending on the company’s next steps, the drug could potentially succeed for pediatric patients before gaining approval for adults with ADHD. It is likely that another efficacy trial in adults will be mandatory for FDA approval,” Biomedtracker analysts concluded.

Dasotraline is a dual dopamine and nor-epinephrine reuptake inhibitor (DNRI). It has an extended half-life (47-77 hours) that supports the potential for stable plasma concentrations, yielding a continuous therapeutic effect over the 24-hour dosing interval. The company is counting on differentiation in ADHD based on once-daily dosing and a lack of the abuse potential associated with current stimulant therapies.

Dasotraline is also in late stage development for binge eating disorder.

Sunovion is expected to file dasotraline in binge eating disorder by the end of the first quarter of 2019. However, Biomedtracker analysts said they question whether it would be able to compete with Shire’s amphetamine Vyvanse (lisdexamfetamine dimesylate).

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APPOINTMENTS

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<td>Bristol-Myers Squibb</td>
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