Immuno-Oncology’s Next Wave: Key Targets And Emerging Players

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Doesn’t every biopharma company have an immuno-oncology strategy these days? It certainly seems that way, considering the number of drug developers that are labeling their therapeutic candidates as immunotherapies regardless of whether the description truly fits their asset. While there are plenty of drug makers that aren’t developing cancer treatments, there’s no denying that immuno-oncology (IO) is the hottest ticket in biopharma today based on the ever-increasing number of novel IO targets, the growing pipeline of immunotherapies in development, and the volume of dealmaking in the space.

The companies who’ve been first to market with programmed cell death-1 (PD-1) and PD ligand-1 (PD-L1) checkpoint inhibitors are leading the way forward in immuno-oncology: Bristol-Myers Squibb Co. with Opdivo (nivolumab), Merck & Co. Inc. with Keytruda (pembrolizumab), and, just recently, Roche’s Genentech Inc. subsidiary with Tecentriq (atezolizumab). Following close on their heels with Phase III compounds are AstraZeneca PLC with durvalumab and avelumab from partners Pfizer Inc. and Merck KGAA.

Bristol-Myers is likely to maintain its commercial lead, and possibly it’s lead in the clinic, since Merck’s Keytruda revenue lags Opdivo, which got the early lead in the lucrative lung cancer market. And, unlike Keytruda, Opdivo’s label doesn’t require lung cancer patients’ tumor samples to be screened for PD-L1 expression levels. Bristol’s immuno-oncology edge in sales and clinical programs is boosted by the firm’s first approved checkpoint inhibitor, the cytotoxic T-lymphocyte antigen-4 (CTLA-4) inhibitor Yervoy (ipilimumab), for patients with unresectable or metastatic melanoma. Bristol then nabbed the first combination approval, for Opdivo and Yervoy in melanoma, and is leveraging both as the base for IO combinations.

TEN KEY TARGETS, MOST DRUGS PRECLINICAL

But PD-1/PD-L1 and CTLA-4 are just the beginning for immuno-oncology as the field expands to other mechanisms and from single-agent therapies to therapeutic combinations that not only take the brakes off of the immune system, but also shift it into overdrive for an even more aggressive attack against tumor cells.

Scrip looked at 10 different immuno-oncology targets for the purposes of this report and spoke with some companies that are focused on novel immunotherapies based on these other targets. The field is so new, however, that most programs still are in early stages of development.

Of 10 targets with 99 different immuno-therapies in development, only five have been approved, 39 are in the clinic and 55 are preclinical, according to Pharma Intelligence’s Biomedtracker database. Those 10 targets are: PD-1/PD-L1, CTLA-4, granulocyte-macrophage CSF or its receptor (GM-
Greetings from San Francisco, where Scrip is engaged in a merry-go-round of meetings, information-gathering, mood-gauging, opinion-sounding and general temperature-monitoring at the annual BIO convention that should yield a steady flow of articles for some time to come. Our BIO Notebook bulletins published online this week have provided a flavor of our gleanings; we will cook up some more substantial offerings once we’re back home.

By some mishap, BIO overlapped this year with the annual congresses of ASCO and EULAR, while ADA is hot on their heels. Fear not, we’re still covering the bases. As an appetizer to our ASCO coverage (see next week’s issue), we bring you Mandy Jackson’s helicopter view of the current state of the rapidly evolving immune-oncology space (see cover story). Follow the links below for more data crunching and analysis on deal trends in the space. If diabetes is more your thing, check out Lucie Ellis’s curtain raiser for the ADA meeting on p15.

Whatever your therapeutic area of preference, don’t miss Jo Shorthouse’s interview with biopharma’s most inspirational moat-afficionado, Sir Greg Winter, who is also known for his pioneering work in therapeutic antibodies (p19).

Immuno-Oncology Data Drive Deal Dollars Higher
http://bit.ly/1Xwxl5t

Immunoncology deals command relatively high values, but transaction volumes are increasing annually at a steady pace, not skyrocketing despite intense interest in the field as big pharma companies remain selective IO dealmakers based on the strength of early-stage data.

INFOGRAPHIC: Immuno-Oncology Targets And Deal Trends

Immunoncology R&D is surging, though most programs still are in preclinical studies or early clinical trials. Even so, dealmaking is thriving and generating lucrative terms compared with cancer deals in general as big pharma and large biotech companies look for the safest and most effective IO drug combinations.
Biogen/AbbVie MS Drug Zinbryta Approved; Faces Crowded Market, Liver Concerns

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Biogen Inc. and its partner AbbVie Inc. gained the FDA’s blessing to market the firms’ new multiple sclerosis (MS) medicine Zinbryta (daclizumab) – the first once-monthly, self-administered treatment available for US patients with the disease.

But the drug has several hurdles to overcome in making a place for itself on the US market – most notably, it’s entering a space that’s already crowded and the new medicine is linked to concerns about adverse liver events.

The FDA, which gave its go-ahead to Biogen and AbbVie late on May 27, has imposed a black-box warning on Zinbryta’s labeling alerting prescribers and patients about the risk the drug can cause severe liver injury, including life-threatening events, liver failure and autoimmune hepatitis.

Prescribers are advised to obtain transaminase and bilirubin levels before initiating Zinbryta – an interleukin-2 (IL-2) receptor blocking antibody, which is indicated for the treatment of adults with relapsing forms of MS. They’re also advised to check those levels monthly and up to six months after the last dose.

The drug is contraindicated in patients with pre-existing hepatic disease or hepatic impairment.

Zinbryta’s labeling emphasizes that because of its safety profile, the drug should generally be reserved for patients who have had an inadequate response to two or more medicines indicated for the treatment of MS.

The drug is restricted to only prescribers, pharmacies and patients enrolled in the Zinbryta risk evaluation and mitigation strategy program.

With all of that, analysts predicted limited commercial potential for Zinbryta in the MS landscape.

“Taking into account Zinbryta’s safety issues that rose in its clinical trials and are now reflected in its label, it is apparent that there will be limited motivation for physicians to prescribe it,” said Leerink analyst Geoffrey Porges.

Zinbryta will be going up against several other MS products in the US – including Biogen’s own Plegridy (peginterferon beta-1a), Tecfidera (dimethyl fumarate), Tysabri (natalizumab) and Avonex (interferon beta-1a).

Other products Zinbryta must contend with in the US marketplace include Teva Pharmaceutical Industries Ltd’s Copaxone (glatiramer acetate), Novartis AG’s Gilenya (fingolimod), Sanofi’s Aubagio (teriflunomide), Bayer AG’s Betaseron (interferon beta-1b) and EMD Serono Inc’s and Pfizer Inc’s Rebif (interferon beta-1a).

Trying to make the case for Zinbryta, Alfred Sandrock, executive vice president and chief medical officer at Biogen, pointed out that clinical data showed the drug significantly reduced relapses and brain lesions for up to three years, versus Avonex intramuscular injection.

But Leerink’s Porges said that even before its approval, key opinion leaders (KOLs) said they anticipated Zinbryta most likely would be used only in patients positive for John Cunningham virus on Tysabri who wish to switch to a moderate-to-high efficacy drug that has no progressive multifocal leukoencephalopathy risk.

He noted the KOLs expected that even that niche would likely be overtaken by Roche’s and its US unit Genentech Inc’s ocrelizumab, once it launches in 2017 – a drug Porges anticipated to have a dominant position in the MS category.

With its limited labeling and safety risks, analysts have put peak worldwide sales of Zinbryta at only about $500m, having only a modest contribution to Biogen’s revenue.

Comprehensively, Tecfidera revenues for 2015 were $3.6bn, $2.9bn of which was in the US. Revenues last year for Biogen’s interferon products, including Avonex and Plegridy, were $3bn in 2015, while Tysabri brought in $1.9bn.

Biogen will pay AbbVie tiered royalties in the mid-to-high teens on net sales of Zinbryta, analysts noted.

MUM ON PRICING

Biogen and AbbVie have kept mum on Zinbryta’s pricing.

Biogen spokesperson Andrew Law told Scrip the companies don’t expect to disclose the cost until closer to the product’s availability in the third quarter, but he said the list price “will generally be in line with other disease-modifying therapies for people with relapsing forms of MS.”

Zinbryta will only be available through specialty pharmacies, Law said, noting Biogen is solely responsible for manufacturing the drug.

In the US, AbbVie and Biogen will be co-promoting Zinbryta, with both firms supporting sales of the product with a field force.

“We are prepared and ready to support the US commercial launch of Zinbryta,” Law declared.

He noted Biogen’s sales force will co-promote Zinbryta with the biotech giant’s other approved MS therapies.

ZINBRYTA APPROVAL

Zinbryta’s approval was primarily based on the results from the Phase III DECIDE and Phase IIB SELECT trials, which demonstrated the drug significantly reduced the annualized relapse rate of MS by 45% compared to Avonex for up to 144 weeks and by 54% versus placebo at 52 weeks.

While the precise mechanism of action of Zinbryta is unknown, it’s thought to work differently from other disease-modifying therapies by binding to CD25, a subunit of the IL-2 receptor found on activated lymphocytes, cells believed to underlie the biology of MS, Biogen and AbbVie said.

They noted that total lymphocyte, T and B cell counts decreased less than 10% from baseline during the first year of treatment.

The effects on total lymphocyte counts returned to baseline within about eight to 12 weeks after the last dose of Zinbryta, the companies reported.
News that Valeant Pharmaceuticals International Inc. had a suitor sniffing around has given the greatly-depressed stock a small bump in recent days, but analysts are skeptical that the drug company could attract other offers.

Recent reports from The Wall Street Journal say that Takeda Pharmaceutical Co. Ltd. and private equity fund TPG approached the beleaguered specialty pharma more than a month ago, interested in a takeout of the whole company. Yet, the report also notes that the talks never went far enough to result in a price being established and that the discussions have ended.

Valeant is hoping to give new CEO Joe Papa a chance to develop a new strategy for the company and carry that out.

While investors took the unsubstantiated rumors as a positive sign that Valeant could be in the midst of a turn around, analysts are more skeptical – even going as far as to say that Valeant is not worth a whole-company buyout.

“We find it difficult to fathom why a strategic or financial buyer would have interest in the entire asset portfolio, particularly given our view that the value of the various segments is meaningfully below the $31bn in total debt outstanding,” wrote Piper Jaffray analyst David Amsellem in a May 27 note to investors.

BMO Capital Markets analyst Alex Arfaei said in a recent note that he does not have “enough conviction in the new trajectory” to give the stock an outperform rating and that there is too much uncertainty regarding pricing pressures, as well as the amount of volume going through the new Walgreen’s channel of distribution.

Most analysts are expecting the company to sell off pieces. Amsellem thinks the gastrointestinal assets like Xifaxan (rifaximin) for irritable bowel syndrome and Uceris (budesonide) for ulcerative colitis could be valuable, potentially $1.2bn and $281m, respectively. He noted that these are the assets that Takeda was likely interested in. Valeant picked these up before all the trouble began with its $15bn (including debt) buy of Salix Pharmaceuticals Ltd. in March 2015.

Ironically, Valeant now has a market cap below the Salix purchase price. Being able to pick up the Salix assets at Valeant’s discounted price could have been the motivator for the Japanese pharma.

“We could envision a sale of some or all of the Bausch & Lomb assets, or some of the higher-quality US dermatology assets, or some of the overseas brand generics segments (and none of these businesses on the whole are without issues),” wrote Amsellem.

Arfaei agreed, saying there are $6bn worth in assets that Valeant could offload, including dentistry, women’s health, neuro, the surgical Bausch & Lomb Inc. assets and prescription ophthalmology.

Arfaei estimates that the surgical assets of Bausch & Lomb could be worth $681m and could be a good asset for divestiture because of its low single-digit growth and Valeant’s lack of scale in the space. Prescription ophthalmology, valued at $1.5bn by Arfaei, is also an area that Valeant has a small share of the market – Novartis has a 60% market share.

Meanwhile, Arfaei values the neuro and other business at $2.5bn, but notes the assets are considered toxic and will be hard to sell. And don’t forget the female arousal pill Addyi (flibanserin) that Valeant acquired for $1bn with the acquisition of Sprout Pharmaceuticals Inc. in mid-2015 – the drug hasn’t taken off and Valeant will likely only be able to unload it for significantly less than it paid.

Ultimately, all analysts agree that Valeant has a lot to prove before a serious turnaround can be expected. The company has lost about $290, or 90%, of its stock price since August 2015. Probes into drug pricing practices, a questionable relationship with specialty pharma Philidor as its dermatology distribution channel and high levels of debt due to the acquisition-spree it’s been on for several years have left Valeant in an extremely shaky state.

While former Perrigo CEO Papa has been called in to help right the ship, a clear strategy has not yet been laid out. Investors will be looking to the company’s June 7 conference call when it’s scheduled to finally discuss its first quarter results for any signals from Papa, but analysts worry the only way out might be a total breakup of the company.
BioMarin Kills Kyndrisa, But Duchenne Pursuit Not Over

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With the FDA already rejecting BioMarin Pharmaceutical Inc.’s experimental Duchenne muscular dystrophy (DMD) drug Kyndrisa (drisapersen) and now European regulators indicating they saw no chance for success, the biotech said it was ending development of the drug, plus three other first-generation follow-on products – BMN 044, BMN 045 and BMN 053 – which currently are in Phase II studies for distinct forms of the disease.

BioMarin CEO Jean-Jacques Bienaimé said the decision to terminate the R&D programs for the investigational DMD drugs was “difficult but necessary” at this time.

The move comes as DMD patients await word from the FDA on Sarepta Therapeutics Inc.’s experimental drug eteplirsen – a verdict that was supposed to come last week, but was put off by regulators, who didn’t provide a new timeline.

DMD patients have been on a rollercoaster over the past year – first watching as the FDA in January denied BioMarin permission to market Kyndrisa in the US, which came after an advisory committee declined to back the drug, followed by the agency’s refuse-to-file action on PTC Therapeutics Inc.’s Duchenne drug Translarna (ataluren).

Then came the blow in April when the FDA’s Peripheral and Central Nervous System Advisory Committee said it also could not back Sarepta’s drug – a meeting that ended in angry shouting from parents and patient advocates. BioMarin pledged to work with physicians, patient groups and regulatory authorities to develop a transition plan for those patients currently being treated with Kyndrisa, BMN 044, BMN 045 and BMN 053.

But the company insisted it was not the end of its DMD pursuit, pointing out it was continuing to “explore” its next-generation oligonucleotides as potential treatments for the rare, progressive muscle-wasting disease, which primarily affects boys, who generally don’t live beyond 30 years.

“Our plan now is to invest in research of next-generation oligonucleotides with the goal of making a safe and effective treatment available for boys with this devastating disorder,” Bienaimé said.

FINANCIAL, WORKFORCE IMPACTS

BioMarin spokesperson Debra Charlesworth told Scrip that as the company winds down the program for Kyndrisa and the first-generation follow-on drugs, “we expect that we are going to have to do some restructuring of parts of the organization that are focused” on those products.

While she said it was too early right now to go into any specifics, “it’s likely to have the greatest impact on our operations in Leiden, The Netherlands” – the former home to Prosensa, which BioMarin acquired for $680m in cash last year.

BioMarin’s acquisition of Prosensa came after GlaxoSmithKline PLC had pulled out of its deal with the Dutch firm on Kyndrisa following the failure of its Phase III DEMAND study, which showed that the antisense oligonucleotide didn’t meet the primary endpoint of statistically significant improvement in the six-minute walking distance test, versus placebo.

Charlesworth said that because of the discontinuation of Kyndrisa and the other three drugs, the company expected to write off the one-time impairment of approximately $580m in the second-quarter.

She said the impact on GAAP net loss guidance was to be determined based on the final restructuring plans, which will be updated in the second-quarter financial results.

“We continue to expect to achieve non-GAAP breakeven or better in 2017,” Charlesworth said.

She emphasized DMD is only part of BioMarin’s portfolio, which includes five FDA-approved products and a robust pipeline of other products nearing submission in the US and Europe.

SAREPTA’S OPPORTUNITY

RW Baird analyst Brian Skorney looked at BioMarin’s abandonment of “essentially the entire Prosensa portfolio” as presenting an opportunity in Europe for Sarepta to step in.

Skorney noted that currently, expectations for European sales of eteplirsen are essentially non-existent, given the ongoing litigation between BioMarin and Sarepta over intellectual property covering exon-51 skipping for DMD.

But with BioMarin out of the race, he said Sarepta may have a shot at meaningful European DMD sales.

“Though the argument can be made that BioMarin is still in possession of Prosensa’s IP, without active development of any programs covered by the IP, we do not believe it is likely to be a major roadblock and expect Sarepta to more aggressively pursue a path forward in Europe,” Skorney declared. “We believe the news that Biomarin is abandoning the Prosensa programs could lead to a settlement that allows Sarepta license to the patents for a relatively low royalty.”

BioMarin’s Charlesworth declined to comment on whether there was a settlement in the works.

“We will seek to ensure that we receive appropriate value for our IP assets,” she said.
Biogen’s Aducanumab And Three Other Drugs Get First EU PRIME Designations

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Biogen Inc’s aducanumab for early Alzheimer’s disease is one of the first four drugs to be accepted into the European Medicines Agency’s PRIME (priority medicines) scheme, which offers early, proactive and enhanced support for the development of products that address unmet medical needs, as well as the possibility of accelerated assessment.

The other three products now eligible for EMA support under PRIME are ChemoCentryx’s CCX168 for valvulitis, Kite Pharma’s KTE-C19 for lymphoma, and Novimmune’s NI-0501 for hemophagocytic lymphohistiocytosis (HLH).

Biogen said that aducanumab’s acceptance into the scheme was “a significant benefit to its development and to the European Alzheimer’s disease community,” and that it looked forward to collaborating with the EMA on development plans and potential accelerated assessment of aducanumab with the hope of bringing effective treatment to patients as soon as possible.

PRIME is intended mainly for products at an early stage of development, either at the proof-of-concept stage or, for smaller firms, at proof-of-principle stage. Biogen’s aducanumab is further advanced – it is entering global Phase III studies – but the company said it was accepted into PRIME on the basis of its Phase Ib placebo-controlled study in patients with prodromal or mild Alzheimer’s disease.

Two Phase III trials with the drug are now underway and recruiting for patients: ENGAGE and EMERGE, which are being conducted in centers in the US, Canada, Europe, Australia and Asia to assess the efficacy and safety of aducanumab in slowing cognitive impairment and the progression of disability in people with early Alzheimer’s.

Biogen chief medical officer Alfred Sandrock acknowledged in January this year that recruitment into the studies could take some time because of the inherent challenges in recruiting patients with early Alzheimer’s and the limited availability of PET scanners. He added that there had been substantial interest in the aducanumab program because of the “positive” Phase I data released last year.

PRIME, which was launched on March 7, 2016, is intended to foster R&D into new medicines that have the potential to address an unmet medical need, i.e., that offer a major therapeutic advantage over existing treatments, or benefit patients with no current treatment options, using existing regulatory tools such as accelerated assessment.

Eligibility for the PRIME scheme will depend on the availability of adequate non-clinical and exploratory data to justify a potential major public health interest prior to the initiation of confirmatory clinical studies at proof of concept stage (i.e., prior to confirmatory clinical studies).

OTHER PRODUCTS
The CHMP examined a total of 18 substances submitted for PRIME as of April 6, 2016, and turned down 14. Of the four products that were recommended for assessment under the scheme, two already have breakthrough designation in the US, a mechanism that, like PRIME, is also intended to ensure timely patient access to innovative new drugs.

Details of the other three substances entering PRIME are as follows:

• ChemoCentryx’s CCX168, an orphan drug for active ANCA-associated vasculitis. The company said that positive results from the European Phase II CLEAR (C5aR inhibitor on Leukocytes Exploratory ANCA-associated Renal Vasculitis) trial were announced in January 2016. "With these results, combined with information from our ongoing CLASSIC (Clinical ANCA vasculitis safety and efficacy study of inhibitor of C5aR) trial, we plan to conduct our US and European regulatory meetings in the middle of 2016, and then to initiate a Phase III registration trial by the end of 2016,” it added.

• Kite Pharma’s KTE-C19, which received US breakthrough status in December 2015. It is being tested in adults with diffuse large B-cell lymphoma (DLBCL) who have not responded to prior therapy, or who have had disease progression after autologous stem cell transplant (ASCT). The company announced at the end of May that updated data from the Phase I portion of the KTE-C19 ZUMA-1 study in chemorrefractory aggressive disease would be presented at the ASCO meeting on June 3-7, as would a poster on the study design for ZUMA-4, an ongoing Phase II study in children and young adults with previously treated acute lymphoblastic leukemia.

• Novimmune’s NI-0501, an anti-interferon-gamma MAb for primary hemophagocytic lymphohistiocytosis (HLH). The product has US and EU orphan status and was also granted US breakthrough designation in March this year on the basis of clinical data from a Phase II trial in children with primary HLH. Preliminary data from the Phase II study were presented at the American Society of Hematology meeting in Orlando, US, last year. HLH is a hyperinflammatory syndrome characterized by uncontrolled and aberrant activation of the immune system and a life-threatening cytokine storm presenting with non-remitting fever, pancytopenia, coagulopathy, and hemophagocytosis potentially leading to death, Novimmune noted.

REJECTIONS
The 14 candidates turned down for PRIME at the CHMP meeting were for various indications in oncology, infectious diseases, pneumology-allergology, vaccines, cardiovascular, and ophthalmology. Three of them were advanced therapy medicines.

The EMA said that it assessed all PRIME applications taking account of the available treatments for the target disease, the stage of development of the product, and the data presented. It did not say why the 14 had been turned down, although an EMA official told a conference in London recently that two thirds of the 18 applications were lacking a pediatric investigation plan (PIP) or a PIP waiver request.

"The fact that a medicine is not accepted in PRIME does not mean that its development should not be pursued," the agency said.
While Intercept Pharmaceuticals Inc. said it anticipates the uptake of its newly approved farnesoid X receptor agonist Ocaliva (obeticholic acid) to be gradual in the primary biliary cholangitis (PBC) population – with the firm declaring it plans to initially target only 700 gastroenterologists and hematologists, or about 30% of treating physicians, although the most experienced – the company insisted it does intend to reach its full target of up to 80% of doctors, or about 4,000, over the course of this year.

Nonetheless, Intercept is now on its way of transitioning from a research and development company to a full-fledged commercial entity, with the PBC approval putting it on the path of gaining the needed capital to fund what’s expected to be a much more lucrative opportunity: NASH, or nonalcoholic steatohepatitis, said RW Baird analyst Brian Skorney.

Intercept revealed late into the night on May 27 at the start of a three-day holiday weekend it had won an accelerated approval from the FDA for Ocaliva in PBC – a verdict that was widely expected.

During a May 31 conference call with investors and analysts, the company disclosed it had put Ocaliva’s wholesale acquisition cost (WAC) at $69,350 per year, or about $5,700 for a 30-day supply, which was mostly in line with Wall Street’s expectations.

**PRICE REFLECTS VALUE, EXPECTED OUTCOMES BENEFIT**

Investors seemed rattled at first blush on the pricing news, however, pushing shares of Intercept down 3.3%, or a loss of $4.66, in morning trading.

But the stock picked up after analysts began to weigh in – with shares gaining $9.15, or 6.4%, before closing at $148.36, up $6.59, or 4.6%.

Lisa Bright, chief commercial and corporate affairs officer at Intercept, said Ocaliva’s price reflected the value the medicine provides to patients and payers based on the clinical data and the cost of inadequately controlling PBC, which has had no new treatments for nearly 20 years until now.

Bright said Intercept mulled over several “important factors” when setting Ocaliva’s price, including its benefit and the innovation it provides as the only treatment option for patients who have an inadequate response to UDCA or as intolerance to ursodeoxycholic acid (UDCA) – the standard of care and historically the only approved treatment for PBC.

In setting Ocaliva’s WAC, she said Intercept also considered the consequences of an inadequate treatment in a progressive liver disease, including compensated and decompensated cirrhosis, hepatocellular carcinoma, liver transplants and death, and the savings associated with slowing disease progression.

**ARE PAYERS GOING TO PAY, PAY, PAY, PAY, PAY?**

Richard Kim, senior vice president and US commercial head at Intercept, said the company’s interactions with payers have been “quite fruitful.”

He admitted, however, there’s lots of details that still need to be worked out.

“But I think so far, the conversations have been very, very positive, and really just a good reflection around speaking about a new disease that a lot of the payers really haven’t had on the radar screen for quite some time,” Kim declared.

He said that prior to Ocaliva’s approval, Intercept had “profiled every town in the country” and had face-to-face PBC disease-state discussions with over 60 national and regional health plans, which Kim said cover more than 90% of patients in the US.

Kim said Intercept already had notified commercial payers, Medicare Part D plans, state Medicaid agencies and the Department of Defense and Veterans Administration of Ocaliva’s approval and product profile and plans to communicate the WAC to various pricing compendia and hold other face-to-face meetings.

He acknowledged that as with most “specialty” new product launches, it could take several months for Ocaliva to have broad formulary coverage.

“As a result, initially we expect it could take up to four weeks to six weeks on average from the time a physician writes the prescription to the time that a patient receives Ocaliva,” Kim said.

He said meanwhile, Intercept’s patient services hub, known “Interconnect,” would assist patients and providers in navigating coverage through that process – pointing out the company anticipates “a fair degree of initial rejections” with “a lot of back and forth with this for the first wave.”

Ocaliva is indicated as a treatment for PBC in combination with UDCA in adults with an inadequate response to UDCA or as a monotherapy in adults who are unable to tolerate UDCA.

Kim said Intercept’s goal is to focus on gaining coverage for the PBC patients who meet the criteria from the Phase III POISE study – alkaline phosphatase (ALP) ≥1.67x upper limit of the normal range (ULN) and/or total bilirubin >ULN or less than 15% ALP reduction.

BMO Capital Markets analyst Ian Somaiya said Ocaliva’s price reflected the expected outcomes benefit from the company’s Phase IV confirmatory COBALT study, whose data are anticipated in 2022.

Somaiya modeled 2016, 2017 and 2018 sales of $16.6m, $94.6m and $208.5m, versus Wall Street’s $18m, $119m and $251m, respectively, despite all patients already having been identified due to prior treatment with UDCA.

He predicted peak PBC sales of about $850m, versus $3.5bn for NASH – an indication for which he insisted Intercept was “uniquely positioned as the market leader.”

**Ocaliva PBC Uptake May Be Slow, But Builds Capital For NASH**

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He said meanwhile, Intercept’s patient services hub, known Interconnect,” would assist patients and providers in navigating coverage through that process – pointing out the company anticipates “a fair degree of initial rejections” with “a lot of back and forth with this for the first wave.”

Ocaliva is indicated as a treatment for PBC in combination with UDCA in adults with an inadequate response to UDCA or as a monotherapy in adults who are unable to tolerate UDCA.

Kim said Intercept already had notified commercial payers, Medicare Part D plans, state Medicaid agencies and the Department of Defense and Veterans Administration of Ocaliva’s approval and product profile and plans to communicate the WAC to various pricing compendia and hold other face-to-face meetings.

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There is so much interest in them. Among the 10 targets, there are no approved CAR-T therapies. The five FDA-approved immuno-oncology agents include four monoclonal antibodies and one oncolytic viral therapy – Amgen Inc’s Imlygic (talimogene laherparepvec), which produces the immunostimulatory protein GM-CSF and is indicated for local treatment of unresectable melanoma lesions that recur after surgery. The PD-1/PD-L1 inhibitors, Yervoy, Imlygic and the forthcoming CAR-T therapies were preceded by Dendreon Corp’s Provenge (sipuleucel-T), an autologous cellular immunotherapy. However, the prostate cancer treatment generally has been a commercial failure with Dendreon filing for bankruptcy to pay its debts and selling Provenge and related assets to Valeant Pharmaceuticals International Inc. in 2015.

EARLY-STAGE DOESN’T REDUCE EXCITEMENT

Among the 10 targets, 40% of the therapeutic candidates in the pipeline are being studied in humans and only four therapies are in Phase III clinical trials. Another five are in Phase II, seven are in Phase I/II and 23 are in Phase I trials. Yet the early stage of development in these targets hasn’t reduced the interest in them.

In fact, Genentech probably wouldn’t present its Phase I data for the OX40 inhibitor RG7888 (MOXR0916) at ASCO, given the monoclonal antibody’s early development stage. But there is so much interest in immuno-oncology, especially in relation to new targets, that the company decided to share its OX40 data at the annual cancer treatment meeting. Genentech VP-BioOncology and exploratory clinical development Stuart Lutzker told Scrip. The company also wanted to share noteworthy efficacy that’s been observed even in early dose escalation results.

In a June 4 presentation at ASCO, data will show objective response rates among 44 patients treated with RG7888 plus the company’s newly approved PD-L1 inhibitor Tecentriq in seven different dose cohorts (n=25) and a serial biopsy cohort (n=19) during the Phase I dose escalation portion of an ongoing clinical trial. The abstract indicates that the combination was well tolerated with no treatment-related adverse events leading to study discontinuation. Efficacy data will be presented at the meeting.

Lutzker noted that patients with sarcoma – a group that hasn’t been well-served by anti-PD-1 monotherapy – and renal cell carcinoma were among the Phase I study’s participants, which included five people previously treated with a PD-1 inhibitor. Some of the renal cell carcinoma patients had confirmed partial responses and some patients experienced tumor shrinkage.

“We think that mechanistically [RG7888] will work best in a combination,” Lutzker said. “Atezolizumab as a single agent provides benefit to patients, but we think the benefit could be enhanced by an agonist antibody that increases the pool of effector immune cells where atezolizumab takes the brakes off the immune system. We think that’s a very exciting combination.”

Biomedtraker analysts were optimistic about RG7888 in a mid-May report issued after ASCO released abstracts for its annual meeting. “The observation of objective responses here is promising, particularly if the five patients who had previously received PD-1/PD-L1 antibody therapy showed enhanced responses,” the report notes.

COMBINATIONS TO FOLLOW IN PD-1 FOOTSTEPS

Regeneron Pharmaceuticals Inc. also has a PD-1 inhibitor in the clinic – the mid-stage biologic REGN2810 – that it’s developing as a backbone for immunotherapy combinations that contain the company’s other immune system-boosting therapeutic candidates.

Regeneron chief scientific officer and president of Regeneron Laboratories George Yancopoulos told Scrip in an interview during the J.P. Morgan Healthcare Conference in January that combinations can improve the impressive efficacy seen with PD-1 inhibitor monotherapy and the right combinations will do so with manageable side effects.

“There are few companies that have made a long-term, deep commitment in this area, years ago, to come up with a lot of different potential agents to bring to bear on this problem,” Yancopoulos said.

Preclinical programs in Regeneron’s immuno-oncology portfolio include therapies that target LAG3 and glucocorticoid-induced tumor-necrosis-factor-receptor-related protein (GITR). The company also has a Phase I bispecific antibody called REGN1979 that targets CD20 on B cells and CD3 receptors on T-cells.

Regeneron and Sanofi agreed to expand their long-term relationship in July with a new collaboration worth more than $2bn to Regeneron, including a $640m upfront fee, to co-develop immuno-oncology therapies. The deal included REGN2810, which is in Phase II for the treatment of advanced cutaneous squamous cell carcinoma – a study that could support US FDA approval.

In Phase I data for REGN8210 that will be presented at ASCO on June 5, the disease control rate was 62.8% in patients with solid tumors, including 27 out of 43 clinical trial participants who achieved complete responses, confirmed and unconfirmed partial responses, or stable disease.

LESS COMPETITION, BUT A LOT OF INTEREST

Incyte Corp. has one of the hottest properties in immuno-oncology, an IDO inhibitor called epacadostat that is or will be tested...
in combination with all three of the approved PD-1/PD-L1 inhibitors as well as AstraZeneca’s PD-L1 inhibitor durvalumab. There are just eight IDO-targeting therapies in the development pipeline with only three in the clinic, although two of the clinical drug candidates are in Phase II, including epacadostat.

Scrip also interviewed Incyte Chair, president and CEO Herve Hoppenot about his company’s immuno-oncology pipeline during the J.P. Morgan Conference in January, and Hoppenot claimed that Wilmington, Delaware-based Incyte began developing its IDO inhibitor before anyone else was interested in the target. Now, the company has clinical collaborations with multiple big pharma players to test its drug in combination with their PD-1/PD-L1 inhibitors.

Incyte and Merck announced a pivotal Phase III clinical trial in October to test Keytruda plus epacadostat as a first-line treatment for advanced metastatic melanoma. Other epacadostat trials include a Phase I/II study with Keytruda and another in combination with Opdivo in certain advanced solid tumors and lymphomas; a Phase I study with Tecentriq for previously treated metastatic non-small cell lung cancer (NSCLC); and a Phase I/II study in combination with durvalumab for certain advanced solid tumors.

And like Regeneron, Incyte also is developing its own PD-1 inhibitor – an asset licensed from Jiangsu Hengrui Medicine Co. Ltd. in September – which it will market in combination with its other immuno-oncology drugs. The Hengrui deal was about “adding optionality to our portfolio for the long term,” Hoppenot said.

“We have to prove that a PD-1 inhibitor plus an IDO drug is better than PD-1 plus CTLA-4;” he said.

FORGET BOOSTING ANTI-PD-1 THERAPIES; CAN A PD-1 INHIBITOR BOOST NOVEL AGENTS?

PD-1 inhibition may be just the savior that Berkeley, California-based Aduro Biotech Inc. needs to rescue its lead development program. Aduro had a setback recently with two of its lead therapeutic candidates in the Phase I/II ECLIPSE clinical trial testing its immunotherapies CRS-207 and GVAX Pancreas in patients with advanced pancreatic cancer.

Median overall survival for patients with metastatic pancreatic cancer, who failed at least two prior therapeutic regimens and were treated with the company’s combination of CRS-207 and GVAX Pancreas, was 3.8 months – significantly lower than the 5.4 months of survival achieved by patients treated with CRS-207 alone and 4.6 months for individuals who received chemotherapy.

CRS-207 is a product of Aduro’s live, attenuated, double-deleted Listeria monocytogenes (LADD) technology. It uses the listeria virus to deliver mesothelin to provoke an immune system attack against tumor cells expressing that antigen. GVAX Pancreas is a cell-based cancer vaccine that is designed to induce an immune response against multiple pathogens, including GM-CSF.

Incyte Chair, President and CEO Stephen Isaacs noted during a conference call after the ECLIPSE results were revealed on May 16 that late-stage, metastatic pancreatic cancer is very difficult to treat, but he said the company still was “surprised” that the Phase IIb results diverged from Phase Ila data for Aduro’s combination regimen.

While the company will no longer pursue CRS-207 plus GVAX for heavily pretreated pancreatic cancer patients, Aduro remains hopeful for success in the ongoing Phase II STELLAR trial, which is testing CRS-207 and GVAX in combination with Opdivo versus CRS-207 and GVAX alone in metastatic pancreatic cancer patients who’ve gone through one prior round of chemotherapy.

William Blair analyst John Sonnier said in a May 16 research note that Aduro’s LADD platform is likely to perform well when used in combination with other immunotherapies, because it “has continually shown the ability to stimulate an immune response to the target antigen while also exhibiting a favorable safety profile.”

There are higher hopes for the STELLAR trial. Prior to the ECLIPSE failure, Isaacs told Scrip in an interview that “We all hope the ECLIPSE trial is positive, and we think it will be, but we think STELLAR will be even better.”

Sonnier noted that overall survival for advanced pancreatic cancer patients treated with standard-of-care chemotherapy combinations is six to eight months, so STELLAR will have to exceed that to prove the value of CRS-207 and GVAX in combination with Opdivo.

In addition to STELLAR, Aduro is testing CRS-207 plus Incyte’s epacadostat in a Phase I/II clinical trial called SEASCAPE, which began in March to evaluate the combination in up to 126 women with platinum-resistant ovarian, fallopian or peritoneal cancers. Aduro is funding the trial, but Incyte is supplying its drug for the study; neither firm has any rights to the other company’s asset.

BEYOND THE 10 KEY TARGETS, BUT STILL COMBINED WITH PD-1

Armo BioSciences Inc. has a fresh perspective on immuno-oncology outside of key targets like PD-1 and IDO. The company is developing pegylated formulations of recombinant human interleukins, starting with lead program AM0010, a pegylated Interleukin 10 (IL-10) that’s being studied in a Phase Ib/Ib clinical trial. ARMO’s $50m Series C venture capital round, which closed in February, will fund a Phase II/Ill trial and support clinical development of pegylated versions of additional cytokines – IL-12 and IL-15.

The drug candidates are designed to boost the activity of PD-1 inhibitors and other first-generation immuno-oncology therapies. A cytokine, such as a pegylated interleukin, should cause the immune system to produce more T-cells, so that the immune system is more fully activated upon administration of an anti-PD-1 therapy or chemotherapy.

The combination could make PD-1 inhibitors viable treatments for cancers in which they are not particularly effective as a monotherapy, such as pancreatic, triple-negative breast and colorectal cancers. ARMO is testing AM0010 with approved PD-1 inhibitors, but the company is developing its own anti-PD-1 therapy that it plans to study in combination with its pegylated IL-15 in a Phase I trial that could kick off in 2017.
Gilead’s Epclusa And Merck’s Zepatier Hep C Combos Get EMA backing

The European Medicines Agency is recommending EU marketing approval for Gilead Sciences Inc.’s Epclusa (sofosbuvir/velpatasvir) and Merck & Co. Inc.’s Zepatier (grazoprevir/elbasvir) after the two doublet therapies were backed by EMA’s Committee for Medicinal Products for Human Use (CHMP). Europe’s top drug regulator on May 27 said the two regimes allow cure of patients with long-term hepatitis C virus infection without the need for interferons, which are associated with poor tolerability and potentially serious side effects. Epclusa and Zepatier belong to a new generation of medicines for chronic HCV infection, direct-acting antivirals, that give high rates of cure of HCV infection by blocking proteins essential for viral replication. Epclusa targets the proteins NS5B and NS5A, while Zepatier targets the proteins NS3/4A and NS5A. Epclusa contains sofosbuvir, already approved under the name Sovaldi and as a combination therapy with ledipasvir under the name Harvoni, and velpatasvir which is a novel HCV protein inhibitor. This fixed-dose combination of direct-acting antivirals targets all six genotypes (GT) of the virus, EMA noted in a statement. Zepatier contains the two novel HCV protein inhibitors grazoprevir and elbasvir. This fixed-dose combination of direct-acting antivirals targets genotypes (GT) 1 and 4 of the disease, it added.

Jazz Singing A Stronger Oncology Tune Through Celator Buy

Ireland-headquartered Jazz Pharmaceuticals PLC will pay $30.25 per share in cash, or approximately $1.5bn, to acquire small US pharma Celator Pharmaceuticals Inc. for its lead cancer therapy, Vyxeos. As the rest of Celator’s pipeline appears void of other smash hits, Vyxeos could be a number one for Jazz. The product has a likelihood of approval rate in Saigent Research’s BioMedTracker database of 50% – 15% higher than similar products at the same stage of development. It is also the first product candidate to demonstrate a significant improvement in overall survival in patients with high-risk (secondary) AML. Celator has also started Phase II clinical trials for the drug in two other oncological indications: myelodysplastic syndrome (MDS) and acute lymphocytic leukemia (ALL). Vyxeos has received a breakthrough therapy designation in the US and orphan drug status in both the US and Europe. The drug is a liposomal formulation of a synergistic 5:1 molar ratio of cytarabine and daunorubicin, two agents commonly used to treat hematologic malignancies, and Celator managed to net $41m for development of the product through an initial public offering (IPO) earlier this year. The company is expected to submit a new drug application for Vyxeos to the US FDA in the third quarter of this year following release at the ASCO (American Society of Clinical Oncology) conference in June of final results from a Phase III trial.

Boehringer Ingelheim Reveals Battle Plans For Olmutinib

Boehringer Ingelheim GMBH Boehringer Ingelheim has announced Phase III plans in non-small cell lung cancer for olmutinib, the third-generation epidermal growth factor receptor (EGFR) mutation-specific tyrosine kinase inhibitor (TKI) it licensed from Hanmi Pharmaceutical Co. Ltd. last July. Following the product’s recent success in its originator’s home market, South Korea, BI says it will comprehensively investigate olmutinib as a monotherapy in the ELUXA clinical trial program in a range of settings as well as in combination with investigational and existing anti-cancer drugs, including Merck’s anti-PD-1 therapy, Keytruda (pembrolizumab). Olmutinib is one of a number of drugs being positioned against non-small cell lung cancer (NSCLC) that has developed resistance to the earlier EGFR inhibitors such as AstraZeneca PLC’s Iressa (gefitinib) and Roche/Astellas Pharma Inc.’s Tarceva (erlotinib). Most initial responders to these therapies develop resistance through secondary mutations, the most common is the T790M mutation, which occurs in about 60% of patients. Two of the ELUXA studies will be Phase III trials set to begin this year; one comparing olmutinib in combination to standard, platinum-doublet chemotherapy for patients with EGFR T790M mutation-positive lung cancer, whose disease progressed on one prior EGFR-TKI treatment (ELUXA 2). The other (ELUXA 3) will investigate olmutinib as a first-line treatment compared to BI’s second-generation EGFR TKI, Gilotrif (afatinib), in patients with EGFR mutation-positive NSCLC.

Peregrine Officially Ends Late-Stage Development Of Bavituximab

After a Phase III blow-up in February, Peregrine Pharmaceuticals Inc. has finally decided what to do with its flailing immuno-oncology program, all while trying to put the focus on its more successful contract manufacturing business. Peregrine announced June 2 that it will no longer initiate any further Phase II or Phase III clinical trials for bavituximab, but will instead conduct small early-stage studies combining the drug with other immuno-oncology agents. The company said that the trials may be conducted in conjunction with AstraZeneca or the National Comprehensive Cancer Network (NCCN). Peregrine said in a statement that the “goal of these trials will be to generate compelling data capable of driving partnering interest.” While it’s a commendable goal, it’s an unlikely to result in much success for Peregrine.
Teva’s Huntington’s Rejection May Be Neurocrine’s Good Fortune

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The FDA’s rejection on May 31 of Teva Pharmaceutical Industries Ltd’s new drug application (NDA) for its experimental Huntington disease drug deutetrabenazine (SD-809) may be Neurocrine Biosciences Inc’s good fortune in another indication – tardive dyskinesia (TD), a disease for which the two companies may end up competing against each other.

Teva’s bad luck had shares of Neurocrine jumping more than 10% on May 31, before closing at $41.65, up $3.46, or 7.5%.

The beat down by the FDA of Teva’s drug in Huntington’s could mean a significant delay in the firm filing its NDA in TD

Teva investors, however, didn’t panic much – only driving the firm’s shares down 1.5%, before the stock recovered, to close at $51.87, a gain of 21 cents.

Teva is developing deutetrabenazine as a treatment to help control involuntary jerky movements, known as chorea, associated with Huntington’s, a fatal neurodegenerative condition that affects about 30,000 Americans.

But the company also is developing deutetrabenazine as a potential treatment for TD, a condition characterized by involuntary, repetitive movements of the extremities or face. If eventually successfully secured, the TD indication could significantly boost deutetrabenazine’s US sales.

Teva noted that it currently is conducting a Phase III efficacy and safety study, known as AIM-TD, of deutetrabenazine in patients with moderate-to-severe TD and expects additional data from the trial later this year, with a regulatory submission in that indication to follow.

Analysts suspected the beat down by the FDA of Teva’s drug in Huntington’s could mean a significant delay in the firm filing its NDA in TD, possibly until early next year – giving an advantage to Neurocrine, which is expected to file its own TD application for its investigational product, valbenazine (NBI-98854), later this year.

SURPRISE REJECTION
The rejection of the deutetrabenazine NDA, which was accepted by the FDA in August 2015, came as a shock to Wall Street, which had widely expected an approval, given the clinical data from Teva’s FIRST-HD trial “looked clean,” said Jefferies analyst Biren Amin.

The good news for Teva is that the FDA hasn’t asked it to conduct any new trials, but rather, to examine blood levels of certain metabolites with deutetrabenazine, which is a ‘deuterated’ form of tetrabenazine, a vesicular monoamine transporter 2 inhibitor sold in the US under the brand name Xenazine by Lundbeck Inc. and Valeant Pharmaceuticals International Inc. as a treatment for Huntington’s chorea. “These metabolites are not novel, and are the same seen in subjects who take tetrabenazine or deutetrabenazine,” Teva emphasized, noting its product is the first deuterated drug ever to go before the FDA.

Jefferies analyst Biren Amin said the question he’s asking is if those metabolites are not novel, then similar criteria should have also applied to the FDA’s approvals of generic forms of tetrabenazine.

“Therefore, the question is whether this is related to some influence of Teva’s deuterated technology on the metabolites of tetrabenazine,” he said.

Amin pointed out that the initial tetrabenazine NDA, which was submitted by Prestwick Pharmaceuticals Inc., which was acquired by Biovail Pharmaceuticals Inc., the predecessor of Valeant, came up against similar questions from the FDA, with the firm initially failing to identify the presence of four active enantiomers to a metabolite of tetrabenazine.

“It’s possible that Teva may have been relying on these data given the company may have referenced certain data from the tetrabenazine label,” Amin said.

Analysts at Biomedtracker, an affiliate of Scrip, said the FDA may be exercising ‘extra caution’

They pointed out that the primary active metabolite of tetrabenazine, dihydrotetrabenazine, readily crosses the blood-brain barrier and is primarily responsible for its activity.

The most common adverse effects of tetrabenazine include sedation, drowsiness, parkinsonism and depression, with the drug carrying a black-box warning for increasing the risk of depression and suicidality, the Biomedtracker analysts said.

“The FDA is possibly concerned that possible prolonged exposure to dihydrotetrabenazine compared to tetrabenazine will add to this risk,” they said.

While the Biomedtracker analysts said they expected Teva’s deuterabenazine to eventually be approved, because of the FDA’s apparent extra caution and the delay ahead for Teva in bringing the product to the market, they reduced the likelihood of approval to 58%.

Teva said it has accelerated its re-analysis process and would submit its response to the FDA’s complete response letter (CRL) in the third quarter.

Given the FDA’s concerns seemed “addressable,” Credit-Suisse analyst Vamil Divan said the CRL should be viewed as a “fairly modest negative” – calling the delay Teva is facing “minor.”

But, he said, “it does not help matters on a stock where we believe sentiment has been pretty mixed.”

Divan anticipated a slow initial launch for deutetrabenazine, but expected an estimate of peak unadjusted sales to reach $3.5bn in 2027, should the product also receive approvals for use in TD and for tics associated with Tourette syndrome, which Neurocrine also is pursuing as a possible indication for valbenazine, with top-line data expected by the end of this year.

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StemCells Inc. to Wind Down Operations After Phase II Failure

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StemCells Inc. plunged 81.2% to $0.57 per share on May 31 after the company revealed little chance of success for a Phase II spinal cord injury study, which has been terminated, and said that it may not be able to return any cash to shareholders after StemCells winds down its operations this year.

The Newark, California-based company has struggled to keep its share price above $1 and executed a 12-for-1 reverse stock split on May 6 to boost its stock value from $0.24 to $2.50. StemCells shares now are heading back to pre-stock split levels with the discontinuation of the lead development program for the company's HuCNS-SC human neural stem cells and the revelation that it has too little cash and too few strategic alternatives to avoid a shutdown.

Based on six-month data from the Phase II Pathway Study in the treatment of chronic spinal cord injuries, StemCells thought that its stem cell therapy may significantly improve patients' physical strength and function, but a 12-month assessment revealed a more rapid than expected decline. In other words, the treatment's effects were not maintained over time in the study's 17 patients.

StemCells, after consulting with its Interim Assessment Data Monitoring Committee (IA-DMC), determined that: “While the results showed overall improvement in patients treated with the company's proprietary cells, the magnitude of the effect and the perceived trend of the effect over time did not justify continuing the study or exploring the variability in the initial patient observations, given the financial resources available to the company.”

StemCells had $5.5m in cash as of May 31, but given that small sum and the minimal prospects of attracting buyers for its technology in light of the Pathway Study's termination, the best option was determined to be an orderly winding down of operations. The company will seek buyers for its intellectual property, but even if the assets are sold, there may not be enough cash to distribute to shareholders after the company meets outstanding obligations and pays for the shutdown.

President and CEO Ian Massey expressed the company's disappointment in the Pathway results in a statement from StemCells and said he was proud of its employees' work over the last several years. However, Massey only joined the company about 14 months ago as president and chief operating officer. He was named CEO in January to replace long-time chief executive Martin McGlynn in a planned transition to facilitate commercialization of the company's stem cells.

GSK Ups Ante In Triple COPD Therapy Race; Payers Wary

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GlaxoSmithKline PLC has brought forward plans to file an NDA with the US FDA for its triple combination therapy for patients with COPD. The US regulatory submission is now anticipated by the end of 2016, rather than the first half of 2018. An EU filing continues to be expected by the end of 2016.

It is estimated that a third of COPD patients already receive triple therapy: a combination of an inhaled corticosteroid (ICS), a long-acting muscarinic antagonist (LAMA), and a long-acting beta agonist (LABA), via multiple inhalers. The late-phase pipeline for COPD has a strong focus on triple combination therapies delivered via a single inhaler. These include CHF 5993 (Chiesi Farmaceutici SPA) and PT010 (AstraZeneca PLC), both of which are in Phase III.

Datamonitor Healthcare anticipates triple therapies to predominantly target very severe COPD patients who are currently using multiple inhalers. According to analyst Christina Vasiiliou, pulmonologists “eagerly anticipate” the arrival of triple combination therapies to increase compliance among patients already on the regimen with two separate inhalers.

However, “Payers are unconvinced about the long-term benefits triple therapies will offer and are concerned about the potential overuse of such therapies,” warned Vasiiliou.

Payers have expressed concerns about the unnecessary costs that will result from overprescribing triple therapies to patients who can be successfully managed with simpler treatments. Adherence to COPD medications remains a major issue and payers have highlighted that this should not be addressed by treating patients more aggressively.

Payers and payer advisors interviewed by Datamonitor Healthcare expect the triple combination inhalers to be priced at a modest premium to ICS/LABA or LAMA/LABA inhalers. While there is no agreement on the level of this premium, some have stated that the products would be reimbursed if priced lower than their individual components, while others have indicated they are likely to encounter reimbursement difficulties if priced higher than 10% more than ICS/LABAs.

GSK said that it brought forward the plan to file an NDA following discussions with the US FDA for the once-daily closed triple combination therapy, fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) for patients with COPD.

“GSK is clearly trying to protect its respiratory franchise, particularly in light of the availability of generic versions of Advair, and highly efficacious LABA/LAMA combinations,” suggested Vasiiliou on GSK's decision to move up the filing of its triple therapy.
Biogen Adds To Biosimilar Anti-TNF Portfolio In EU

Biogen became the first company able to market two biosimilar anti-TNF products in Europe on May 30 when the European Commission approved Samsung Bioepis Co. Ltd.’s infliximab biosimilar, Flixabi, a biosimilar of Merck & Co. Inc./Johnson & Johnson Remicade, holding out the intriguing possibility that having more than one TNF-inhibitor might be of benefit to Biogen when discussing market access with payers. Flixabi is indicated in the EU for the treatment of adults with rheumatoid arthritis, Crohn’s disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and psoriasis. It was also approved for children aged six to 17 years old with severe active Crohn’s disease or severely active ulcerative colitis.

It is expected to be introduced over the coming months, to compete with the other biosimilar infliximab products already available in the region, Pfizer Inc./Hospira Inc.’s Fletra and Celltrion Inc.’s Remsima. Samsung Bioepis is a joint venture between Samsung BioLogics and Biogen, and it also received an approval earlier this year in Europe for Benepali, a biosimilar version of Pfizer/Amgen Inc.’s Enbrel (etanercept), making it the first company to gain a European approval for a biosimilar etanercept.

AC Immune Targets $50m IPO

Alzheimer’s disease drug and vaccine developer AC Immune SA is aiming to raise $50m via an initial public offering that will take the company public on Nasdaq in the US. This follows a successful series E financing round in May this year that saw the company net $43.5m. The Swiss company plans to use proceeds from the IPO to continue development of its lead product, the anti-Alpha antibody crenezumab, which is being researched as a passive immunization treatment for Alzheimer’s disease. Crenezumab, which is currently in Phase III clinical trials, is partnered with Roche company, Genentech Inc. A US Securities and Exchange Commission filing from AC Immune did not disclose how many shares it plans to sell or their price. AC Immune has two other Alzheimer’s vaccines in development, ACI-35, which is partnered with Johnson & Johnson subsidiary Janssen, and ACI-24; as well as an anti-tau antibody in preclinical studies. ACI-35 is an active therapeutic vaccine stimulating the patient’s immune system to produce a polyclonal antibody response against phosphorylated Tau protein. It became the world’s first anti-pTau Alzheimer’s disease vaccine to enter a clinical trial when AC Immune initiated a Phase I study in January 2014.

Ariad Retreats From EU

Ariad Pharmaceuticals Inc., a company which has been plagued by setbacks for its leading marketed product, Iclusig (ponatinib), has completed the sale of its European business to Incyte Corp. for $140m. It appears as though Cambridge, Massachusetts-based Ariad has wiped its hands clean in Europe of its only marketed product that still has patent protection – as parallel to the sale of its European operations to Incyte, that company has also picked up exclusive European rights to Ariad’s main revenue stream, Iclusig, a kinase inhibitor approved for the treatment of chronic myeloid leukemia (CML) and Philadelphia-chromosome positive acute lymphoblastic leukemia (Ph+ ALL). Incyte now holds exclusive rights to develop and commercialize Iclusig in the EU and 22 other countries, including Switzerland, Norway, Turkey, Israel and Russia.

AstraZeneca’s ‘Clear-Out’ Strategy Sees Gout Drug Go To Grunenthal

Aachen, Germany-based Grunenthal GmbH has licensed rights for AstraZeneca PLC’s gout medicine Zurampic (lesinurad) in Europe and Latin America whereby Britain’s second biggest drug maker will receive up to $230m in sales and other milestones over the lifetime of the contract and low double-digit royalties. AstraZeneca PLC will initially manufacture and supply Zurampic to Grunenthal and will handle the European post-approval commitment on its behalf. From October 2021, Grunenthal will have the option to take over manufacturing. AstraZeneca says the deal will not impact its previously announced guidance for 2016. Zurampic was approved by the European Medicines Agency in February 2016, in combination with a xanthine oxidase inhibitor (XOI), for the adjunctive treatment of hyperuricemia (excess of uric acid in the blood) in adult patients with uncontrolled gout. It was approved in the US by the FDA in December 2015 but has not yet launched there either.

ContraVir Strikes Rival Deal

ContraVir Pharmaceuticals Inc. is merging with competitor early stage hepatitis B drug developer Ciclofilin Pharmaceuticals to strengthen its pipeline offering in antivirals. ContraVir CEO James Sapirstein said the deal would “firmly position ContraVir as an important player in the hepatitis B space.” Ciclofilin’s lead development candidate, CPI-431-32, is a next-generation non-immunosuppressive cyclophilin inhibitor shown to have a significantly larger selective index compared with previously known cyclophilin inhibitors. Ciclofilin’s compound is still in preclinical studies but is expected to enter the clinic in 2017. ContraVir highlighted that CPI-431-32 blocks the hep B virus’s ability to “hijack” CyP, and has also been shown to inhibit entry of the virus into liver cells as well as reduce or eliminate production and secretion of key hepatitis B antigens (HBsAg and HBeAg).

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Prosecutors unsealed an additional charge of conspiracy to commit securities fraud against Martin Shkreli – infamously known for hiking up the price of a toxoplasmosis medicine by 5,000% – bringing the total number of criminal counts against the former drug company CEO to eight.

Former pharmaceutical company CEO Martin Shkreli – once dubbed the most hated man in America for hiking up the price of a toxoplasmosis drug last year by 5,000% – has racked up another criminal charge, which could add to the possible jail time he’s already facing with the earlier seven counts, including securities fraud, brought against him this past December.

Prosecutors said Shkreli had used Retrophin as his ‘personal piggybank’ to pay back the shareholders at both funds

In a superseding indictment filed in the US District Court for the Southern District of New York, which was unsealed on June 3, prosecutors accused Shkreli of conspiring to hide from investors of Retrophin Inc. – a publicly traded company he started and used to run before being fired – about two million unrestricted shares by masking them under other employees’ names.

Prosecutors said Shkreli had the help of his former outside lawyer Evan Greebel in concealing the shares, which the two men essentially controlled. Both men were arrested this past December, but were freed after they posted bond - $5m for Shkreli and $1m for Greebel.

Shkreli, who was “perp-walked” out of his New York apartment in front of news cameras early on Dec. 17, 2015, initially was charged with defrauding investors of his former hedge funds, MSMB Capital Management and MSMB Healthcare, and misappropriating more than $11m in assets from Retrophin.

Prosecutors said Shkreli had constructed a “Ponzi-like scheme,” under which he used money from MSMB Healthcare to pay off debts from a series of bad trades he’d made under MSMB Capital. They accused Shkreli of dipping into MSMB Healthcare’s cash to use for “seed” money to start Retrophin and lied to investors about how both funds were doing.

Prosecutors also said Shkreli had used Retrophin as his “personal piggybank” to pay back the shareholders at both funds and perpetrated the fraudulent activities in a number of ways, including backdating documents.

Four months before Shkreli was charged, Retrophin last fall had filed a lawsuit against the former company chief, alleging, among other things, that he defrauded the company. At a May 3 hearing, prosecutors said they potentially might bring additional charges against Shkreli. He’s expected to appear in federal court in Brooklyn on June 6.

Shkreli’s lawyer Benjamin Brafman told Scrip on June 3 that the new indictment “does not in any way impact on the flawed theory of the case as applied” to his client. Shkreli’s criminal charges are unrelated to what initially made him infamously – his move when he was CEO of Turing Pharmaceuticals AG to jack up the price by more than 5,000% of Daraprim (pyrimethamine), the only FDA-approved drug to treat toxoplasmosis, a parasitic infection often seen in HIV-infected patients, pregnant women and children, which can cause serious complications in people with weakened immune systems.

The spike in Daraprim’s price also caught the attention of former Secretary of State and presidential candidate Hillary Clinton, who when first learning about Shkreli’s action, declared in a tweet she’d bring him and other price gouging drug makers down. That simple Sept. 21, 2015 tweet was attributed to causing a panic on Wall Street – knocking off $132bn in biotech investment.

Other presidential candidates also piled on and threatened to take aim at Shkreli, who also was fired from his CEO position at Kalobios Pharmaceuticals Inc. after being indicted.

Capitol Hill also wasted no time in making him a target – issuing a subpoena for Shkreli to appear at a hearing on drug prices, which he eventually did in February, although he invoked his Fifth Amendment rights under the US Constitution to dodge questions, but his eye rolls and smirks didn’t go unnoticed by members of the House Committee on Oversight and Government Reform.

Shkreli also quickly became the most despised person in the biopharmaceutical industry, with the big trade groups distancing themselves from him and executives like Merck & Co. Inc. CEO Kenneth Frazier calling the now-former Turning CEO a “hedge-fund manager masquerading as a pharma company” and an “aberration.”
ADA Curtain-Raiser: CV Data To Steal Show At Diabetes Meeting

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In the lead up to 2016’s American Diabetes Association (ADA) meeting, to be held June 10-14 in New Orleans, Scrip has handpicked the most exciting data presentations you should check out onsite or catch up with online.

CVOT WARS
This year will be the battle of best cardiovascular outcomes, as ADA gears up to present full data for Novo Nordisk AS’s Victoza (liraglutide) from the LEADER trial and additional analyses for Boehringer Ingelheim GMBH and Eli Lilly & Co’s Jardiance (empagliflozin), which wowed doctors at last year’s European Association for the Study of Diabetes annual meeting with data from its EMPA-REG study.

Full data for the Novo Nordisk’s highly anticipated LEADER cardiovascular outcomes trial for type 2 diabetes therapy, Victoza, are being presented on Monday 13 June at a special session – during which investors will be looking for answers to a couple of key questions about the GLP-1 product.

The Danish company has already released positive top-line results from the CVOT study, but the true magnitude of cardiovascular benefit for Victoza has not yet been clarified. Analysts at Leerink Swan have estimated that the minimum benefit for Victoza in the LEADER study will be approximately 12-13% risk reduction. They noted in a March 4 note, on LEADER’s top-line data readout, that positive results from the trial bode well for Victoza and perhaps more importantly for Novo Nordisk’s basal insulin/GLP-1 combination product, Xultophy (insulin degludec + liraglutide). With positive CVOT results Novo Nordisk “will continue to establish itself as the premier player in the diabetes space for the next five to seven years,” Leerink analysts said.

The top-line data released for Victoza show that the drug met its primary MACE endpoint, with all three components contributing to this result (CV death, myocardial infarction, and stroke).

However, analysts at Sagient Research’s BioMedTracker noted in their 2016 ADA Conference Planner that the trial had twice the number of MACE events that were originally planned for.”Since this high number of events could lead to statistical significance with more modest reductions in MACE, it will be important to see the magnitude of the effect,” they noted. If data from the LEADER study are able to show more than a 15% risk reduction with use of Victoza across all components of the primary endpoint this would provide the product with a sturdy efficacy and safety profile.

BioMedTracker analysts also highlighted that ADA attendees will be seeking answers on how the results from the LEADER study will impact usage of injectable Victoza, especially versus oral SGLT2 inhibitors, and whether the benefit is likely to be a GLP-1 agonist class effect.

Novo Nordisk’s drug will need an edge in order to compete with Lilly and Boehringer’s type 2 diabetes therapy, Jardiance. The pair have recently filed an sNDA with the US FDA to update Jardiance’s label to include indications to reduce the risk of all-cause mortality, CV death or hospitalization for heart failure, based on the EMPA-REG cardiovascular effects study. Lilly and Boehringer will be presenting further data analyses, including mechanistic insights, from Jardiance’s CVOT at ADA on Tuesday June 14.

PHASE III HIGHLIGHTS
Merck & Co. Inc. will be presenting first Phase III data during the conference for its SGLT2 inhibitor, ertugliflozin. BioMedTracker noted that while the product is “not expected to necessarily have major advantages over other SGLT2 inhibitors, it is being developed as a fixed-dose combination with Merck’s popular Januvia (sitagliptin), so the poster presented on combination treatment will be interesting.” Meanwhile, Novo Nordisk will be making a first conference presentation of Phase III data for its once-weekly GLP-1 agonist, semaglutide, from the SUSTAIN 2 trial comparing the product to Merck’s Januvia and the SUSTAIN 3 trial testing semaglutide against AstraZeneca’s Bydureon (exenatide).

And Intarcia will readout Phase III data from its FREEDOM-2 study of ITCA 650 (implantable GLP-1 exenatide) versus sitagliptin.

BioMedTracker noted that while top-line details have already been released, showing an expected A1c and weight loss advantage over Januvia, “it will be useful to get more details on rates of vomiting, which appeared somewhat high in FREEDOM-1, as well as infections due to implantation of the device, which the top-line release noted occurred in less than 1%.”

VICTOZA IN TYPE 1 DIABETES
Novo Nordisk discontinued development of its leading type 2 diabetes drug Victoza in type 1 patients last year, but according to Data-monitor Healthcare’s proprietary diabetes primary research survey the drug is still used off-label in some patients with inadequate glycemnic control. ADA 2016 will see data presented for Victoza in type 1 patients from a single center Canadian study.”Rates of hypoglycemia in Victoza treated patients will be important to note in this presentation,” BioMedTracker analysts highlighted.

INNOVATION AND EARLY DATA
While diabetes patients are a well-served population in contrast to some disease groups, there is still unmet need that requires novel approaches and there are older treatment options demanding innovative methods. In this area, a number of companies will presenting data for faster-acting insulins during 2016’s ADA conference.

Adocia – a company considerably behind the pack in this development area – will present data for BioChaperone Lispro, an ultra-rapid formulation of insulin lispro licensed to Lilly. BioChaperone Lispro is being investigated for use in both type 1 and type 2 diabetes patients. In prior data from a Phase Ib/IIa trial, the product was associated with a 61% reduction in post-prandial glucose excursion over the first two hours compared to Lilly’s Humalog (insulin lispro injection).

Leerink analysts also highlighted in a May 31 note that during the conference there will be a number of presentations on novel dual GLP-1/glucagon receptor agonists.
Imbruvica Gets Broad CLL Okay in EU But Draft Rebuff From UK’s NICE

JOHNSTON & JOHNSON/ABBVIE Inc’s blockbuster chronic lymphocytic leukemia drug Imbruvica has received mixed messages in Europe – getting an expanded CLL label for the European region but a draft rejection on cost and efficacy grounds from the UK’s HTA, NICE, which added insult to injury by suggesting the first-in-class Bruton’s tyrosine kinase (BTK) inhibitor should seek alternative inclusion in the country’s revamped Cancer Drug Fund.

IMBRUVICA GETS WIDER EU USAGE
The EU’s executive European Commission on May 31 approved Imbruvica (ibrutinib) for treating adult patients with previously untreated chronic lymphocytic leukemia, thus broadening the indication beyond the initial CLL approval by the EU’s executive body in October 2014 so that the BTK inhibitor is now approved for all patients with CLL. The expanded ibrutinib indication in the 28-nation EU is based on data from the Phase III, randomized, open-label Resonate-II trial that showed ibrutinib significantly prolonged overall survival with 98% of patients still alive after two years, compared to 85% for patients randomized to the chlorambucil arm.

Ibrutinib is a first-in-class BTK inhibitor, blocking the transmission of cell survival signals within the malignant B cells and thereby delaying progression of the cancer.

This latest Imbruvica approval follows a recommendation by Europe’s top drug regulator and follows the US FDA’s decision to okay the expanded use of ibrutinib capsules for treatment-naive patients with CLL, further cementing the therapy’s dominant position in the chronic lymphocytic leukemia market with a first-line indication there.

Ibrutinib is co-developed by Cilag GmbH International, a member of the Janssen Pharmaceutical Companies, and Pharmacyclics LLC, an AbbVie company. Janssen affiliates market ibrutinib in Europe, the Middle East and in Africa as well as the rest of the world, except for the US, where Janssen Biotech, Inc. and Pharmacyclics LLC co-market it.

AS NICE REJECTS IMBRUVICA FOR CLL IN ADULTS WITH GENETIC CHANGES
But the National Institute for Health and Care Excellence (NICE) in a statement on June 1 said its appraisal committee was “minded not to recommend ibrutinib as an option for treating chronic lymphocytic leukemia in adults with a 17p deletion or TP53 mutation” due to uncertainties over the drug’s efficacy and cost-effectiveness in the setting, and suggested the company submit a proposal for inclusion in the UK’s government-funded Cancer Drugs Fund.

Up to one in 10 adults with chronic lymphocytic leukemia have a form of cancer with genetic changes that make their disease progress quicker and more difficult to treat. The treatment options for CLL with these genetic changes, known as 17p deletion or TP53 mutation, are very limited.

NICE said its independent advisory committee “felt ibrutinib could benefit patients whose CLL has these genetic changes, particularly those who have not yet received treatment. The committee recognized that with the current proposal, ibrutinib was not cost effective for these patients. However, it was also aware that available data focused on how well ibrutinib worked as a second treatment, and was mainly from people whose CLL did not have these genetic changes. The committee felt it would be important to find out whether further evidence could be collected on the 17p deletion group, and on the use of ibrutinib as the first treatment, before they made their final decision,” NICE said in its statement.

It noted that the refusal to back Imbruvica in this indication is not NICE’s final guidance on this technology and that a consultation period is now in place having a closing date for comments of June 17 while the next appraisal committee meeting on the subject is scheduled for Aug. 4, 2016.

The drug’s manufacturers reacted by saying they were “extremely disappointed” with the UK body’s decision.

“We consider this latest draft decision from NICE to be very disappointing for patients with CLL, who currently have very limited treatment options. What is even more concerning is that, without changes to the way NICE appraises cancer medicines, such decisions are likely to become commonplace, under the new Cancer Drugs Fund or ‘Managed Access Fund’ process; resulting in patients receiving access to even fewer innovative cancer medicines in the future,” Janssen UK’s Managing Director Mark Hicken said in a statement.

Analysts were also bemused by NICE’s decision.

“This is definitely unwelcome news for Janssen and somewhat surprising since these patients with relapsed/refractory CLL who are not suitable for chemo-immunotherapies, such as regimens which include the standard-of-care, Roche/Biogen’s Rituxan (rituximab), have poor prognoses and very limited treatment options,” said Datamonitor Healthcare analyst Dominique Fontanilla.

Currently, Rituxan-based regimens and Gilead Sciences’ Zydelig (idelalisib) in combination with Rituxan are available on the UK’s publicly funded National Health Service for relapsed/refractory CLL patients, and Datamonitor Healthcare’s primary research data shows that Rituxan is heavily used in high-risk patients in the UK in later lines of therapy.

“But the therapy choices for patients who are unable to take Rituxan-based chemotherapy regimens or for those who carry cytogenetic abnormalities in the 11q and 17p chromosomes are slim, at best,” Fontanilla noted. Imbruvica and Zydelig are the front-runner targeted single agents for these patients. “At this point it is unclear what kind of cost-effective evaluation NICE will need to accept these therapies to fulfill this high unmet need,” Fontanilla said.

Janssen did get some other good news on May 31 when the European Commission approved Trevicta (paliperidone palmitate) for the maintenance treatment of schizophrenia in adult patients, a decision that follows a positive opinion recommending the three-monthly injection by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency in April 2016.
India’s Risk-Based Inspection Plan: Well Begun?

India’s Central Drugs Standard Control Organization (CDSCO) is taking definitive steps to strengthen the regulatory regime and enforcement, including across areas such as data integrity, in the backdrop of industry’s patchy manufacturing compliance story. The regulator has developed risk-based inspection criteria for manufacturing sites, backed by a comprehensive draft checklist and evaluation tool but the real test may lie in resolute implementation. The CDSCO said that while inspections will assess the compliance of manufacturing units with the specified good manufacturing practice (GMP) and good laboratory practice (GLP) requirements, it also hopes to harmonize the procedure for the conduct of such inspections throughout India, identify compliance gaps and communicate these to the manufacturers. “The inspections are planned to be carried out jointly by CDSCO officials and drug inspectors of the states concerned,” Dr GN Singh, Drugs Controller General of India, said in a public notice dated May 26. Industry experts told Scrip that the regulator’s risk-based approach is likely to focus initially on companies that have, during routine examinations, had maximum number of samples that were “not of standard quality.” “Such companies are expected to be the initial focus under the risk-based system,” one expert told Scrip. The DCGL could not immediately be reached for an official comment, though the CDSCO has been capturing data on non-standard quality drugs in its monthly “drug alerts.” The CDSCO’s efforts also include a training program pertaining to the checklist and the evaluation tool and related areas, in order to ensure that the inspections do not cause “any undue harassment” to manufacturers or their employees and are done in an “objective and transparent” manner, the public notice added. The expert indicated that the CDSCO’s efforts on inspections have met with some resistance from certain small and medium enterprises (SMEs), though the industry in general has welcomed and supported the regulator’s plans. “There is bound to be some opposition and SMEs should be asked to fall in line. At least a beginning has been made to strengthen and enforce the regulatory regime,” the expert said.

US Subpoena For Sun Amid Pricing Heat

US lawmakers continue to scrutinize drug firms amid ongoing concerns over price-related issues and their impact on healthcare costs. The US Justice Department’s antitrust division has subpoenaed Sun Pharma for information pertaining to generic drugs, pricing and certain company records, though the Indian firm claimed the move would have no immediate impact on its earnings. India’s top ranked pharma firm, Sun Pharmaceutical Industries Ltd. said that its US subsidiary Sun Pharmaceutical Industries Inc (SPII) had received a US grand jury subpoena and that the firm was currently responding to it. The summons seeks documents from SPII and its affiliates relating to corporate and employee records, generic pharmaceutical products and pricing, communications with competitors and others regarding sales of generic drugs and certain other related matters, Sun informed the Bombay Stock Exchange on May 28. “The outcome of the above-referred inquiry is unlikely to have any material adverse impact on the consolidated operations or financial results of the company,” Sun said. The Indian firm is due to announce its results for the fourth quarter and year ended March 2016 on May 30. Sun’s spokesperson declined to comment on details pertaining to the subpoena. Manish Jain, a founder partner of SageOne Investment Advisors, told Scrip, that while the development may pose no major concerns in the short term, Sun would clearly need to take cognizance of such issues going forward while effecting price hikes in the US market.

India Clears Off-The-Shelf Stem Cell Therapy for Buerger’s

Stempeutics, which is backed by Cipla Ltd., has received limited approval from the Drugs Controller General of India for manufacturing and marketing its stem cell based biological product, Stempeucel, for Buerger’s Disease. Cipla told Scrip that the limited approval gets “converted to a regular marketing authorization,” upon submission of Phase III data. “Phase II results showed an improvement in pain reduction and ulcer healing due to improved blood flow. Secondary endpoints included pain-free walking distance, quality of life and improvement in blood flow,” the company explained. Phase I studies for Buerger’s disease had 20 patients, while Phase II involved 90 patients. Buerger’s Disease is characterized by inflammation and occlusion of the vessels of extremities resulting in reduced blood flow to these areas. It could lead to severe pain and ulcers or necrosis, which finally may require amputation. Stempeucel therapy is designed to enhance the body’s limited capability to restore blood flow in ischemic tissue by reducing inflammation and improving neovascularization, a statement from Cipla said. On the potential additional indications that Stempeucel may be able to address, Cipla told Scrip: “With bridging trials it could be possible to extend to other critical limb ischemic conditions and diabetes foot ulcer.” Cipla did not immediately share pricing details for Stempeucel and only underscored that the product should be used for patients where “vascularization is not an option anymore” and limb amputation may be the only option.
Involvements of senior FDA officials may be the reason the agency put off its much-anticipated decision last week on Sarepta Therapeutics Inc’s Duchenne muscular dystrophy drug eteplirsen, analysts said.

Is high-ranking meddling behind the FDA putting off issuing a much-anticipated verdict on Sarepta Therapeutics Inc’s new drug application (NDA) for its experimental Duchenne muscular dystrophy (DMD) medicine eteplirsen?

Such involvements of senior FDA officials could be the reason for the delay, said Jefferies analyst Gena Wang, who said that conclusion came after a discussion she’d had with a key opinion leader (KOL), Brian Harvey, executive vice president at the Global Liver Institute and a former executive at Pfizer Inc. and Sanofi, who also spent 11 years at the FDA.

Wang noted that Ellis Unger, director of the FDA’s Office of Drug Evaluation I, has the signatory authority to approve eteplirsen, although the ultimate authority rests with Health and Human Services Secretary Sylvia Mathews Burwell and the food and drug agency’s commissioner, Robert Califf.

Wang pointed out that Janet Woodcock, director of the FDA’s Center for Drug Evaluation and Research (CDER), also is a key decision maker.

Woodcock has been visibly involved in the agency’s interactions with DMD drug makers and the Duchenne community – even publicly disclosing during a December 2013 forum hosted by the advocacy group Parent Project Muscular Dystrophy she planned the next day to review the first analyses of data about drisapersen, which at the time belonged to Prosensa Holding BV, before the Dutch firm was acquired by BioMarin Pharmaceutical Inc., which has now dropped development of the drug.

Given the FDA, as a rule, doesn’t disclose information about specific applications, Woodcock’s remarks were highly unusual.

Woodcock also personally responded to a White House “We the People” petition from Duchenne advocates, in which she pledged the FDA was “willing to explore the use of all potential pathways” for the approval of drugs to treat DMD, including accelerated approval.

“We share your sense of urgency to make safe and effective drugs available for patients with Duchenne muscular dystrophy as soon as possible,” Woodcock said in her July 2014 response to the petition.

The CDER chief also made remarks at the April 25 advisory committee meeting for eteplirsen and was vocal throughout the nearly 12-hour hearing.

Woodcock specifically made a point of emphasizing the FDA had been “instructed” by Congress to take the patient community’s views into account when asked by a committee member whether the panel should consider the testimony they heard at the meeting from the more than 50 public speakers, which also included young boys with Duchenne.

She even suggested it may be worse for the FDA not to approve a drug for a “devastating” disease that’s actually effective – declaring the consequences would be “extreme” for patients.

Woodcock also reportedly met with Duchenne patients and their families after the April 25 adcom and posed for photos with them. But her remarks at the April meeting appeared to clash with those of the FDA’s reviewers, who emphasized Sarepta’s data were weak – pointing out the company’s trial included only 12 patients.

There’s been no public complaints or whistleblowing from FDA reviewers they are being pressured by Woodcock or other high-ranking officials at the FDA to approve eteplirsen.

But Harvey, the Jefferies KOL, predicted that if the FDA approves eteplirsen based on the weak data, such an action could lead to “significant consequences,” including perceived inconsistency and a shift in future trial design, Wang reported in a research note.

She said Harvey told the Jefferies analysts that if US regulators clear eteplirsen, other companies whose DMD drugs or other orphan products are rejected by the FDA might view a high-level inconsistency in the review process.

An approval without sufficient data also may have a negative impact on clinical trial designs for other orphan disease drugs and “shift the focus from statistical-oriented to more patient-focused,” Wang said.

Oppenheimer analyst Christopher Marai said he thought the FDA’s holdup on the eteplirsen NDA was to give it more time to negotiate with Sarepta over what conditions the agency may be able to grant an approval. But he also said the delay may be, in part, due to an internal debate over the logic and consistency of approving eteplirsen with a restricted label, while balancing prior statements and access.

Jeffries’ Wang, who said she continued to believe eteplirsen’s chances for approval were “slim,” noted the FDA has other options, specifically, allowing Sarepta to provide the drug under compassionate use.

In fact, RW Baird analyst Brian Skorney even suggested compassionate use may be the “best compromise” available for Sarepta’s drug – a declaration that came in the midst of Wall Street speculation the FDA’s June 2 release of revised expanded access guidelines and a streamlined process was tied to last week’s delay of the agency’s decision on the eteplirsen NDA and was a tactic to shield it from criticism if regulators reject the drug.
Humanizing Antibodies And Inventing Humira; Greg Winter’s Story So Far

Biochemist Greg Winter has scientifically contributed to some of the pharmaceutical industry’s biggest commercial and therapeutic success stories. He tells Scrip how he feels about being labelled a pioneer and why he is still wary of the boardroom.

Travelling to Cambridge to meet Sir Gregory Winter on a beautifully blue day is a little like taking a holiday into a world of intellectual prowess that few have the opportunity to experience. Even the taxi driver is listening to ‘Summer’ from Vivaldi’s violin concerto The Four Seasons. Nestled among this university city’s winding River Cam and pockets of college tourists wearing sweatshirts emblazoned with their adopted college is Winter’s alma mater, Trinity College. And it is here that he is now Master, having been installed in 2012.

Met at the Master’s Lodge by an aproned butler named Paul, he shows me around the rooms while we make our way to the Master’s boardroom. Portraits of kings, queens and distinguished Trinity College alumni look down, all dominated by large portraits of Queen Elizabeth I and Sir Isaac Newton.

Although it is not Trinity College that we are here to discuss, history will undoubtedly look back at the man that I have come to meet and attribute huge scientific significance to his work. A biochemist, Winter’s pioneering research into therapeutic monoclonal antibodies led to the development of methods for making human therapeutic antibodies. Previously, antibodies had been derived from mice, which made them difficult to use in humans because the human immune system recognized them as foreign. It was just so hard,” he recalls, “keeping up that level of commitment, I threw everything into it. At that stage, we didn’t know for sure that it would all work out so well, because in the early 1990s, there was nothing to indicate that antibodies were going make it as mainstream pharmaceuticals. We didn’t even know whether human antibodies would have an edge over humanized antibodies in the clinic. Actually, they probably don’t, but people thought that they might, which was one reason they invested in CAT. That isn’t to say that we didn’t develop a good product with the folks at BASF Pharma.”

When I ask Winter how he feels about being labelled a pioneer he looks into the walled Master’s garden below us, and smiles. “Well that depends,” he says, “a pioneer of what?” Winter is comfortable with being labelled as a biotech pioneer, although he accredits luck to what he describes as “transformational” work, and admits that at the time he didn’t realize quite how significant it would be. If people consider him to be an industry visionary, he says, that would be a mistake. “I am a good scientist who was lucky; I was only interested in industry to the extent I needed to turn my ideas into medicines,”

“I’m not even a good businessman,” he chuckles. “If I had been I wouldn’t have made billions for other people and so much less for myself.”

If Winter doesn’t believe himself to be a good businessman, he will at least admit that he is a very hard working one. Launching CAT in 1989 with David Chiswell, the Medical Research Council (MRC) and with a major scientific contribution from John McCafferty, Winter divided his time between his academic work and the company, working what “seemed like seven days a week for seven years.”

“It was just so hard,” he recalls, “keeping up that level of commitment, I threw everything into it. At that stage, we didn’t know for sure that it would all work out so well, because in the early 1990s, there was nothing to indicate that antibodies were going make it as mainstream pharmaceuticals. We didn’t even know whether human antibodies would have an edge over humanized antibodies in the clinic. Actually, they probably don’t, but people thought that they might, which was one reason they invested in CAT. That isn’t to say that we didn’t develop a good product with the folks at BASF Pharma.”

SERIAL BIOTECH ENTREPRENEUR

The success of CAT’s research, and the possibility that large pharma might find themselves locked out of technologies for making human antibodies, meant that big pharma came courting; in 2006 AstraZeneca PLC bought the company for £702m. AZ subsequently bought MedImmune LLC for $15.6bn and merged the two operations to form its biologics arm.

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INTERVIEW

Not put off by the sheer level of work required to form CAT, in 2000 Winter formed his second company, Domantis Ltd, with Ian Tomlinson, although Winter freely acknowledges that Tomlinson, as chief scientific officer, carried the much larger burden of work after foundation. Domantis pioneered the development of smaller antibodies based on single, rather than paired, domains. The use of single domains also potentially simplified the construction of bispecific antibodies directed against more than one disease target.

GlaxoSmithKline PLC bought Domantis for £230m in 2006 to become part of its Biopharmaceuticals Centre of Excellence for Drug Discovery.

When asked about his level of comfort at being at the sharp end of a boardroom, Winter says he is still a scientist first and foremost, with the business only coming as an enabler of the fruits of the research. “I’ve always been in academia and I’ve never jumped full-time into a company. People said, ‘You can’t have your cake and eat it’. I said, ‘Why not? What gives you the right to moralize?’ I am basically an academic with an interest in practical things, but my ideas would have remained as scientific curiosities, unless I had refined them in the fire of the market. That’s why I started the companies.”

One might be forgiven for assuming that the quintessentially English Winter might be a touch meek when dealing with company boards. You’d be wrong. He tells me a story of his time on the board of Peptech Ltd, the Australian investors in both CAT and Domantis. Faced with open hostility from the new chair who did not believe that Peptech should have invested in Domantis, Winter (who had been co-opted to the board of Peptech as part of the deal) was careful to start the companies.

Kevin Lee, Bicycle’s CEO, describes Winter as “entrepreneurial, very down to earth and approachable.” To work with, Lee says that Winter is a “great team player, able to think outside the box and ready to bring new dimensions to any discussion.”

Winter has an unrelenting drive to create therapeutics based on his ground-breaking research. He has also surrounded himself with peers who have the same attitude. “You’re only as good as the next thing you do.” That was [Nobel-prize winning biochemist and member of CAT’s scientific advisory board] César Millstein’s thinking. There’s certainly more we can do, and so I think we should get on and do it,” he states.

In 1997 he was appointed CBE in Her Majesty the Queen’s New Year’s Honours List for services to science. In 2004 Winter became a Sir Gregory when he received a Knighthood for services to molecular biology. He was elected a Fellow of the Royal Society and awarded the Royal Medal by the society in 2011 “for his pioneering work in protein engineering and therapeutic monoclonal antibodies, and his contributions as an inventor and entrepreneur.”

TO AFRICA AND BACK

Winter smiles as he thinks about what his father would have thought of his success, of the millions of people that take drugs such as Humira, Benlysta (belimumab) and Herceptin (trastuzumab) which are all based on his research. “He was not given to lavish praise. He probably would have said ‘Well, not bad. It makes me feel better about all those school fees.’”

Winter was born six weeks prematurely in April 1951. With post-war coal rationing still in place, his mother found it increasingly difficult to heat the family home and keep her young son warm enough. By serendipity, Winter’s father found a post in West Africa’s Gold Coast, Ghana as it is now, to teach French and by September 1951, before the English cold set in, Winter was thriving in the African heat.

Despite contracting malaria and other tropical fevers Winter says that he owes Africa his life. “If I’d been stuck in the UK with coal rationing, I probably would have been done for despite our wonderful NHS.”

By his teenage years, the family had returned to England, and he proved to be academically gifted and won a scholarship to study Natural Sciences at Trinity College. It was here that the young scientist found himself tested and questioned by his “terrifying” supervisor at Trinity. Wanting to discuss some interesting results, he was met with the advice: “Bugger interesting, is it an important question? Don’t mess around with results that suggest or imply something. Do it properly, prove it - put a stake through its heart.”

“The world is all too full of interesting questions, many of which turn out to be uninteresting when you finally know the answer. If you’re going to do something, do something important because it’s not worth wasting your time if it isn’t,” says Winter.

LONG-TERM AMBITION

When asked what is left for him to achieve Winter says that he would like to live long enough to make a profit from his pension contributions. But on a more serious note, the life that lies ahead of him is a paradox. While wanting to still “be useful, in some context or another,” Winter would also like more time to himself than his current role at Trinity College allows.

He’d like to be able to enjoy the weather on a sunny day, or spend more time reading, he says. In contradiction to what he has previously espoused about the fundamental questions one should ask as a scientist, as a human being he’d like to spend some time pondering the not-so-important questions in life, such as the history of the English moat, for example. And given the scientific breakthroughs his work has contributed to, anyone would agree that he has earned that much.

Click here to watch Sir Gregory Winter winning Scrip’s Lifetime Achievement Award in 2015: http://bit.ly/205SLY6
Is Biotech Investing A State Of Mind?

ANDY SMITH

The American Society for Clinical Oncology (ASCO) conference that has just opened in Chicago is traditionally thought of as one of the key catalysts of the year for biotechnology and pharmaceutical companies. The stock prices of companies presenting their latest data usually run up in anticipation of ASCO and subsequently sold off after the conference. While this is now expected by investors, this year may be different.

This is not to say that the post-ASCO sell-off will be avoided, but rather that, with far fewer interested investors this year, anything could happen. Last week the analysts from Jefferies published a comprehensive series of notes summarizing the current attitudes of investors, the flow of funds into the sector, M&A trends and the drug pricing issues affecting the industry. Towards the end of last week the analysts from Piper Jaffray published a note entitled “What investors are asking/talking about in Biotech,” while throughout the week, the trading commentary from Cowen provided some interesting insights into which of their clients had been active in healthcare.

The reason for all this introspection has been the recent rise in the NASDAQ Biotech index (NBI). As the trading commentary from Cowen pointed out, the NBI has risen by 14% since the middle of May. However, the reduced fund flows into the sector and the departure of the generalist investor have not made this rise a smooth one. June 2 saw the NBI almost reach the level of its most recent peak, which occurred in mid-April before it retracted 13% – a pattern that has occurred at least twice this year to date. This volatility marks the machinations of a low trading volume sector that is out of favor, but is still punctuated by price-moving news.

On day three of their biotechnology macro trend retrospective, the analysts at Jefferies focused on M&A as a key near-term driver for the sector. This has always been the case, but the recent transactions may not be the cure-all that many have hoped for. At best, recent transactions have provided a short-term fillip to the sector and a helping hand towards the top of the most recent NBI peak. The ‘at best’ transactions are those where the acquirer is not thought to have significantly overpaid for the target and where there is a good strategic fit between the two companies. Last week’s opening salvo was the announcement of the $1.5bn acquisition of Celator Pharmaceuticals Inc. by Ireland’s Jazz Pharmaceuticals PLC. Strategically the acquisition of Celator fits one of Jazz’s therapeutic areas that came with its acquisition of EUSA Pharma. But the 73% premium to Celator’s previous closing price raised eyebrows and led the analysts at Roth Capital to entitle their note “Now THAT’s a Premium.” Celator shareholders would have been very pleased; Jazz’s holders perhaps less so. The Jazz share price closed down about 1% on the day of the announcement and went on to underperform the NBI by about 3.4% on the week. This was possibly due to the concern at Jazz’s increasing debt burden at a time when the Federal Reserve’s rhetoric on increasing rates has also been increasing. Jazz – but not Celator – is an NBI constituent but nevertheless the NBI finished the day of the announcement up just under 1% as it basked in the reflected glow of the transaction and endorsed the Jefferies analysts’ proposition that any NBI-related transaction is good for the sector, blush to have strategic merit. With oncology products like Imbruvica (ibrutinib) and Venclexta (venetoclax), AbbVie’s acquisition of a company with a Phase III product directed against cancer stem cells sounds logical. However, the product is a drug-antibody conjugate (DAC) and comes at a time when most would agree that DACs, like antisense, have not been the therapeutic panacea in oncology that they were once expected to be. The acquisition was greeted with a sell-off in AbbVie’s shares which the pre-ASCO run-up was only getting close to recovering until June 3’s sector sell-off. Whether it is the linker technology or the toxin or both, it is ironic that naked full-length antibodies (directed against PD-1 or its ligand) and not DACs are likely to have produced more and longer treatment responses at this year’s ASCO conference.

To reverse John Steinbeck’s quote about Texas, if investing in biotechnology stocks is a state, rather than a state of mind, then it would be a Spanish province where all the young (generalist) investors have left to find employment elsewhere. With a reduced flow of funds into the sector and lonely specialists left feeling lukewarm after the first-quarter earnings season, M&A is going to have to be more convincing to attract the generalist investor back.

The Magna Biopharma Income fund holdings include AbbVie.

Andy Smith is chief investment officer of Mann Bioinvest. Mann Bioinvest is the investment adviser for the Magna BioPharma Income fund which has no position in the stocks mentioned, unless stated above. Dr Smith gives an investment fund manager’s view on life science companies. He has been lead fund manager for four life science-specific funds, including International Biotechnology Trust and the AXA Framlington Biotech Fund, and was awarded the Technology Fund Manager of the year for 2007.
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.

## Late-stage clinical developments for the week 27 May - 2 June 2016

<table>
<thead>
<tr>
<th>LEAD COMPANY</th>
<th>PARTNER COMPANY</th>
<th>DRUG</th>
<th>INDICATION</th>
<th>MARKET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biogen Inc.</td>
<td>AbbVie Inc.</td>
<td><em>Zinbryta</em> (daclizumab)</td>
<td>multiple sclerosis</td>
<td>US</td>
</tr>
<tr>
<td>GlaxoSmithKline PLC</td>
<td>–</td>
<td>Strimvelis</td>
<td>severe combined immunodeficiency</td>
<td>EU</td>
</tr>
<tr>
<td>Amicus Therapeutics Inc.</td>
<td>–</td>
<td><em>Galafold</em> (migalastat)</td>
<td>Fabry disease</td>
<td>EU</td>
</tr>
<tr>
<td>Samsung Bioepis Co. Ltd.</td>
<td>Biogen Inc.</td>
<td><em>Flixabi</em> (infliximab)</td>
<td>RA, Crohn’s, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis, psoriasis</td>
<td>EU</td>
</tr>
<tr>
<td>Teva Pharmaceutical</td>
<td>–</td>
<td><em>Braltus</em> (tiotropium bromide)</td>
<td>chronic obstructive pulmonary disease</td>
<td>EU</td>
</tr>
</tbody>
</table>

**SUPPLEMENTAL REGULATORY APPROVAL**

| AbbVie Inc | – | *Imbruvica* (ibrutinib) | chronic lymphocytic leukemia | EU     |
| Janssen-Cilag International | – | *Trevicta* (paliperidone) | schizophrenia maintenance | EU     |
| Novartis AG | – | *Afinitor* (everolimus) | neuroendocrine tumors | EU     |
| Roche | – | *MabThera* (rituximab) sc | chronic lymphocytic leukemia | EU     |
| Merck & Co. Inc. | – | *Keytruda* (pembrolizumab) | melanoma | Canada   |
| Eli Lilly & Co. | BI | *Jentadueto CR* (linagliptin plus metformin) | diabetes | US     |
| Allergan PLC | – | *Teflaro* (ceftaroline fosamil) | community-acquired pneumonia, and skin infections | US     |

**ACCELERATED/CONDITIONAL APPROVAL**

| Intercept Pharmaceuticals | – | *Ocaliva* (obeticholic acid) | primary biliary cholangitis, hepatic fibrosis | US     |

**ORPHAN DRUG DESIGNATION**

| Therabron Therapeutics Inc. | – | CG100 (recombinant human club cell 10 kDa protein) | bronchopulmonary dysplasia and chronic respiratory morbidity | US     |
| Alexion Pharmaceuticals | – | ALXN1210 | paroxysmal nocturnal hemoglobinuria | EU     |

**FAST-TRACK STATUS**

| Galena Biopharma Inc. | – | *NeuVax* (nelipepimut-S) | breast cancer | US     |
| Viamet Pharmaceuticals | – | VT-1129 | cryptococcal meningitis | US     |
| Cidara Therapeutics Inc. | – | CD101 | vulvovaginal candidiasis | US     |
| Soligenix Inc. | – | SGX943 | melioidosis | US     |

**CHMP NEGATIVE OPINION**

| Takeda Pharmaceutical | – | *Ninlaro* (ixazomib) | multiple myeloma | EU     |

**CHMP POSITIVE OPINION ON FIRST APPROVAL**

| Merck & Co. | – | *Zepatier* (elbasvir + grazoprevir) | hepatitis C | EU     |
| Gilead Sciences Inc. | – | Epclusa | hepatitis C | EU     |

**COMPLETE RESPONSE LETTER**

| Teva Pharmaceutical | – | SD-809 (deutetabenazine) | chorea associated with Huntington’s disease | US     |
| AstraZeneca PLC | – | ZS-9 | hyperkalemia | US     |

**PRIORITY REVIEW**

| Lexicon Pharmaceuticals | – | telotristat etiprate | carcinoid syndrome | US     |
| Vertex Pharmaceuticals Inc. | – | Orkambi | cystic fibrosis | US     |

**PRODUCT LAUNCH**

| Acadia Pharmaceuticals | – | *Nuplazid* (pimavanserin) | hallucinations/delusions in Parkinson’s disease | US     |
| Amicus Therapeutics Inc. | – | *Galafold* (migalastat) | Fabry disease | Germany |
| UCB SA | – | *Briviact* (brivaracetam) | partial seizures in epilepsy | US     |

*Source: Sagient Research’s BioMedTracker*
**APPOINTMENTS**

**Sangamo Biosciences**, a company focused on treating monogenic and infectious diseases using its DNA-binding protein technology, has appointed **Alexander ‘Sandy’ Macrae** president and CEO. Macrae will be succeeding current president and CEO Edward Lanphier, who will be retiring from his leadership position but will continue as board member. Macrae previously held roles of increasing responsibility at Smith Kline Beecham and Glaxo SmithKline, where his last role was senior vice president, emerging markets research and development.

Chiltern has named **Richard Pilnik** chair replacing current chair, **Nick Thornton**. Pilnik joined the company’s board of directors in 2015 and prior to Chiltern, he was executive vice president (VP) of its commercial solutions division. Previously he also held various positions at Eli Lilly and Company including group VP and chief marketing officer; president, Europe, Middle East and Africa; and area VP of Latin America and Canada.

The oncology company, **Presage Biosciences**, has appointed **David Johnson** to its board of directors. With 25 years’ experience Johnson joins Presage from the oncology focused company, Acerta Pharma, where he was CEO. He has held roles with increasing responsibilities within clinical development, medical affairs, pipeline development, and commercial at companies including Calistoga (acquired by Gilead), Gloucester (acquired by Celgene), Favilure, Millennium, Immunox (acquired by Amgen), and Hoffman-La Roche.

**Sutro Biopharma** has appointed **Shabbir T. Anik** to the newly created position of chief technical operations officer. Anik has more than 30 years’ experience in the industry and most recently was senior vice president of technical operations at Onyx Pharmaceuticals. Prior to this, he was president and CEO of Althea Technologies.

**Achaogen Inc.** a biopharma developing antibacterial addressing multi-drug resistant gram-negative infections, has appointed **Tobin Schilke** chief financial officer (CFO). For 13 years Schilke was at Roche/Genetech where he was most recently CFO and company director of Roche Products Limited in the United Kingdom.

The molecular diagnostics company, **Agendia Inc.** has appointed **Gabriel Hortobagy** chair of its medical advisory board. Currently, Hortobagy is professor and chair emeritus of the department of breast medical oncology at the MD Anderson Cancer Center (MDACC) and is also the past president of the American Society of Clinical Oncology (ASCO). He is currently the chair of the Southwest Oncology Group Breast Committee and a member of the Scientific Advisory Board of The Breast Cancer Research Foundation.

**Homology Medicines Inc.** a recently formed genetic medicines company, has named **James Warren** vice president of manufacturing. Warren joins the company from bluebird bio, where he was senior director of vector development and manufacturing. Prior to this, he led teams in the early and late stage development of clinical and commercial therapeutic protein product candidates at Shire.

Spanish biopharma company **Sanifit S.L.** has appointed **Dr Preston S. Klassen** chief medical officer and president of its new US subsidiary, Sanifit Inc., which was launched this week. Klassen joins the business from Orexigen Therapeutics, where he headed the global development team as executive vice president. He previously held various positions at Amgen Inc., including therapeutic area head for nephrology, prior to which he was a faculty member at Duke University’s division of nephrology for five years.

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