Biogen/Ionis’s Spinraza Approved; Second Antisense Drug For Neurodegeneration In 2016

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Analysts expect strong uptake for the antisense oligonucleotide (ASO) given the high unmet need in SMA and positive data in multiple studies, while the first ASO approved in 2016 – Sarepta’s Exondys 51 – has seen some pushback from payers despite the lack of DMD therapies.

Biogen and partner Ionis Pharmaceuticals Inc. are ended 2016 with US FDA approval for Spinraza (nusinersen) in the treatment of spinal muscular atrophy (SMA), marking the second antisense drug approved in 2016 to treat a rare neurodegenerative disease.

Spinraza follows in the footsteps of the controversial approval of Sarepta Therapeutics Inc’s Exondys 51 (eteplirsen) for Duchenne muscular dystrophy (DMD); both drugs convince RNA to produce proteins needed for proper muscle strength and function. Investors and analysts that follow both companies have high hopes for blockbuster Spinraza sales – despite payer pushback on high-priced drugs – evidence by the fact that Biogen and Ionis have gotten some of their biggest stock boosts in 2016 from positive Spinraza news.

The companies announced the FDA approval late on Dec. 23 after the stock market closed, so on Dec. 27 when trading resumed following the Christmas holiday, Biogen closed up 1.3% at $291.12 per share and Ionis rose 3.2% to $55.12. Their stocks also saw major gains in August and November when the companies reported positive results from the Phase III ENDEAR clinical trial in infants with SMA and the Phase III CHERISH trial in SMA patients aged 2 to 12.

The CHERISH results in children with type 2 and 3 SMA were particularly important for Biogen and Ionis – Ionis discovered Spinraza and granted a worldwide license to Biogen in August – because the data showed a significant improvement in developmental milestones and seemed to guarantee a broad label for the drug. In fact, the FDA did approve Spinraza for both pediatric and adult patients, which essentially makes the drug available to individuals with any type of SMA.

“Spinraza’s label is broad – meaning that it is approved for all subtypes of SMA – which is likely the best case scenario from a commercial perspective, and was somewhat expected (but not guaranteed) given the success of the Phase III ENDEAR and CHERISH readouts earlier this year,” Evercore ISI analyst John Scotti said in a Dec. 23 note.

**A FIRST FOR SMA, NEARLY GUARANTEEING UPTAKE**

Spinraza is the first medicine approved for SMA, a neurodegenerative disease that is particularly deadly for babies with type 1 SMA – it’s the leading genetic cause of death.

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Our first edition of the year is a bumper issue, packed with extra analysis and insights to help bring you up to speed on key industry developments over the festive period and to prepare for the year ahead.

The end of December saw the FDA approve Biogen and Ionis’ antisense drug Spinraza for the rare and deadly neurodegenerative disease spinal muscular atrophy and reject Cempra’s antibiotic Solithera. See cover story, p3 and Stockwatch on p34 for more on the commercial implications.

We gaze into our crystal balls to consider what this year holds for pharma (p4), looking more closely at the IPO market in 2017 (p14-15) and the likely trends in the biosimilar spaces (p12); then take a deeper dive into the prospects for a particular generic entrant this year (p21). Looking further into the future, we highlight the challenge the industry faces in replacing lost sales of top-selling drugs over the next few years (p10).

Scrip would like to wish its readers all the best for a productive and successful 2017.

from the editor
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exclusive online content

The R&D Year In Numbers, An Infographic
A snapshot of the industry’s research and development activity in 2015/2016.

Inositec CEO On 2017 Financing Plans
Mattias Ivarsson, co-founder and CEO of Swiss biotech company Inositec, talks to Lucie Ellis, senior writer at Scrip, about the company’s technology and progress since being founded in 2015.

AdAlta CEO On Shark Antibody Technology
Sam Cobb discusses development of the company’s novel technology platform that engineers the key stability features of the antigen binding domain of shark antibodies into human proteins to create unique compounds

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Solithera’s Prospects Look Grim Following Complete Response Letter

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Even if Cempra has the funds to conduct another trial, there is no guarantee for approval; if approved, solithromycin’s labeling would likely limit use of the community-acquired pneumonia antibiotic.

The US FDA’s complete response letter for Cempra Inc’s community-acquired bacterial pneumonia (CABP) antibiotic Solithera (solithromycin) puts the company on a difficult and uncertain path forward. The agency went against the recommendations of its advisory committee, apparently unwilling to wait until Phase IV to sort out solithromycin’s potential hepatotoxicity and approve the drug based on the limited 920 patient safety database. The complete response letter also cited good manufacturing practices (GMP) deficiencies at manufacturing facilities owned by Hospira (now Pfizer Inc) and Wockhardt Ltd.

Interim Cempra CEO David Zaccardelli noted in a Dec. 29 investor call that the company still needs to meet with FDA to establish the next steps for Solithera, including the specifics of a future clinical study. “Those answers can’t be determined until we meet with the FDA and understand the study in its totality, including what endpoints for safety would need to be achieved,” Zaccardelli said of Solithera’s prospects going forward. “Also, what labeling would be included at the end of that has not been determined. And so I think more information on our decisions around that will come after our meeting with the agency.”

Zaccardelli said the company is committed to working with FDA to obtain approval of Solithera, although any path forward for the drug appears bleak.

FDA is recommending that Cempra conduct a study of roughly 9,000 patients exposed to Solithera alone, nearly 10-fold the company’s current safety database. Tack on a comparator arm, and the clinical-stage company – which has around $225m in cash on hand – is likely looking at a very costly trial with no guarantee of approval. Jefferies analysts Eun Yang and Carmen Augustine also offered a grim outlook on Solithera, pointing out that the additional trial, which could require up to 18,000 people, is likely more than Cempra can accomplish on its own. (The company did not comment on whether it would seek a partner.)

“While [the] CRL for Solithera (Soli) was widely expected, FDA recommendation for a ~9,000+ patient comparative study to exclude possibility of serious drug-induced liver injury is impractical for a company of CEMP’s size,” the analysts wrote in a Dec. 29 note. “Even if CEMP elects to run the study, it would need additional capital & there is no guarantee for approval upon study completion.”

**LABELING WILL BE ANOTHER CHALLENGE**

Even if Solithera eventually does gain approval – which the company does not expect prior to 2018 – the drug will likely have a restrictive label that limits its use.

Several members of FDA’s Antimicrobial Drugs Advisory Committee recommended stringent labeling regarding the risks of hepatotoxicity. One panelist recommended that the label state that, if approved, Solithera should not be the first treatment off the shelf for run-of-the-mill CABP. Another suggested a risk evaluation and mitigation strategy (REMS). Even if the costly clinical trial does not find cases of Hy’s Law (the measurement for drug-induced liver injury), FDA has already signaled that differences in transaminase elevations already seen versus moxifloxacin would need to be in labeling, signaling the risk of hepatotoxicity to physicians.

“The CRL noted that while the FDA reserves comment on the proposed labeling until the NDAs are otherwise adequate, even in the absence of a case of Hy’s Law or of another form of serious [drug-induced liver injury] in future studies, labeling will need to include adequate information about the potential for hepatotoxicity, limiting use to patients who have limited therapeutic options and limitations regarding duration of therapy,” Cempra said in a statement. “A comprehensive plan for post-marketing safety assessment including an enhanced pharmacovigilance program would also be required.”

Cempra also has Solithera in development for uncomplicated urogenital urethritis caused by chlamydia in an ongoing Phase III trial. The company also has an antibiotic candidate called tatska fusidic acid that has completed Phase II development for the treatment of acute bacterial skin and skin structure infections and is in an ongoing Phase II trial for patients with prosthetic joint infections.

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What Does 2017 Hold For Pharma?

Few would argue that 2016 threw a number of curveballs into the global arena. With the New Year upon us, Scrip took a deep breath and asked a number of internal and external contributors across the pharma and biotech spectrum for their expectations for 2017. Scrip spoke to a range of people involved in the industry to get their take on what we can expect over the next 12 months. Their responses make for an interesting, and varied, read.

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BREXIT

The biopharmaceutical industry will continue to lobby the UK government for some sort of harmonization framework that averts regulatory divergence with the EU. This could be looking ever so slightly more plausible given the apparent softening of UK ministers’ stances on sectoral deals and some sort of transitional period post-Brexit. “But so much will depend on how tough the EU negotiators choose to be in offering any sort of ‘tailored’ deal to the UK, and how far the European Parliament will want to have a say in the final agreement,” explains Scrip’s Ian Schofield.

He expects that “early-ish” in the year we should have at least an inkling of what kind of deal the UK government will be seeking to strike with the EU, “whether paying for access to the single market, taking out part-membership of the EU Customs Union, or pulling out of the whole thing, which would of course be the least favorable option for the highly regulated life science industry.”

Once things become clearer, companies may begin making decisions as to whether to continue investing in the UK or shift some operations to mainland Europe – or indeed Ireland. “This could affect areas like manufacturing, research, clinical trials, distribution networks, HQ location, etc.,” warns Schofield.

In 2017, we may also get more clarity on which EU countries are likely to be in the running to host the EMA.

“Given the amount of work involved in relocating the agency to another member state, preparations will have to begin well in advance so that the EMA is up and running in its new home as soon as Brexit happens,” states Schofield. Once the location is decided, new premises will have to be found with all the necessary infrastructure, and hundreds of jobs will have to be replicated – assuming a large proportion of people decide not to or are unable to follow the agency to the new location. “This work will probably have to begin in earnest next year, given the tight timelines allowed by Article 50 – although this could be mitigated somewhat if a transitional arrangement is agreed.”

On a more positive note, Schofield says it’s likely that the UK will stick by its decision to ratify the Unified Patent Court Agreement, which should happen next year. “This means that, all being well, pharma firms will be able to take out patents with unitary effect across the UK and the EU after all. It would also mean London gets to keep its branch of the Court dealing with life science and chemical patents.”

IMMUNO-ONCOLOGY

With major developments in 2016 – including the surprise failure of Bristol-Myers Squibb Co’s Opdivo in first-line lung cancer and Roche’s debut of Tecentriq – 2017 will start to see some major shifts, notes Scrip’s Mary Jo Laffler.

Some have been long-anticipated, like cancer heavyweight Roche’s entry into the field with approvals in breast and lung cancers for Tecentriq (atezolizumab), the slow trickle of combination data, and the expected approval of CAR-T therapies. “But the bombshell failure of BMS’s CheckMate 026 trial in October 2016 has had seismic implications,” she says.

BMS’s once unassailable lead (still on the order of $500m above the nearest competitor, Merck & Co. Inc’s Keytruda) virtually disappeared overnight. The release of full results, which failed even in high-expressing PD-L1 patients, at ESMO combined with promising chemo combo data for Keytruda have laid a new path for the field. Merck compounded its advantage when Keytruda nabbed the first approval for first-line lung cancer. “The full-year earnings reports will show how the market dynamics are changing, though continuing developments throughout the year could narrow the gap even more,” she states.

The PD-L1/L1 market will further expand with new entrants in 2017: Pfizer Inc./Merck KGaA’s avelumab should be coming in Merkel cell cancer and AstraZeneca PLC is due to introduce durvalumab monotherapy for urothelial carcinoma. “AstraZeneca may wind up being last in the first wave of checkpoint inhibitors, but it is better positioned for combination therapy,” Laffler points out. Its MYSTIC trial of durvalumab plus the firm’s CTLA-4 inhibitor tremelimumab in first-line lung cancer is set to report early in the year, well ahead of BMS’s similar pairing of Opdivo and its CTLA-4 inhibitor Yervoy in lung cancer (the duo is already approved for melanoma). Merck is due to report Phase III data for Keytruda + chemo in first-line lung cancer from KEYNOTE-189 in September. “This means, by the end of the year, we’ll finally see if the promise of IO combinations lives up to the hopes.”

DIABETES

The diabetes market will be one to watch in 2017, with significant changes expected. Eli Lilly & Co’s launch of the basal insulin biosimilar Basaglar will alter the landscape, most significantly for Novo Nordisk AS and Sanofi. In addition, the US approval of the first cardiovascular label expansion for an anti-diabetic medicine, Boehringer
Ingelheim GMBH/Lilly’s Jardiance (empagliflozin), is likely to mark a significant change in diabetes management, according to Data-monitor Healthcare's Kevin Shannon.

ADDITION

Opian Pharmaceuticals Inc’s CEO Roger Crystal says in 2017 he expects there to be increasing recognition of addiction as a disease requiring medical treatment, and better reimbursement for pharmacotherapy. Additionally, "we anticipate increased abuse of more potent opioids such as fentanyl, but also increasing access to medical treatment for opioid addiction, especially on the back of the US Surgeon General’s recently released report, ‘Facing Addiction in America.’ He also foresees additional advances being made into the vaccine space, as well as the limited success of abuse-deterrent formulations in preventing addiction.

PRICING

PwC Partner Rick Judy expects more pharmaceutical manufacturers will develop "social contracts" with consumers as part of their pricing strategies, along the lines of the one Allergan PLC unveiled earlier this year.

With the antics of former Turing CEO Martin Shkreli and the outcry over Mylan NV’s price increases on EpiPen both dominant stories in 2016, industry is bracing for further pushback on drug pricing. Allergan CEO Brent Saunders and other industry CEOs are warning that drug pricing will be viewed as a populist issue.

Saunders took the lead in getting ahead of the issue, with his September 2016 pledge that Allergan would only take single-digit price increases once a year. Allergan has already been followed by Novo Nordisk and other companies are likely to follow in the hopes that voluntary action may dissuade more direct intervention.

“The reality of the problem is a lot more nuanced, and biopharmaceutical manufacturers are trying to share the blame with other parts of the distribution chain, including pharmacy benefit managers (PBMs),” explains Laffer. “Further Congressional noise is a surety – but what remains to be seen is what will come of it.”

TRUMP

Scrip’s Eleanor Malone believes it is important to consider the possibility that the incoming US president will enable US corporations to repatriate foreign-held cash by offering new and favorable taxation terms for overseas cash. "Many big companies have amassed sizeable amounts of cash abroad, which they would like to bring home if only the tax burden wasn’t so onerous,” she explains. “I’m not sure how quickly he’d implement something like this, but if he did, it could be a trigger for more domestic M&A among the big US biopharma corporations.”

GENERICS

Generics companies have had a tough time in recent years, with price erosion and FDA approval delays weighing heavily on the group. Jami Rubin and analysts at Goldman Sachs, in a 2017 generics outlook note, believe that “pricing pressure shows no signs of abating and earnings beats will largely depend on ANDA approvals.”

They say that companies with global diversified portfolios, such as Teva Pharmaceutical Industries Ltd. and Mylan, “appear better positioned to offset pressure” while the more “concentrated” companies like Impax Laboratories Inc., Akorn Inc., Perrigo Co. PLC and Endo International PLC remain the most exposed.

"Robust pipelines are increasingly critical for growth but, even then, lack of visibility on FDA approvals will likely add volatility to earnings. M&A has proven to be a more reliable cushion as the contribution from acquired products has offset base erosion for most; we view acquired products to be the most secure buffer going forward.”

Therefore, the analysts expect that further consolidation in the generics sector is “inevitable”, particularly among companies with concentrated portfolios and scarce pipelines. “While Mylan and Teva are likely acquirers, we only expect bolt-ons in the near-medium term as each focuses on de-levering. We expect Endo’s current leverage to limit its capacity, though see some relative flexibility for Akorn, Mallinckrodt AG and Impax.”

JAPAN

Scrip’s man in Japan, Ian Haydock, says the biggest pharma-related issue in the country is a reform of the reimbursement pricing system, following an urgent high-level review ordered by Prime Minister Shinzo Abe late in 2016. This includes a shift to regular annual – rather than biennial – general price revisions, which the research-based pharma industry has strongly opposed. Political pressure on drug pricing looks set to continue given the attention it received in 2016 and the rise in national healthcare costs driven by high-priced new treatments for cancer and hepatitis C.

INDIA

According to Scrip’s Anju Ghangurde in India, 2017 is expected to be action-packed for the Indian pharmaceutical industry. A focus on compliance-related issues, potential consolidation triggered by multiple factors, including evolving quality standards, that could make it tough for some small players to stay relevant and the playout of new and anticipated rules are some of the key areas that are expected to engage industry in the new year.

Tension has been simmering over India’s recent guidelines on similar biologics; there are also expectations that India may make mandatory a new Uniform Code of Pharmaceuticals Marketing Practices (UCMP).

Price-related headwinds, both on the domestic market and in the US, is another area that may impact industry’s fortunes. Indian firms are among those being probed by the US Department of Justice over the sharp increases in the prices of specific generic drugs. The US Justice Department’s antitrust division has subpoenaed Sun Pharmaceutical Industries Ltd. for information pertaining to generic drugs, pricing and certain company records.

CHALLENGES AND CHANGES

Shire PLC’s CEO Flemming Ornskov highlights the “significant period of challenge” that the pharma industry is going through that will continue into 2017. Challenge “in terms of justification of prices, justification of value, contribution to society. There is discussion about almost everything from patents to prices to drug importation or not providing proof of value to outcomes,” he tells Scrip. But he believes that the pharma industry is one of the most attractive industries to be in “because it’s about innovation, it’s about smart people working for better medicines and cures for diseases, it’s a huge employer around the world, it’s a big contributor to value in society. That there’s going to be some pressure … that’s probably only going to make us all better, more cost efficient, more innovative.”

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Was Sanofi’s Offer One That Actelion Could Refuse? J&J Back At Bargaining Table

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Johnson & Johnson is back at the M&A bargaining table with Actelion after walking away from negotiations a week ago, raising questions about whether Sanofi’s deal terms were harder to digest than J&J’s.

Actelion Pharmaceuticals Ltd. and Johnson & Johnson revealed on Dec. 21 that the two companies are back at the M&A bargaining table with “exclusive negotiations” ongoing, raising the question of whether Sanofi’s offer was unacceptable while J&J’s is easier to digest.

The latest twist in Actelion’s merger and acquisition saga, raised eyebrows yet again, since J&J was the first company confirmed as a prospective buyer for the Swiss biopharma firm in late November only to walk away by mid-December and have its seat at the table taken by Sanofi.

Was the amount of money offered by the French big pharma much lower than its American competitor or were other terms, such as upfront cash versus future earn-outs, a deal-breaker? Did Sanofi’s offer force Actelion back into the kitchen to cook up a deal with J&J or did the original bidder whip up a new M&A recipe on its own?

None of the parties are providing specifics publicly. Actelion and J&J simply said in separate, similarly worded statements on Dec. 21 that they have “entered into exclusive negotiations” regarding a possible transaction – the word “exclusive” implying that Sanofi is out of the picture – and they each made a point of saying “there can be no assurance any transaction will result from these discussions.”

Actelion and J&J both said they won’t make any additional comments about their negotiations “unless and until it is appropriate to do so, or a formal agreement has been reached.”

J&J previously said on Dec. 13 that it walked away from negotiations with Actelion when the health care giant “was not able to reach an agreement that it believed would create adequate value for its shareholders.” Neither Actelion nor Sanofi issued statements to confirm their talks, but various news outlets reported the French pharma’s interest in doing a deal with the pulmonary arterial hypertension (PAH) specialist, which has various pipeline programs aimed at diversifying its portfolio.

The entire saga – from initial speculation that a big pharma was interested in buying Actelion to the company’s confirmation that it was talking to at least one prospective buyer – has been somewhat surprising, because of the Swiss firm’s previous position about remaining an independent company.

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Emicizumab Data Will Shake Up Hemophilia

Positive data from the HAVEN 1 Phase III study of Genentech’s emicizumab put pressure on the hemophilia franchises of both Shire and Novo Nordisk.

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Genentech Inc. (Roche) reports that the primary endpoint has been met for the Phase III HAVEN 1 study evaluating emicizumab (ACE910) prophylaxis in people 12 years of age or older with hemophilia A and inhibitors to Factor VIII.

Emicizumab, discovered by Chugai Pharmaceutical Co. Ltd., is a bispecific monoclonal antibody designed to bring together Factors IXa and X, proteins required to activate the natural coagulation cascade and restore the blood clotting process.

Given once weekly subcutaneously, emicizumab has the potential to streamline treatment of haemophilia A as it has demonstrated prophylactic efficacy regardless of the presence of Factor VIII inhibitor antibodies (which develop in around 30% of haemophilia A patients). Currently, patients who develop inhibitor antibodies are treated with bypass agents such as Novo Nordisk AS's NovoSeven and Shire PLC’s Feiba. Roche expects to file for approval of emicizumab during 2017.

Shire’s CEO Fleming Ornskov spoke to Scrip recently about the threat from emicizumab, and stressed Feiba’s “very strong safety record,” noting that the product “is recognized for its many benefits and is serving patients extremely well.” Shire did not provide a breakdown of Feiba revenues in its third quarter earnings statement, but stated that total sales for its hemophilia franchise in the three months ended Sept. 30 were $702m, of which inhibitor therapies made up $182m, the majority of which would be from Feiba. Shire has also highlighted several segments of the non-inhibitor market that new entrants to the hemophilia market might find hard to break into.

Novo Nordisk has said that if emicizumab is approved, around 50% of NovoSeven’s $1.5bn in annual sales are at risk.

The HAVEN 1 study showed a significant reduction in the number of bleeds over time in people treated with emicizumab prophylaxis compared to those receiving no prophylactic treatment. The study also met all secondary endpoints, including a significant reduction in the number of bleeds over time with emicizumab prophylaxis treatment in an intra-patient comparison in people who had received prior bypassing agent prophylaxis treatment.

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among infants and toddlers. The progressive, debilitating muscle weakness characteristic of SMA cause infants and children to miss developmental milestones and leads to early death, even for people with less severe forms of the disease.

“We believe the broad [Spinraza] label will lead to robust uptake of the drug, particularly in type 1 and type 2 patients,” William Blair analyst John Sonnier wrote in a Dec. 27 note. “Although new safety warnings were disclosed in the label of the drug, including thrombocytopenia and elevated urine protein, we believe these warrant increased monitoring, but do not believe they will hinder the drug’s uptake at this time.”

Thrombocytopenia and renal side effects were observed in Spinraza clinical trials, and thrombocytopenia in particular has been a problem for other Ionis drug candidates using a similar backbone technology, Sonnier noted. However, the analyst said in his report, the platelet and urine protein levels did not reach numbers indicative of severe adverse events.

Multiple analysts noted the side effects included in the Spinraza label, but concluded that the FDA’s language would not be offsetting for prescribers given the severity of SMA for these young patients and the lack of approved or in-development treatments. Only six drugs are in clinical development for SMA, including four Phase II programs, one Phase VII and one Phase I asset, according to the Biomedtracker database.

“Until now, we had to tell parents that the only treatment was to manage symptoms as their children became weaker. Now, Spinraza offers patients currently living with SMA hope for disease stabilization or improvement, and it raises the possibility that infants with SMA could be prevented from developing weakness if identified early enough,” John Day, director of the Neuromuscular Disorders Clinic at Lucile Packard Children’s Hospital and professor of neurology and pediatrics at California’s Stanford University School of Medicine, said in a statement from Ionis.

The approval also gave Biogen a pediatric priority review voucher (PRV), which it may sell to another company or retain to seek speedy approval of another drug in its pipeline. Evercore ISI analyst Scotti pointed out in his note to investors that Biogen “hasn’t yet decided how it will be used, i.e. to sell it or keep it … though Biogen did say they will give preference towards using it for a Biogen/Ionis development program.” However, he noted the high value of PRVs to drug makers, such as the $350m price that AbbVie Inc. paid United Therapeutics Corp. for a PRV in 2015.

**NEW SCIENCE FOR UNMET NEURODEGENERATION NEED**

SMA is a rare genetic disease caused by a lack of or defect in the SMN1 gene that produces the survival motor neuron (SMN) protein. Spinraza is an antisense oligonucleotide (ASO) that splices the SMN2 RNA to make full-length, functional SMN protein. Stanford’s Day said in Ionis’s announcement of the drug’s approval that “the success of Spinraza increases our optimism that anti-sense oligonucleotides could also control other neurodegenerative disorders.”

Ionis chair and CEO Stanley Cooke said in the Carlsbad, California-based company’s statement: “Spinraza is truly a precision medicine that works by altering the processing of a single cellular RNA. We are proud that Spinraza exists because Ionis created and validated a new platform for drug discovery – antisense technology.”

Ionis’s rare disease development pipeline includes the Phase III candidate IONIS-TTNRx, partnered with GlaxoSmithKline PLC for familial amyloid polyneuropathy; the Phase II assets IONIS-DMPK-2.5Rx for myotonic dystrophy and IONIS-SOD1Rx for amyotrophic lateral sclerosis (ALS), both of which are collaborations with Biogen; and the Roche-partnered IONIS-HTTRx for Huntington’s disease in Phase II.

“Spinraza offers new hope for the SMA community and exemplifies our mission of applying cutting-edge science to make a meaningful difference in the lives of patients with devastating, life-altering diseases,” Biogen CEO George Scangos said in a separate statement. Scangos, who will leave Biogen in the hands of incoming CEO Michel Vounatsos on Jan. 6, thanked patients, families, investigators and Ionis for their roles in Spinraza’s development and noted “the urgency demonstrated by the FDA in rapidly reviewing and approving this treatment.”

The agency approved the drug months earlier than expected based on interim data from ENDEAR and results from patients with types 1-3 SMA who were treated in open-label clinical trials; the study showed that significantly more patients treated with Spinraza reached milestones and significantly fewer died from SMA. More than 170 patients have been treated to date with Spinraza, which is administered by periodic intrathecal injections.

“Dosing is fixed regardless of SMA subtype, age or weight of the patient, as 12mg doses of Spinraza are to be administered on days 0, 14, 28 and 58 (as a series of loading doses) followed by maintenance dosing every four months thereafter, which implies that the drug will be more costly up front for induction and then lower for maintenance,” Evercore ISI’s Scotti wrote.

**PAYER RESPONSE TO SPINRAZA PRICE TAG UNCLEAR**

Spinraza is different from Exondys 51, because it was not approved in the middle of Biogen’s and Ionis’s development program. The controversial approval for Sarepta’s DMD drug came at the end of a contentious review process that relied on data from just 12 patients. The $300m price tag has been difficult for payers to stomach, because the approval was based on a biomarker rather than proof that increased production of the dystrophin gene results in long-term gains in muscle strength.

But while some DMD patients have been denied access to Exondys 51, Spinraza’s cost may be easier for US payers to swallow, since the drug was approved based on positive data from several dozen symptomatic and pre-symptomatic individuals who have been diagnosed with or are likely to develop SMA types 1-3.

Leerink’s Geoffrey Porges said in a Dec. 26 note that “given [the] significant benefit shown in the trials presented or published to date, payers seem to have limited grounds for denying [patients] access” and he predicted that there will be widespread reimbursement for Spinraza by the end of the first quarter of 2017.

Pricing for Spinraza was not revealed in Biogen’s initial approval announcement, but the company later revealed a wholesale acquisition cost of $125,000 per vial, bringing the first year’s cost to $750,000 and subsequent years’ costs to $375,000 annually. The price exceeds analyst estimates of $200,000 to $400,000 per year, so given payers’ recent sensitivity to high-cost medicines it is unknown whether there will be resistance to Spinraza’s price tag.

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BRENT SAUNDERS
Allergan PLC CEO Brent Saunders has emerged over the past couple of years as one of the most respected leaders in the industry, and 2016 was another positive year for him.

The first part of 2016 saw Saunders handling a $160bn merger proposal from Pfizer Inc., which subsequently fell through after the US Treasury unveiled new rules on Apr. 4 cracking down on inversion deals that challenged the economics of the merger. Saunders dusted himself off and got on with the day job, leading from the front in matters such as the drug pricing debate, where he declared Allergan would limit price increases, and urging other companies to do the same. He was also quick to warn drug makers of the false security of Donald Trump’s US election win. “To think President Trump isn’t a populist, that he won’t jump on the next EpiPen scandal and tweet more on a pricing scandal than Hillary Clinton tweeted or anybody else… you are fooling yourself,” he said.

Saunders’ warnings on Dec. 1 over Trump were speedily corroborated by the man himself in an interview in Time magazine a few days later, where he stated he was “going to bring down drug prices.” The immediate result was the bringing down of share prices in the pharma industry.

Obviously 2017 (and beyond) will be when Trump truly puts his stamp on the fortunes of the pharma industry. Expect his name near the top of next year’s list.

FLEMMING ORNSKOV
Another pharma executive that put a failed chase behind him was Shire PLC’s CEO Flemming Ornskov. AbbVie Inc’s takeover of Shire was also stymied by the US tax inversion crackdown back in 2014, but Ornskov has gone on to build Shire’s fortunes and this year completed the purchase of Baxalta Inc. for $32bn, the biggest pharma deal of the year.

The year has not all been plain sailing for Shire and Ornskov but the exec’s attempt to bring confidence to its $20bn revenue target by 2020 impressed Scrip.

ROGER PERLMUTTER
Scrip’s next entry is Merck & Co. Inc’s R&D head Roger Perlmutter, for his part in the successful KEYNOTE-024 trial and the predicted erosion of market share from Bristol-Myers Squibb Co’s market leader Opdivo (nivolumab) by Merck’s Keytruda (pembrolizumab) in lung cancer in the coming months.

Merck reported positive results earlier this year for its PD-1 inhibitor in the KEYNOTE-024 first-line lung cancer study in patients with over 50% expression of PD-L1, about 30% of the overall trial population. The drug is now under review at FDA in this indication, with a Dec. 24 user fee date.

Merck was further boosted by BMS’s rival drug Opdivo failing the CheckMate 026 trial in first-line non-small cell lung cancer without even a trend towards efficacy in patients with high levels of PD-L1 expression.

JANET WOODCOCK
Center for Drug Evaluation and Research director Janet Woodcock has made the 2016 list for her role in the controversial accelerated approval of Sarepta Therapeutics Inc’s Exondys 51 (eteplirsen) in September. Memos released concurrent with the approval paint a picture of Woodcock taking a highly activist role, both before and after the NDA submission, in the effort to get eteplirsen approved as the first drug treatment for Duchenne muscular dystrophy.

FDA reviewers and managers within the Office of New Drugs raised several concerns about whether eteplirsen had shown enough efficacy in clinical trials. Many argued an approval was not appropriate, but Woodcock overruled them and granted the approval.
HILLARY CLINTON
She may have lost the US presidential election, but Hillary Clinton still makes Scrip’s list as a 2016 pharma influencer.

She followed up her September 2015 “price gouging” tweet after Martin Shkreli’s antics at Turing Pharmaceuticals AG with another market-rocking tweet about Mylan NV and EpiPen pricing in August 2016. She stated there was “no justification” for price hikes for “life and death” medications.

SHINZO ABE
Drug reimbursement prices in Japan are to be revised annually – rather than every other year – following top-level political support. Scrip has therefore added Japan’s Prime Minister Shinzo Abe, as a representative of the collective members of the country’s Central Social Insurance Medical Council (Chuikyo), as one of the top pharma influencers of the year.

Chuikyo was also behind the decision to slash the price of Opdivo in the country by 50%, with Merck’s Keytruda likely to see a lower price set at launch.

STEVE MILLER
The US’s largest pharmacy benefits manager Express Scripts Holding Co. threw a curveball into the diabetes arena in August when it decided to exclude Sanofi’s basal insulin Lantus and downgraded Novo Nordisk AS’s Levemir from formularies in favor of Eli Lilly & Co’s upcoming biosimilar Basaglar. This is not the only decision by Express Scripts, presumably instigated by its chief medical officer Dr. Steve Miller, that has raised eyebrows during 2016 and sent pharmaceutical companies scrambling to adjust forecasts and commercialization strategies. For the power Miller wields through his own analyses of which drugs deliver the best value to consumers – and taking that job off the hands of drug makers and regulators – Scrip has put Miller on the list for 2016.

HANS BISHOP
This time last year, the chimeric antigen receptor T-cell (CAR-T) therapy space was full of promise and excitement. And while much of that promise is still alive – Novartis AG and Kite Pharma Inc. plan to file their CD19-targeting CAR-T therapies for US FDA approval in early 2017 – some of that excitement turned to dread when the other CAR-T frontrunner, Juno Therapeutics Inc., had two clinical holds put on its lead program owing to unexplained deaths.

For this reason, Scrip has put the CEO of Juno, Hans Bishop, onto the list of people who have shaped the pharma industry in 2016. Bishop is of course no stranger to difficult times: he was chief operating officer of Dendreon Corp., the cell therapy trailblazer that eventually declared bankruptcy after failing to make a commercial success of the personalized prostate cancer cell therapy Provenge (sipuleucel-T).

Published online 23 December 2016

Sanger Institute Spin-Out Microbiotica To Evaluate Bacterial Mixes
The UK Wellcome Trust Sanger Institute’s latest spin-out has received start-up funding to exploit more than six years of gut bacterial genome sequencing in order to develop novel bacteria-based therapies for a range of diseases.

A UK microbiome-focused biotech, Microbiotica Ltd., has become the second company to be spun out of the UK-based genome sequencing research facility. Wellcome Trust Sanger Institute, with financial support from local start-up investor Cambridge Innovation Capital.

The financial firm invests in technology companies set up by the University of Cambridge, where it has preferred investor status, and in other opportunities it finds in the wider Cambridge Cluster region. Cambridge Innovation Capital previously invested in the genomics analytics company Congenica Ltd. that was spun off from the Wellcome Trust Sanger Institute in 2014 to work on using whole genome analysis for disease diagnosis.

CIC and the UK technology transfer expert IP Group plc announced Dec. 19 the investment of £4m each to establish Microbiotica, which will exploit a “first-in-class” gut microbiome culture collection and reference genome library built up by Sanger researchers, that is claimed to be the world’s largest culture collection of intestinal bacteria isolated from the human gut. Microbiotica’s first move is to advance existing bacterial mixes into preclinical development in the next 12 months. These potential bacteriotherapy mixes have shown striking effects in novel models of disease, the company says, and it has been granted exclusive rights to those mixes.

john.davis@informa.com, 19 Dec 2016

http://bit.ly/2j8ggRw
Pharma companies with drugs ranked in the top 10 by global sales in 2015 will need to find an extra $26bn in revenues just to make up for the anticipated loss in sales through to 2020. Of the ten best selling drugs of 2015, only Celgene’s Revlimid, according to Informa’s Datamonitor Healthcare, is expected to see an increase in revenues in 2020.

The amount of money lost by drugs currently topping the charts is forecast to slip by 2020. The year Avastin will be relegated from the top ten selling drugs on the market.

Cumulative sales of the TEN TOP selling drugs.

Humira will retain top spot as best-selling drug in 2020.

Other 2015 chart toppers expected to feature in the 2020 top ten are:

- Avastin
- Enbrel
- Remicade
- Revlimid

Harvoni will lose its runner up position, replaced by Gilead Sciences’ follow-up hepatitis C drug with forecast revenues of $12.1bn (2020) and $11.5bn (2023).

### TOP 10 Selling drugs of 2015 ($m)

1. **Humira** (adalimumab) - Inflammatory - Abbvie - $14,012
2. **Harvoni** (ledipasvir/sofosbuvir) - Hepatitis C - Gilead Sciences - $13,864
3. **Enbrel** (etanercept) - Inflammatory - Amgen/Pfizer - $8,697
4. **Remicade** (infliximab) - Inflammatory - J&J/MSD - $8,355
5. **Mabthera/Rituxan** (rituximab) - Cancer - Roche - $7,115
6. **Lantus** (insulin glargine) - Diabetes - Sanofi - $7,029
7. **Avastin** (bevacizumab) - Cancer - Roche - $6,751
8. **Herceptin** (trastuzumab) - Cancer - Roche - $6,603
9. **Revlimid** (lenalidomide) - Blood related disorders - Celgene - $5,801
10. **Sovaldi** (sofosbuvir) - Hepatitis C - Gilead Sciences - $5,276

Source: Scrip, Company filings

### 2020 vs. 2023

<table>
<thead>
<tr>
<th>Year</th>
<th>Cumulative Sales</th>
</tr>
</thead>
<tbody>
<tr>
<td>2020</td>
<td>$70.7bn</td>
</tr>
<tr>
<td>2023</td>
<td>$67.6bn</td>
</tr>
</tbody>
</table>

Source: Datamonitor Healthcare
AbbVie Picks Up Dong-A Candidate

JUNG WON Shin jungwon.shin@informa.com

Dong-A ST has scored a major early success in its inroads into cancer R&D through a sizable immuno-oncology deal with AbbVie, which also underscores the US firm’s push to expand its assets in the area.

AbbVie has picked up a novel Mer receptor tyrosine kinase inhibitor candidate from Dong-A. The agreement is significant for Dong-A as the company has not had much experience in the development of oncology drugs, but “it has now gained recognition from a big pharma for its very early stage, first-in-class drug candidate,” Eugene Investment added.

Seong said the new research center is focusing primarily on oncology and immuno-oncology drugs. "The deal size is seen as unprecedented considering the drug candidate hasn't entered preclinical trials yet," he added.

The agreement is significant for Dong-A ST as the company has not had much experience in the development of oncology drugs, but “it has now gained recognition from a big pharma for its very early stage, first-in-class drug candidate,” Eugene Investment & Securities said in a research note on Dec. 29.

“The deal size is seen as unprecedented considering the drug candidate hasn’t entered preclinical trials yet”

ABBVIE’S ONCOLOGY PUSH

The latest deal is in line with AbbVie’s recent moves to invest heavily in its oncology pipeline, including through partnerships. Oncology represents a newer, promising growth area for the company as it prepares to face sales losses due to biosimilar competition with its global blockbuster Humira (adalimumab).

The new alliance also underscores the ongoing robust appetite by global pharma for immuno-oncology and allies with views that such deals will continue to dominate the global pharma industry in 2017.

STRING OF DEALS

Dong-A ST’s recent deals include a licensing out agreement reached in April this year to grant development and sales rights in the US, Europe, Canada and Australia to evo-gliptin, its in-house developed DPP-4 inhibitor, to US-based Tobira Therapeutics Inc.

The leading South Korean pharma is also looking for global partners for other pipeline assets including DA-9801, its herbal-derived diabetic neuropathy pain drug which underwent a Phase II clinical trial in the US last year.

Published online 29 December 2016
From the editors of PharmAsia News.
The sustained dominance of “second-wave” biosimilars in both development pipelines and approval flow, and a crescendo in the debate around the naming of biologicals and interchangeability were some of the issues discussed at a recent QuintilesIMS roundtable in Mumbai on “Biosimilar Trends In 2017.”

While the year could see the approval of trastuzumab, rituximab and bevacizumab biosimilars in the EU and/or the US, the focus on second-wave biosimilars is a reflection, in part, of these products having been the biopharmaceutical industry’s “top grossers” for the last few years.

“Wave Two will rule pipelines for some time to come; these are the products that hold a majority of the market in dollar terms. Unless there is a big market, companies don’t want to invest in biosimilars development since it isn’t like generics,” Dr. Charu Manaktala, senior medical director and head of the Asia Pacific Biosimilars Centre of Excellence, strategic drug development, QuintilesIMS Asia, said at the roundtable on Dec. 20.

Biologics with patents expiring between 2015 and 2020 comprise the second wave of biosimilars and include blockbuster products such as Humira (adalimumab), Enbrel (etanercept), Rituxan/MabThera (rituximab), Avastin (bevacizumab), Herceptin (trastuzumab) and Remicade (infliximab).

Informa’s Datamonitor Healthcare recently said that AbbVie Inc’s Humira and Roche’s Avastin and Herceptin are the lead reference biologicals with the most biosimilar candidates in development in preclinical studies through to Phase III trials.

In its report, Datamonitor Healthcare also noted that eight biosimilars have been filed under the 351(k) pathway in the US and are awaiting FDA approval, while there are 14 biosimilars awaiting clearance in the EU. Sandoz has three filings in the EU: in addition to a biosimilar to Amgen Inc’s Neulasta (pegfilgrastim), which is also awaiting US approval, the company has submitted etanercept and rituximab biosimilars for approval.

Manaktala also added that while there are now signs of development of ‘third-wave’ biosimilars, these are at best “sparsely” and quite some time away from regulatory approvals. The second wave of biologics, which have patent expiries beyond 2020, includes products such as Cimzia (certolizumab pegol), Lucentis (ranibizumab) and Simponi (golimumab).

INNS AND INTERCHANGEABILITY

The naming of biologicals and the interchangeability of biosimilars are expected to continue to be strongly debated topics, the Mumbai roundtable heard.

While the European Medicines Agency has approved biosimilars under the same non-proprietary name as for the reference product, the US FDAs 2015 draft guidance on non-proprietary naming of biosimilars recommends that all biologicals should have non-proprietary names that include a four-letter suffix to distinguish them from each other. The suffix would comprise four lowercase letters and not carry any meaning. The proposed US approach aims to clearly identify biological products to improve pharmacovigilance and avoid any unintended substitution.

Manaktala, however, noted that based on current experience that has been reported, there appears to have been “no confusion or concerns” on how to track the product with the same International Non-proprietary Name (INN).

“It’s been 10 long years and 25 products have been approved and the EU hasn’t reported any adverse experience with the use of the common INN. That is quite significant. The EU seems to be doing pretty well using just the INN,” she told Scrip.

Some industry experts and other stakeholders have opposed the FDA’s suffix approach, suggesting that it would impede the uptake of biosimilars and do little to improve pharmacovigilance.

CONFIDENCE BUILDING

On interchangeability, while guidance from the US FDA is awaited, the QuintilesIMS executive referred to Sandoz’s EGALITY study that demonstrated switching between biosimilar etanercept and the originator product had no impact on safety and efficacy.

“Such emerging data is likely to contribute towards building confidence of the prescribers, patients and payers in biosimilars, and this is likely to impact biosimilars’ uptake positively. We see more expert bodies around the world endorsing the use of biosimilars,” Manaktala said.

In the EGALITY study, patients who switched treatments crossed over between biosimilar etanercept and the originator product three times, with no clinically meaningful differences in safety and efficacy. Sandoz’s biosimilar etanercept was approved by the FDA in August 2016.

Manaktala also added that she expected to see more products obtaining marketing approval on the basis of “lean” clinical data packages (especially where validated pharmacodynamic markers are available), backed by strong quality comparability, in vitro biological activity evidence, and clinical PK-PD studies.

CONSOLIDATION?

There are also some early signs of consolidation in the biosimilars space. 2016, Manaktala noted, had seen at least two significant players exiting or then seemingly considering an exit from the biosimilars domain in favor of “other priorities.”

She referred to Shire PLC returning the rights to biosimilars that Baxalta Inc. was developing jointly with other companies – adalimumab biosimilar with Momenta Pharmaceuticals Inc. and etanercept biosimilar with Coherus BioSciences Inc.

In addition, Merck KGAA has been reported to be re-evaluating its biosimilars business. In October, news agencies said that the firm had brought in JPMorgan Chase & Co to sound out potential suitors for its biosimilars business.

She maintained that given the nature of the biosimilars business, partnerships will play a critical role in this domain.

Published online 30 December 2016
**Sun Acquires Novartis Cancer Drug In Specialty Push**

Indian generic drug companies have been on an aggressive quest to build scale in the higher-margin global specialty drug business as generic competition grows fiercer and Sun Pharmaceutical Industries Ltd. has been among firms leading the pack with a string of acquisitions in the branded dermatology and ophthalmology segments. Now the company, led by billionaire founder and hyperactive deal-maker Dilip Shanghvi, has announced one more purchase, saying it will pay $175m along with undisclosed milestone payments to Swiss giant Novartis AG for its branded skin cancer drug Odomzo (sonidegib). The acquisition of Odomzo, which has been approved for sale in 30 countries, including European nations, Australia and most importantly the US, the world’s largest drug market, “gives Sun its first branded oncology product,” the Mumbai-based company said in a stock exchange statement Dec. 22. Shanghvi, who’s India’s second-wealthiest person, has been steering the company’s focus toward more specialty therapies that can achieve higher margins to counter the competition squeezing the pricing power of its traditional generic lines. Branded specialty drugs now represent some 25% of global medical spending. Sun Pharma, like many other big Indian drug firms, has also been buffeted by the headwinds of increased US regulatory scrutiny that has revealed manufacturing shortfalls at its plants in India, curbed earnings and made the company’s shares one of the worst performing pharmaceutical stocks. The purchase announcement coincided with more bad regulatory news for Sun Pharma which has been struggling to bring some of its Indian plants up to US FDA standards and underscored the company’s need to diversify.  

*Penelope MacRae, 22 Dec 2016*

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**Akebia Holds Development Reins In Anemia While Otsuka Jumps On Vadadustat Sleigh**

Akebia Therapeutics Inc. stresses that it will be holding the reins on important aspects of developing vadadustat for anemia in patients with chronic kidney disease (CKD) – including pricing and reimbursement – after shifting course on its US plans in order to bring Otsuka Pharmaceutical Co. Ltd. on board in a 50-50 deal. Otsuka committed at least $265m to partner with Akebia, including upfront fees and development capital, in a co-development and commercialization deal for vadadustat, a once-daily, oral hypoxia-inducible factor prolyl hydroxylase (HIF-PH) stabilizer in Phase III for CKD-related anemia – a condition that affects some 1.8m people in the US. The agreement announced on Dec. 20 also gives Akebia the chance to earn as much as $765m in milestone fees, putting the deal’s potential value at more than $1bn. The Japanese pharma’s initial $265m commitment to Akebia, includes $125m at the time of signing and $35m in the first quarter of 2017 for co-development and commercialization rights, plus at least $105m to cover global development costs. The partners will share all US development and commercialization costs equally and split profits in that key pharmaceutical market on a 50-50 basis.  

*emily.hayes@informa.com, 21 Dec 2016*

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**Sunovion To Commercialize Novartis’s COPD Products In US**

Sunovion Pharmaceuticals Inc., owned by Japanese group Sumitomo Dainippon Pharma Co. Ltd., has exclusively licensed US rights to commercialize three approved respiratory treatments from Novartis AG: the LABA/LAMA Utibron Neohaler (indacaterol and glycopyrrolate), Seebri Neohaler (glycopyrrolate) and Arcapta Neohaler (indacaterol), which are all indicated for chronic obstructive pulmonary disease (COPD). Utibron Neohaler and Seebri Neohaler were approved by the US FDA in 2015, and Sunovion plans to bring them to market in 2017. Arcapta Neohaler was approved in 2011 and has been on the market since 2012. Novartis will continue to manufacture these three medicines and retains rights for the products outside of the US. Financial terms of the deal remain undisclosed. Sunovion’s COPD portfolio already includes the long-acting β adrenoceptor agonists (LABA) Brossana (arformoterol tartrate). In addition, it filed the long-acting muscarinic receptor antagonist (LAMA) SUN-101/eFlow (glycopyrrolate) with the FDA in July 2016.  

*sukaina.virji@informa.com, 22 Dec 2016*

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**Broad-Based Incyte/Merus Collaboration**

Incyte Corp. and Merus BV have announced a broad-based bispecific antibody discovery, development and commercialization partnership that could include up to 11 programs, resulting in potential earn-outs to Merus of nearly $3bn and includes the flexibility to move into novel targets and novel biology. On a Dec. 21 conference call, Merus executives called the agreement “truly transformative” in that it validates the company’s Biclonics bispecific antibody technology platform, while providing a major cash infusion and leaving the Dutch firm with full rights to its two clinical candidates and one of its most advanced preclinical candidates, all in the immuno-oncology space. Analysts called the deal a win for both companies, saying Incyte expands its R&D capacity into one of the more promising areas within cancer.  

*joseph.haas@informa.com, 21 Dec 2016*
US IPOs In Review: Relatively Muted Market In 2016 To Continue In 2017

After biopharma initial public offerings in the US during 2016 outperformed the prior year’s IPOs, expect more of the same in 2017: fewer, but higher quality offerings at lower IPO share prices to keep values at acceptable levels for experienced health care investors.

MANDY JACKSON mandy.jackson@informausa.com

Generalist investors that gambled on the US biopharmaceutical initial public offering market between 2013 and mid-2015 are largely gone, leaving health care specialists to bet on less risky drug developer IPOs in 2016 – a trend that’s expected to continue in 2017.

The biopharma IPO market may be reaching a sort of equilibrium as companies vetted by experienced health care investors and perceived as relatively safe wagers will still get through the IPO window at investor-friendly share prices, but not every therapeutic firm that registers a prospective offering with the US Securities and Exchange Commission (SEC) will be able to go public. Recent investment discipline has paid off: the average return as of Dec. 30 for the 62 drug developers that launched IPOs in 2015 was -24% compared with an 11.2% gain for the 30 therapeutics firms that went public in 2016.

Investors that bought into 2016 offerings bet big on innovation and hot biopharma sectors, such as gene editing and immuno-oncology, but were less enthusiastic about cancer biosimilars, enzyme replacement therapies, ophthalmology, infectious disease and preclinical cancer programs. Even so, per the table below, companies launched IPOs in 2016 at lower per-share prices and grossed less money from their offerings compared with their 2015 peers.

BIOPHARMA VS. OTHER INDUSTRIES

The reduced number of biopharma IPOs and decline in gross proceeds tracked closely with overall IPO performance in 2016, but the industry is expected to diverge from technology and other sectors in 2017, according to the IPO-tracking firm Renaissance Capital LLC.

"With the S&P 500 at record highs and average IPO returns handily beating the broad market indices, the US IPO market should have produced high levels of issuance in 2016. Instead, proceeds fell to their lowest level since 2003 and activity was the worst since 2009," Renaissance said in its annual IPO review. The firm attributed much of the drop in new IPOs to postponed offerings during the first quarter as well as uncertainty caused by the UK’s Brexit vote in the second quarter and the US presidential election in the fourth quarter.

"Health care, down 46% from last year in deal flow, remained the most active sector in the IPO market for the fourth year in a row due to elevated biotech activity. It was the only sector that brought companies public during the volatile first quarter thanks to substantial insider buying," Renaissance noted in its annual IPO review.

Performance remained volatile throughout the year with nine of the worst-performing US IPOs in 2016 credited to biopharma companies, but only four of the year’s 10 top performing IPOs were therapeutics firms. As such, Renaissance expects venture capital-backed biopharma IPO activity in 2017 to be muted relative to offerings in other industries.

AveXis CEO Sean Nolan said his firm, which is developing the gene therapy AVXS-101 for the rare neurodegenerative disease spinal muscular atrophy, remains focused on one key goal, which has resonated with the company’s investors: "We’re relentlessly focused on driving the program forward and getting approvals to make it available to all kids affected by this disease.”

"VC-backed biotech IPOs numbered 20 [in 2016], down 56% compared to last year, and averaged a return of +32%. None priced

2015 Versus 2016 IPO Statistics

<table>
<thead>
<tr>
<th></th>
<th>2015 IPOs</th>
<th>2016 IPOs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number Of Companies</td>
<td>62</td>
<td>30</td>
</tr>
<tr>
<td>Average IPO Price Per Share</td>
<td>$13.87</td>
<td>$12.03</td>
</tr>
<tr>
<td>IPO Price Range</td>
<td>$2.75 to $68.56</td>
<td>$5 to $24</td>
</tr>
<tr>
<td>Total Gross Proceeds</td>
<td>$5.38bn</td>
<td>$2.02bn</td>
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<tr>
<td>Average Gross Proceeds</td>
<td>$86.8m</td>
<td>$67.4m</td>
</tr>
<tr>
<td>Average Return Year-End 2015</td>
<td>12%</td>
<td>NA</td>
</tr>
<tr>
<td>Average Return Year-End 2016</td>
<td>-24%</td>
<td>11.2%</td>
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</table>

Top Five Biopharma IPOs Of 2016

<table>
<thead>
<tr>
<th>COMPANY</th>
<th>SPECIALTY</th>
<th>RETURN VS. IPO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novan Inc.</td>
<td>Topical dermatology medicines</td>
<td>145.6%</td>
</tr>
<tr>
<td>AveXis Inc.</td>
<td>Gene therapies for rare neurological diseases</td>
<td>138.9%</td>
</tr>
<tr>
<td>Merus NV</td>
<td>Bi-specific antibodies; immuno-oncology</td>
<td>111.1%</td>
</tr>
<tr>
<td>Reata Pharmaceuticals Inc.</td>
<td>Targeting cellular metabolism and inflammation in cardiovascular and rare diseases, ophthalmology and immuno-oncology</td>
<td>98.5%</td>
</tr>
<tr>
<td>Protagonist Therapeutics Inc.</td>
<td>Oral peptide drugs with targeted delivery to the gastrointestinal (GI) compartment; disease targets are currently addressed by biologics; initial focus on GI diseases</td>
<td>83.3%</td>
</tr>
</tbody>
</table>
Bottom Five IPOs of 2016

<table>
<thead>
<tr>
<th>COMPANY</th>
<th>SPECIALTY</th>
<th>RETURN VS. IPO</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhaseRx Inc.</td>
<td>mRNA therapeutics for inherited liver diseases</td>
<td>-69%</td>
</tr>
<tr>
<td>Moleculin Bio-tech Inc.</td>
<td>Cancer therapeutics; lead product is an anthracycline for acute myeloid leukemia</td>
<td>-62%</td>
</tr>
<tr>
<td>Aleglea Biotherapeutics Inc.</td>
<td>Engineered human enzymes to treat inborn errors of metabolism</td>
<td>-56.5%</td>
</tr>
<tr>
<td>Kadmon Corp. LLC</td>
<td>Treatments for cancer as well as autoimmune, fibrotic and genetic diseases</td>
<td>-55.4%</td>
</tr>
<tr>
<td>Oncobiologics Inc.</td>
<td>Biosimilars to treat cancer</td>
<td>-49.8%</td>
</tr>
</tbody>
</table>

Above the [proposed IPO price] range, and 40% priced below it. Three prominent gene editing biotechs – Editas, Intellia and CRISPR – went public in the US this year, but initial excitement fizzled quickly. With many of the most promising biotechs already public and the Nasdaq Biotech Index (NBI) down 20% for the year, biotechs relied on insiders to get [IPOs] done and may need to follow the same playbook for activity in 2017, according to Renaissance.

The NBI is down 21.7% year-to-date – and 33% from its July 20, 2015 peak – versus year-to-date gains of 7.5% for the broader Nasdaq index and 13.4% for the Dow Jones Industrial Average. That’s why Renaissance expects biopharma IPOs to attract less interest than offerings from health care companies in general while other industries see a boost in the number and size of IPOs.

*Health care is a trickier call because there are many scenarios by which Obamacare could be repealed or partially dismantled. However, one call we can make with confidence: the biotech boom is over for now because the best companies of the 2013-2016 vintages have already gone public and there are an increasing number of Phase III trial failures,* the IPO firm wrote in its year-end report.

There are not a lot of biopharma companies waiting in line to launch IPOs in 2017. Of the 35 therapeutics firms that registered prospective offerings with the SEC in 2016, 25 priced their offerings (the five other 2016 IPOs originally filed in 2015). Also, two companies withdrew their registrations and one was acquired.

That leaves seven biopharma IPO hopefuls that have yet to leave the runway. One set a preliminary price range but didn’t launch, and six others have yet to outline terms for an offering, but those six include three biopharma companies that filed for an IPO on Dec. 30 – Jounce Therapeutics Inc. seeking up to $75m, ObsEva SA looking for up to $86.25m, and Braeburn Pharmaceuticals SPRL eyeing a $150m offering.

But with 2016 IPOs outperforming biopharma therapeutics companies that went public in 2015, expect 2017 to offer more of the same: fewer offerings than recent frenzied levels at lower share prices and gross proceeds as investors focus on science, innovation and success in the clinic. That formula paid off in 2016 and investors will look for similar or improved returns in 2017 from companies with innovative technology and clinical programs (see table below for individual 2016 IPO performance).

**2016 IPO Performance By Company**

<table>
<thead>
<tr>
<th>COMPANY</th>
<th>IPO PRICE</th>
<th>DEC. 30 PRICE</th>
<th>RETURN VS. IPO</th>
</tr>
</thead>
<tbody>
<tr>
<td>TiGenix NV (TIG)</td>
<td>$15.50</td>
<td>$14.58</td>
<td>-5.9%</td>
</tr>
<tr>
<td>Motif Bio PLC (MTFB)</td>
<td>$6.98</td>
<td>$6.04</td>
<td>-13.5%</td>
</tr>
<tr>
<td>Myovant Sciences Ltd. (MYOV)</td>
<td>$15</td>
<td>$12.44</td>
<td>-17.1%</td>
</tr>
<tr>
<td>Ra Pharmaceuticals Inc. (RAXR)</td>
<td>$13</td>
<td>$15.19</td>
<td>16.8%</td>
</tr>
<tr>
<td>CRISPR Therapeutics AG (CRSP)</td>
<td>$14</td>
<td>$20</td>
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Published online 30 December 2016
2016 Review: Refocus, Reduce, Reform The Watchwords In Japan

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While reimbursement pricing issues and policies dominated the Japanese pharma market in 2016, there was also notable commercial activity during the year, although this was more about refocusing and reducing rather than major mergers and acquisitions.

2016 was a quiet year in terms of transformational mergers and acquisitions in Japan, with nothing that could be considered a “mega-deal” clinched during the calendar period.

Astellas Pharma Inc. was again an active deal maker however, signing or completing several smaller acquisitions valued in the several hundred million dollar range, including of Ganymed Pharmaceuticals AG and Ocata, which build up its expertise and assets in specific areas such as oncology and ophthalmology.

There was also a notable unraveling of some alliances following disappointing clinical results or to move out of deprioritized areas, with Otsuka Pharmaceutical Co. Ltd. ending its ophthalmic partnership with Acucela Inc., and Eisai Co. Ltd. selling AkaRx Inc. to a private equity group.

Indeed for many of Japan’s top pharma companies, including Takeda Pharmaceutical Co. Ltd., the trend was towards continued divestment of non-core assets and molecules as they strive to sharpen their focus on selected therapeutic areas.

Speculation that Takeda was on the prowl for certain gastrointestinal assets from Valeant Pharmaceuticals International Inc. - or even the whole company - remained unconfirmed by any deal by the end of the year. But Takeda is raising a potential war chest of close to $900m from the year-end sale of its majority-owned Wako Pure Chemical Industries Ltd. subsidiary in Japan to Fujifilm Holdings Corp., and the possible deployment of its ophthalmic partnership with Acucella Inc., and Eisai Co. Ltd. selling AkaRx Inc. to a private equity group.

While the usual panoply of licensing in and out deals and R&D collaborations during the year, it was hard to pick a stand-out therapeutic trend, although not surprisingly oncology technology and molecules featured heavily across the board.

This was in line with a continued effort by Japan’s major firms to build their pipelines and expertise in this growing key area, with Daiichi Sankyo Co. Ltd. in particular also bringing in world-class foreign executives to help with its efforts, which have been kick-started by a string of acquisitions over the past few years. The company is looking to generate new sources of growth amid the first loss of exclusivity, although not surprisingly oncology technology and molecules featured heavily across the board.

Companies dipping a toe into novel digital health programs included Astellas, through a new US investment venture that will put money into broad initiatives, and Eisai, which is building a reorganization in July, under which it will simplify global sites and outsource much of its worldwide development activities.

SHEADING MATURE PRODUCTS

Another major area of activity by research-based multinationals in Japan was mature products, with several firms taking concrete steps to pull out of this increasingly competitive and less profitable business. While new drugs are enjoying good prices and growth, and generics are expanding at the other end of the scale, older brands are facing with price cuts, competition, and are generally stagnant.

In the wake of Takeda completing the divestment of a select mature portfolio to a new Japan joint venture with generics giant Teva Pharmaceutical Industries Ltd. in April, major Indian firm Sun Pharmaceutical Industries Ltd. struck up an alliance with Mitsubishi Tanabe Pharma Corp. for a basket of older drugs acquired from Novartis AG Japan. Another Indian-affiliated company, Lupin Ltd.'s Kyowa Pharmaceutical Industry Co. Ltd. operation, then picked up a group of other brands from Shionogi & Co. Ltd.

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PRICING UPHEAVAL

But largely overshadowing these corporate developments were rapid and fundamental changes to the drug pricing environment, which has been relatively stable over the past few years, marked by higher fixed prices for innovative new therapies along with regular but predictable industry-wide reimbursement revisions every other April.

Spurred by political and public concerns over highly effective, but also highly priced, new drugs for cancer and hepatitis C - and the first real impact of these on the national healthcare bill - 2016 will be remembered as a year that new waves began to roll this relatively calm sea. April 2016 saw drug reimbursement prices under Japan’s national health insurance scheme cut by around 6% across the board, as part of the biennial effort to bring levels into line with actual (discounted) market prices. But on top of this, the prices of two new Gilead Sciences Inc. products for hepatitis C - Sovaldi (sofosbuvir) and Harvoni (sofosbuvir plus ledipasvir) - were slashed by around 32%, triggered by new provisions that allow one-off reductions for products that have exceeded by a certain margin above official forecasts at the time of launch.

Later in the year, the price of Ono Pharmaceutical Co. Ltd/Bristol-Myers Squibb Co’s cancer drug Opdivo (nivolumab) also came under intense public, political and mass media scrutiny as a driver of surging national prescription drug costs. Rapidly increasing use of the PD-1-targeting antibody in the additional indication of lung cancer became a factor behind a 9% jump in such spending in the fiscal year to March 31, even prompting projections that it could effectively bankrupt the NHl system.
2016 Review: Pricing, R&D Issues Dominate In China

2016 was again another busy year on the commercial front in China, with market changes, new regulations, and ongoing pricing pressures all affecting the pharma sector. Meanwhile, the push for licensing deals, innovation, and international expansion continued apace.

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JANUARY
Provincial drug procurement processes became a major concern as dozens of provinces started unveiling new rules for pharmaceutical bidding, with companies getting ready to embrace deeper price cuts.

FEBRUARY
China’s ongoing economic woes were found to be denting the pharma industry and directly impacting medical sales personnel, whose absolute numbers were declining despite the industry’s chronic need for talent, said the country’s top pharmaceutical associations.

MARCH
Multinationals changed their traditional direction by expanding their footprints in the promising but challenging county-level hospital market, with Eli Lilly & Co. among those looking to embrace China’s lower-tier opportunities.

During the annual People’s Congress, pharma industry representatives called for appropriate pricing mechanisms and the automatic enrolling of new drugs onto the national reimbursement list to improve the innovation ecosystem.

APRIL
In a crackdown on excessive layers of sales agents and purchase cost manipulation, China’s state regulators kicked off a new battle to combat so-called “guopiao,” or receipt inflation. The State Council issued a rule preventing the issue of more than two receipts during the drug procurement process.

Facing increasing public complaints about the prices of medicines, the Chinese government was poised to kick off a fresh round of probes into pricing practices.

Several drug and device manufacturers including Pfizer Inc. were summoned by the powerful National Development and Reform Commission (NDRC) to provide information.

In an immuno-oncology gold rush, more than 50 biotechs in China were found to be developing anti-PD1 and PD-L1 assets, quickly.

China’s first round of national drug pricing negotiations cut the prices of selected hepatitis C and lung cancer therapies by more than 50%, impacting GlaxoSmithKline PLC’s Viread (tenofovir), AstraZeneca PLC’s Iressa (gefitinib), and Betta Pharmaceuticals Co. Ltd’s Conmana (icotinib).

The goal, according to the National Health and Family Planning Commission (NHFPC), was to lower the prices in China to levels comparable with neighboring markets such as Hong Kong, Macau, Taiwan and Japan.

JUNE
In its “most pessimistic” business confidence outlook in 13 years, the EU Chamber of Commerce in China cautioned about a need for China to implement reform measures, while EU pharma companies foresaw their profits dropping in the world’s second-largest economy.

JULY
China’s Ministry of Industry and Information Technology (MIIT) released quarterly data showing overall growth for the drug manufacturing sector declined to 9.6%, from 9.8% in the whole of 2015.

AUGUST
Despite China’s wider economic slowdown, investment continued to flock to the healthcare sector in the country, noted Bain & Company in its annual Global Healthcare Private Equity and Corporate M&A Report.

China bagged close to $1bn worth of private investments in public equities in 2015, nearly double the previous year’s figure of $575m.

SEPTEMBER
Gilead Sciences Inc. changed its business strategy in China by hiring a former Roche market access executive in a bid to develop the scope of its local operations.

OCTOBER
AstraZeneca announced the out-licensing of exclusive rights to four antidiabetic products in China to Shenyang SinoBio Inc.: Byetta (exenatide), Bydureon (exenatide suspended release) single dose tray, Bydureon dual chamber pen and Bydureon auto-injector, indicating a strategy shift to focus more on its core respiratory franchise.

NOVEMBER
China’s innovation darling Betta Pharmaceuticals Co. Ltd. went public on the Shanghai Stock Exchange, which may herald a new wave of capital inflow and renewed interest in new drug R&D in China, although hurdles to the pursuit of original research were seen as remaining.

To realize its ambitions for novel pharma R&D, China should step up by providing timely and adequate insurance coverage to innovative new drugs, urged an industry report. A government report found that ambitious and confident Chinese pharma firms had begun to enter a brave new world of foreign M&A.

DECEMBER
A shift in dispensing patterns from hospitals to external pharmacies led to predictions that the “direct-to-patient” sales model will become important in China, but only those with the right partnerships and expertise will reap the benefits, leading pharmacy chain executives told a conference.

Published online 29 December 2016
From the editors of PharmAsia News.
2016 Review: Mixed Bag Of Hope And Setbacks For Korean Pharma

JUNG WON Shin jungwon.shin@informa.com

For the South Korean pharma industry, 2016 was largely about major global advances for a wide range of biosimilars, accompanied by some setbacks in the area of novel drug development.

The approval and launch of Celltrion Inc’s biosimilar infliximab in the US could be seen as one of the top commercial milestones for the South Korean pharma industry in 2016, marking as it did the first time that a monoclonal antibody biosimilar had been licensed in this key market. Inflectra (infliximab-dyyb), a version of Janssen Inc’s Remicade, received the green light from the US FDA on April 5, and was also only the second biosimilar to be approved in the country after Sandoz Inc’s Zarxio (filgrastim).

The biosimilar is already widely available in Europe, as Remsima.

Celltrion and commercial partner Pfizer Inc. said they would launch Inflectra in the US in late November, and the entry into the world’s biggest pharma market is expected to give a big boost to global sales of the product. Celltrion said the initial shipments of Inflectra to the US by the end of the year would be worth about KRW260bn ($2.25bn) on a customs clearance basis.

The company is eventually aiming for annual worldwide Inflectra sales of more than KRW1tn, and accumulated global exports to date have been in excess of this figure, making the product a key commercial pillar for Celltrion.

CELLTRION’S RITUXIMAB PROGRESSES

The South Korean firm is also edging ahead of its competitors in the development of a rituximab biosimilar, Truxima, its version of Genentech Inc/Biogen Inc’s monoclonal antibody MabThera/Rituxan, received regulatory approval in South Korea in November, marking the first approval globally for the product.

The company expects the ongoing regulatory process in Europe for biosimilar rituximab to progress “smoothly” following a submission to the European Medicines Agency (EMA) in October 2015. After receiving the green light there, it aims to begin commercialization in the region in 2017, potentially widening the gap with its closest competitors. Celltrion has an exclusive partnership with Teva Pharmaceutical Industries Ltd., reached in October 2016, for Truxima, under which the Israeli generics giant will be responsible for all commercial activities for the product in the US and Canada.

Celltrion plans to submit biosimilar versions of rituximab and another cancer drug, trastuzumab, to the US FDA in the first half of next year. Biosimilar trastuzumab, now in late Phase III development after meeting its primary endpoint, was filed with the EMA in October.

SAMSUNG MOVES AHEAD

Celltrion’s main domestic biosimilars rival, Samsung Bioepis Co. Ltd., also made good progress with its global market entry plans during the year. The FDA accepted for review SB2, the firm’s biosimilar of Remicade, in May, making it the first of Samsung’s biosimilar candidates to be submitted for review in the US.

In October, Samsung Bioepis then filed for approval in Europe of its biosimilar trastuzumab, SB3, marking its fifth biosimilar candidate to be filed for approval in this market.

On top of this, the EMA accepted for review a marketing authorization application for the company’s adalimumab biosimilar candidate SB5 in July.

The South Korean company received European Commission approval earlier in the year for Benepali, its biosimilar etanercept, and biosimilar infliximab Flixbi. Its biosimilar etanercept (SB4) has already received South Korean regulatory approval and is marketed there as Brensys.

HARSH REMINDERS

If 2016 was full of positive news about South Korean biosimilar activities, the year also served up a stark reminder of how risky and tough new drug development can be.

Hanmi Pharmaceutical Co. Ltd., which had made headlines reaching a series of blockbuster licensing out deals with multinationals, hit the news again with a major controversy over the cancellation of a licensing deal for its lung cancer drug olmutinib. A subsequent prosecutors’ probe looked into the company’s possible leakage of undisclosed information and if there was an intentional delay in disclosing the negative news.

Prosecutors eventually concluded that Hanmi did not deliberately put back the announcement of a decision by licensee Boehringer Ingelheim GMBH to end its olmutinib partnership, but several employees were nevertheless arrested over improper information disclosure.

Meanwhile, the Ministry of Food and Drug Safety decided to limit the usage of the EGFR inhibitor, which had been approved in South Korea in May, solely to patients who had agreed to use the drug after receiving thorough explanations from doctors on possible side effects including serious adverse skin reactions.

Adding to the negative news amid the country’s innovation drive, Yuhan Corp. decided to halt clinical trials with its degenerative disc therapy candidate YH14618, as statistical significance over placebo during Phase II trials was not established.

Green Cross Corp. ended US and European trials with hemophilia A therapy Green-Gene F after it modified strategy and decided to focus on the fast-growing China market instead.

MAJOR LICENSING DEALS

Amid the setbacks, foreign companies continued to show an appetite for accessing the rising level of innovation and number of novel drugs coming out of South Korea, as evidenced by a number of significant licensing deals during the year.

Deals reached in 2016 include CrystalGenomics Inc’s licensing out agreement with Aptose Biosciences Inc, Hanmi’s deal with Genentech Inc and Kolon Life Science Inc’s deal with Mitsubishi Tanabe Pharma Corp.

Published online 29 December 2016
From the editors of PharmAsia News.
Alexion’s Soliris Slips Up In Pivotal PROTECT Kidney Transplant Study

Alexion Pharmaceuticals Inc. has been left disappointed by top-line data from the Phase II/III registration trial for its first-in-class terminal complement inhibitor Soliris (eculizumab) in preventing delayed graft function (DGF) after kidney transplantation in adult recipients of a deceased donor kidney. If successful, the study could have paved the way for approval in another indication for Alexion’s mainstay and multibillion-dollar selling product in an area of huge unmet medical need: there are no therapies licensed to prevent or treat DGF after kidney transplantation, a common complication. The failure adds to a difficult end of year for Alexion, which has just lost its CEO David Hallal and CFO Vikas Sinha amid an audit investigation and a delay to its 10-Q filing. Expanding Soliris approval into DGF is part of Alexion’s strategy to grow the product further, and an approval had been slated for 2018 by the company. Other rare indications in late-stage testing include refractory generalized myasthenia gravis (gMG) and relapsing neuromyelitis optica spectrum disorder (NMOSD). The failure is also a setback for the DGF field as a whole. Analysts at Biomedtracker have lowered their likelihood of approval score by 15% to 44% as a result.

Ionis Subsidiary Akcea Encouraged By Safety Data In FCS

Awaiting data from its pivotal AP-PROACH trial during the first quarter of 2017, Akcea Therapeutics was encouraged by safety and efficacy data unveiled Dec. 19 for lead candidate volanesorsen from a separate Phase III study in patients with severe hypertriglyceridemia, including a subset of patients with familial chylomicronemia syndrome (FCS). Akcea, a subsidiary of antisense-focused Ionis Pharmaceuticals Inc., hopes to file volanesorsen for FCS in 2017. It plans a subsequent filing down the road in familial partial lipodystrophy (FPL) for the candidate, which is designed to reduce the production apolipoprotein C-III, a protein produced in the liver that plays a role in regulation of plasma triglycerides. FCS and FPL, both rare metabolic disorders, are unmet medical needs with potentially life-threatening consequences, the company notes. FCS, in which triglyceride levels are 10-20 times higher than normal, often progresses to pancreatitis, and currently available triglyceride-lowering therapies rarely are beneficial in these patients. In the Phase III COMPASS study of 113 patients with severe hypertriglyceridemia, the 75 patients treated with volanesorsen achieved a 71.2% mean reduction in triglycerides from baseline after 13 weeks of treatment, compared to a mean reduction of 0.9% in the placebo group (p<0.0001). The treatment effect was sustained throughout the full 26-week dosing period.

In Novartis, Conatus Lands Experienced, Deep-Pocketed NASH Partner

The broad-based competition in non-alcoholic steatohepatitis (NASH) took another turn Dec. 19, as Conatus Pharmaceuticals Inc. signed an option, collaboration and commercialization agreement with Novartis AG around its caspase inhibitor emricasan, currently in Phase IIb for both NASH cirrhosis and NASH fibrosis. The deal brings Conatus $50m up front, a convertible loan of up to $15m from Novartis, a $7m exercise fee if the pharma elects its option on emricasan and up to $650m in milestones along with potential sales royalties if the drug reaches the market as monotherapy and/or as part of a NASH combination regimen. Novartis also has LJN-452, a non-bile acid farnesoid X receptor (FXR) agonist in Phase II for NASH, as well as for primary biliary cirrhosis and hepatic fibrosis. While Intercept Pharmaceuticals Inc. and Genfit SA have begun pivotal Phase III studies with their NASH candidates – FXR agonist obeticholic acid (Ocaliva) and dual PPAR alpha/delta agonist elafibranor, respectively – the competition to become first to market in this burgeoning indication linked to metabolic syndrome ranges widely both in terms of targets and mechanisms of action as well as the companies involved. Allergan PLC, Gilead Sciences Inc. and Bristol-Myers Squibb Co. are among the more established and well-heeled players in the race, which may ultimately come down to combination therapy strategies as was the case previously in HIV and hepatitis C.

Celgene Joins Evotec In Its First Neurodegenerative Drug Discovery Effort

Celgene Corp. has made its first big foray into CNS by inking a strategic drug discovery and development collaboration with Germany’s Evotec AG to identify disease-modifying therapeutics for a broad range of neurodegenerative diseases. Under the deal – announced Dec. 15 - the duo will focus initially on areas that include amyotrophic lateral sclerosis, Alzheimer’s disease, Parkinson’s disease, and other neurodegenerative disorders. The plan is to develop novel therapies for a broad range of neurodegenerative diseases, based on Evotec’s industrialized drug screening platform using patient-derived induced pluripotent stem cells (iPSCs) by which high throughput screening in iPSC cell-derived neurons is conducted to identify new therapeutic compounds.
Acadia’s Nuplazid Could Have The Alzheimer’s R&D Curse

Acadia’s Nuplazid (pimavanserin) has met its primary endpoint in a Phase II study in patients with Alzheimer’s disease psychosis – but a secondary endpoint miss in the same study has triggered alarm bells for future development of the product in Alzheimer’s, a historically risky scene, marred by many Phase III failures.

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Acadia Pharmaceuticals Inc. has reported mixed Phase II results for its experimental Alzheimer’s drug, pimavanserin, at a time when the diseases space is being watched with great interest following the recent late-stage failure of Eli Lilly & Co’s solanezumab.

While Acadia presented positive data for pimavanserin, with top-line results showing that the drug met its primary endpoint in the Phase II -019 study in patients with Alzheimer’s disease psychosis, analysts have questioned the durability of the product because of a missed secondary endpoint and marginal efficacy.

In the Phase II exploratory study, pimavanserin met the primary endpoint, showing a significant reduction in psychosis versus placebo as measured by the Neuro-psychiatric Inventory-Nursing Home (NPI-NH) Psychosis score at week six of dosing (p=0.0451). Pimavanserin was generally well tolerated and the safety profile was consistent with what has been observed in previous studies.

However, on the study’s secondary endpoint of mean change in NPI-NH Psychosis score at week 12, pimavanserin maintained the improvement on psychosis observed at the week six primary endpoint but did not statistically separate from placebo.

Acadia plans to continue development of the drug in this Alzheimer’s indication, the company’s president, CEO and director, Stephen Davis, said on a Dec. 20 conference call.

Srdjan Stankovic, executive vice president and head of R&D at Acadia, added on the conference call that he is eager to assess these data more before launching a Phase III study for pimavanserin. “Frankly, [I am] excited about the treasure trove of information that we are able to analyze in these data,” he said. “It will certainly guide us very well where we need to go in our next trial and in our pivotal trial in this indication.”

Stankovic said the secondary endpoint miss was “due to improvement observed in placebo from week six to week 12. We did not see a separation between placebo and pimavanserin at that point,” he said.

Acadia’s CEO added that the company will “leverage” the Phase II data “for the benefit of future study designs to help us understand what we should do the same and what we would consider changing.” In the Phase II study, Davis highlighted that “importantly, pimavanserin was able to demonstrate antipsychotic effect without worsening cognition.”

Leerink analysts also highlighted concerns about the secondary endpoint miss in a Dec. 21 research note. They said key opinion leaders they had spoken to called the Phase II data a “minor positive signal.” The KOLs had feelings of skepticism that the results would not be able to be replicated in a large Phase III study, Leerink analysts wrote.

However, “with no approved treatments for Alzheimer’s psychosis and meaningful safety issues with the standard-of-care, specialist commentary suggests that pimavanserin would (even with a modest effect size) still get meaningful traction in Alzheimer’s in the event that it were approved,” Leerink analysts note.

The unmet need in Alzheimer’s is huge and drug development has faced many setbacks over the last decade. Most recently, Lilly’s solanezumab product failed in several Phase III studies in different Alzheimer’s patient populations. Per the Alzheimer’s Association, there are approximately 5.4 million Alzheimer’s patients in the US, approximately one-half of whom are diagnosed with the disease. It is the fifth leading cause of death for people aged 65 and older.

Acadia’s chief Davis noted on the Dec. 20 conference call about pimavanserin that, “Today, there are no drugs approved by the FDA to treat Alzheimer’s psychosis.” Atypical antipsychotics are frequently used off-label to treat psychosis in Alzheimer’s patients to fill the treatment void.

PIMAVANSELIN’S PARKINSON’S APPROVAL

Study -019 is the first to test pimavanserin, a selective serotonin inverse agonist (SSIA) targeting 5-HT2A receptors, in patients with Alzheimer’s disease psychosis. However, the drug is already on the market, having been approved by the FDA in April 2016 for delusions associated with Parkinson’s disease psychosis, under the trade name Nuplazid.

With the results of Study -019, pimavanserin has now demonstrated an antipsychotic effect in three major CNS disorders: Parkinson’s disease psychosis, schizophrenia and Alzheimer’s disease psychosis.

PHASE II STUDY DETAILS

In the -019 study, a 3.76 point improvement in psychosis was observed in the pimavanserin treatment arm at week six compared to a 1.93 point improvement for placebo. Baseline scores were 9.52 for pimavanserin and 10 for placebo-treated group.

On the matter of cognition, pimavanserin did not impair cognition over the course of 12 weeks of treatment and was similar to placebo as measured by the Mini-Mental Status Exam.

Based on a preliminary analysis of safety data, the most common adverse events reported were falls, urinary tract infection and agitation. The mortality rate was the same in the pimavanserin and placebo treatment groups. The mean age of patients in the study was 86 years.

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**Advair: A Big Generic Opportunity And A Big Question Mark In 2017**

**JESSICA MERRILL, jessica.merrill@informa.com**

**Takeda's Velcade, Pfizer's Viagra and Gilead's Viread are among the brand drugs expected to face generic competition in the US for the first time in 2017. One unknown is Advair.**

The launch of a generic version of GlaxoSmithKline PLC's blockbuster asthma drug Advair Diskus (fluticasone/salmeterol) in the US could be one of the biggest commercial opportunities for generic manufacturers in 2017, but it is still uncertain whether or not FDA will pave the way for one to reach the market.

Mylan NV and Hikma Pharmaceuticals PLC both confirmed FDA has accepted their ANDAs to market generic versions of Advair, with action dates of March 28 and May 10, 2017, respectively. But Advair is considered a complex small molecule – a combination of two drugs delivered to the lungs through a specific dry powder inhaler – so there is no certainty of a first-cycle approval by the agency, which has struggled with the approvability requirements for respiratory generics.

The complexity around the development of a generic version of Advair is why the product has maintained exclusivity beyond its patent life. The drug components of Advair lost patent protection in 2010, though the device only lost patent protection in 2016.

Payers are eager for a substitutable generic that could help reduce costs in the expensive respiratory categories, including asthma and chronic obstructive pulmonary disease; they are already pitting competitors against one another to secure significant price concessions. The availability of a generic would likely impact other bronchodilators in the category beyond branded Advair, like AstraZeneca PLC's Symbicort (budesonide/formoterol) and GSK's next-generation, once-daily ICS/LABA Breo Ellipta (fluticasone/vilanterol).

In addition to Mylan and Hikma, Teva Pharmaceutical Industries Ltd. and Novartis AG's Sandoz are racing to bring their own generic versions to market. In October, Sandoz filed a citizen petition with FDA asking the agency not to approve generic versions of Advair.

**A MORE THAN $2BN BRAND OPPORTUNITY**

The opportunity is significant, despite the fact that competition, payer pressure and GSK's own new respiratory entries, including Breo, have chipped away at Advair's blockbuster sales over the last five years. US sales of Advair were $1.87bn ($2.35bn) in 2015. If a generic drug is indeed approved, it will address one of the biggest generic opportunities in 2017.

Other big sellers that are expected to face their first generic competition in the US in 2017 are Takeda Pharmaceutical Co. Ltd's multiple myeloma backbone Velcade (bortezomib), Gilead Sciences Inc's HIV staple Viread (tenofovir/disoproxil) and Pfizer Inc's erectile dysfunction blockbuster Viagra (sildenafil).

Merck & Co. Inc.'s cholesterol-lowering drug Zetia (ezetimibe) faced the first generic rival Dec. 12 so the impact on Merck's franchise and likely the combination pill Vytorin (ezetimibe/simvastatin), now made up of two active ingredients available generically, will be felt throughout 2017. Vytorin also lost patent protection in April 2017. US sales of Zetia and Vytorin were $2.52bn and $1.25bn in 2015.

Being first generic to market when it comes to Advair will be important in terms of the traditional window to make the most money while the exclusivity period lasts. But the high barriers to entry for rivals is also why GSK believes it can continue to extract life out of branded Advair even after generics enter the market.

Mylan, during recent financial calls, said it feels confident about a first-round approval for its generic because of encouraging dialogue with the agency. If Mylan does secure an approval, it will be a big win for the company, which has faced significant backlash and pressure from the public over the price increases it has taken for the allergy medicine EpiPen (epinephrine). Ironically, Mylan has benefited from the inability of generic rivals to bring and keep a generic version of EpiPen on the market because it is also complex to make.

Fueled partly by that scandal, FDA has come under fire from Congress for not getting competitors to expensive drugs like EpiPen to market faster. The agency recently announced it will establish an eight-month priority review path for certain high-quality ANDAs under the reauthorized generic drug user fee program beginning in fiscal year 2018.

BTG analyst Timothy Chiang speculated on the market opportunity for generic Advair in a Nov. 28 research note: “Assuming there are two ANDAs approved in 2017 and pricing drops by 50%, we think the first generic company to enter could generate significant sales at market formation, with sales in excess of $200m within the first six months of launch.”

Given the potential opportunity, he said Mylan's shares are attractive due to recent devaluation of the company's stock following the backlash of the EpiPen pricing scandal. But analysts are mixed on the chances that the first ANDA filers could receive a first-cycle approval.

Leerink analyst Jason Gerberry said in an Oct. 21 research note said that while generic Advair will eventually reach the market, there is a low probability of a first-round approval. The investment firm conducted an analysis of FDA approval rates for complex generics earlier this year and found the average review time for complex ANDAs is in the 66-month range, 55% to 60% longer than standard 42-month reviews.

“If we were to assume a 50% to 100% longer review clock to Mylan’s g-Advair review (22 to 30 months review versus 15 months), then we estimate the earliest possible approval would occur in mid-to-late-2018,” Gerberry speculated.

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Novartis AG has pulled its EU application for Arzerra (ofatumumab) in combination with bendamustine for the treatment of relapsed chronic lymphocytic leukemia (CLL) – a setback for the company which needs to up the drug’s use in the second-line setting.

Arzerra used with bendamustine (Teva Pharmaceutical Industries Ltd; Treanda) is a new combination, but the European Medicines Agency’s scientific committee – the Committee for Medicinal Products for Human Use – put several questions to company after reviewing Novartis’s filing for the product. These queries focused why Novartis did not submit data comparing Arzerra in combination with bendamustine against any other CLL therapies. Had Novartis not withdrawn its application, the CHMP would not have approved the new combination at this time, the committee said in its assessment of the filing.

The CHMP said that Novartis presented with results from a study involving 53 patients with relapsed CLL. All patients received Arzerra plus bendamustine in the trial and Arzerra was not compared with any other treatment. The main measure of effectiveness was based on the number of patients who showed a partial or complete response to treatment.

While Novartis responded to the committee’s initial list of questions about its filing, the CHMP said the answers were not satisfactory. Novartis then withdrew its application for a change to the marketing authorization for Arzerra on Nov. 8, 2016.

The committee was also concerned that the data presented by Novartis were in a small number of CLL patients and that the number of complete responses was not significant. “Although some patients (39 out of 53) responded to the combination Arzerra plus bendamustine, only a few patients (6 out of 53) had a complete response, and these data were not supported by further study results,” the CHMP noted.

The EMA’s scientific committee did not consider the data robust enough to approve the new combination of Arzerra and bendamustine as a treatment for relapsed CLL.

Novartis told Scrip it was now “evaluating its options” for Arzerra as a treatment for relapsed CLL in Europe. However, it highlighted that earlier this month, the European Commission granted a marketing authorization in the EU for the use of Arzerra in combination with fludarabine and cyclophosphamide for the treatment of adult patients with relapsed chronic lymphocytic leukemia. However, this is not an ideal combination as many relapsed CLL patients are fludarabine refractory.

The Swiss big pharma picked up Arzerra, a fully human CD20-targeting monoclonal antibody, from GlaxoSmithKline PLC in 2014 as part of a deal for GSK’s oncology portfolio. Novartis has since acquired the rights for the drug from GSK in autoimmune indications as well.

Arzerra has been authorized in the EU since April 2010; it was designated an orphan medicine for CLL in November 2008. Arzerra plus bendamustine is used as a combination therapy already in previously untreated CLL patients who cannot be treated with fludarabine (Sanofi’s Ofotora).

**CLL MARKET CHANGES**

Novartis wants to expand the use of Arzerra and bendamustine into relapsed CLL patients to fill a large unmet need. The company also needs to expand its reach for Arzerra within CLL now because the therapy area has seen a dramatic change in the number of available therapies in the last two years. Predominantly, Johnson & Johnson/AbbVie Inc’s Imbruvica (ibrutinib) has rapidly established itself as standard of care in relapsed/refractory CLL; worldwide sales of the drug topped $1bn in 2015. Though prognosis for this relapsed disease population is still poor, the introduction of Imbruvica and its fellow Bruton’s tyrosine kinase (BTK) inhibitors have changed treatment dynamics significantly. As such, Novartis needs to establish itself in these second- and third-line treatment settings to stay relevant in CLL.

However, Datamonitor Healthcare analysts Dominique Fontanilla noted that even another approval for Arzerra in relapsed CLL would not help the product win out against its increasing number of competitors. “One of the only potential areas that Arzerra had to grow in was the maintenance setting where it has won approval in the US, but it was rejected in the EU based on a lack of corroborating overall survival and progression free survival endpoint data,” Fontanilla said. “Arzerra will be used in the third-line settings or later – it just hasn’t been able to demonstrate the level of clinical efficacy as other drugs such as Rituxan and Imbruvica.”

Arzerra needs to keep up with other available anti-CD20 therapies, such as Roche’s mainstay Rituxan (rituximab) – which, in combination with chemotherapy, has been physicians’ choice treatment for relapsed CLL since its approval in this population. Roche’s product has five approved indications, including non-Hodgkin’s lymphoma, CLL and rheumatoid arthritis; but the drug’s main patents start to expire in the US in 2018, following expiration of some patents in Europe in 2013, and biosimilars are in development. Roche’s follow-on product to Rituxan, Gazyva (obinutuzumab), won European approval in combination with chlorambucil chemotherapy for the treatment of people with previously untreated CLL in 2014 – however, the drug has not yet won approval for relapsed CLL. Phase II studies are ongoing for Roche’s follow-on drug in this second-line setting.

Published online 20 December 2016
Novartis Takes On Colombia Over Glivec Pricing
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Novartis is taking Colombian authorities to court over moves to cut the price of its anticancer Glivec (imatinib) and warns that the intellectual property rights of other products are under threat. Companies selling hepatitis C drugs should pay attention as their products could be next to face similar measures.

Novartis AG is fighting what it thinks are unfair tactics by the Colombian health ministry to undermine intellectual property rights and cut the price of its anticancer Glivec (imatinib). It claims it is taking action to stop the same thing happening to other pharmaceuticals. Indeed, pressure is mounting from civil society to make hepatitis C treatments, including Gilead Sciences Inc’s Sovaldi (sofosbuvir), Bristol-Myers Squibb Co’s Daklinza (daclatasvir) and Merck & Co Inc’s Victrelis (boceprevir) more accessible.

In the latest development in the wrangling over Glivec, the Colombian health ministry has announced the national pricing commission’s decision to cut the price of Glivec by 44%, from 368 pesos (US$0.12) per mg to 206 pesos (US$0.7 per mg). The move marks a “full stop in a new chapter on pharmaceutical policy,” says the health ministry. “That chapter includes not only the first ever declaration of public interest for a medicine in the country, but which also turns Colombia into a pioneer of such declarations for cancer drugs,” it said in a statement published on December 21.

Glivec, which is on the WHO essential medicines list, has been the source of much contention in Colombia for some time. When Novartis originally brought the drug to Colombia, its request for a patent was rejected. However, Novartis kept the drug on the market, which it shared with generic rivals, until 2013 when the patent office granted the patent. In 2014, civil society groups, IFARMA, Misión Salud and CIMUN, brought a request that the government issue a compulsory license for the drug, arguing the patent was weak, that the drug was expensive and that generic competition could bring the price down. The declaration of public interest (DPI) was published in June as the prelude to a price cut, rather than a compulsory license. Following the DPI, the government published new regulations outlining new methodology for fixing the price of a medicine, which was how the new price for Glivec was formulated.

It is the declaration of public interest that Novartis is challenging and it says it has filed an annulment action. Novartis claims that financial losses are not its main motivation for challenging the DPI, particularly given that Glivec’s patent rights expire in 2018. “We are pursuing this case out of concern for the repercussions it could have for the intellectual property system and future of innovative medicines. Novartis believes that the circumstances surrounding the DPI for Glivec could create a damaging precedent that could be applied to other patent-covered treatments in Colombia and other countries. At a stroke, this could destroy intellectual property - one of the fundamental frameworks the biomedical research sector relies on for its existence,” said the company.

Novartis wants to show that there are no reasonable grounds for the DPI for the following reasons: there are already non-infringing generics on the market; there are “no access issues for Glivec in Colombia”; and because Glivec’s price is lower than the price demanded by local regulations and has already been lowered twice. “In fact, the Glivec price in Colombia is one of the lowest globally,” said Novartis.

The groups that initiated compulsory license proceedings say the DPI and price reduction are necessary to protect Colombia’s public health budget. They accuse Novartis of picking and choosing its arguments for convenience. They claim that there are no generic versions available on the market. “Glivec is the beta-polimorph of imatinib. There are no generic versions of the beta-polimorph because if they were they would be infringing the patent. The generic versions that Novartis says that are in the market are generic of the alpha-polimorph,” they told Scrip.

Although they welcome the price reduction, they would like to see bigger savings for the public health system and want the patent office to proceed with a compulsory license. This could lead to a price of just 68 pesos per mg and was the price of one of the generics available on the market before Glivec’s patent was granted.

Meanwhile, the NGO, Health Action International says it “supports the move to issue a declaration of public interest for imatinib (marketed as Glivec), which is on the WHO’s essential medicines list and which Novartis was selling for a price in Colombia per patient that is approximately twice the Colombian gross national income (GNI) per capita.”

“There was no unwillingness from Novartis to voluntarily lower the price in Colombia and given that Novartis had already made 47bn in global sales on Glivec there is surely no rationale for earning back R&D costs. Colombia is a small market for Novartis which means it has less clout in price negotiations and they are fully dependent on companies to lower the price of drugs voluntarily. If this does not happen they are fully entitled to use the legal means available and compliant with international law to lower the price of a drug,” HAI told Scrip.

HEPATITIS C DRUGS NEXT?
Gustavo Morales, president of AFIDRO, is concerned about the precedent that the DPI and price cut will set. “If Glivec is a public interest medicine every other medicine, especially those that are complex, high cost and innovative, could be subject to the same treatment,” he says. He points to procedures to issue DPI for hepatitis C treatments that are underway.

The same groups have requested that all hepatitis C treatments, including sofosbuvir, daclatasvir, simprevir, boceprevir, and telaprevir, be declared of public interest. They claim such action is necessary because the latest treatments are unaffordable in several countries for both out of pocket payers and public healthcare systems. HAI adds: “The prices of these new but highly effective hepatitis C treatments are so high that they are unsustainable even for European countries. For Colombia the med would be too expensive in the absence of a voluntary price reduction by the pharmaceutical company.”

AFIDRO supports Novartis’ legal action and in the new year will challenge the government on the new pricing regulations for drugs that have been declared of public interest, says Morales. He claims that events in Colombia may make companies think twice about launching there.

Published online 22 December 2016
Ex-Sanofi Exec Stoeckli Primes Glenmark’s Cancer Therapy Ambitions

Glenmark’s president and chief scientific officer, Dr Kurt Stoeckli, believes that some big pharma companies may have missed the opportunity to embark on immunotherapy cancer treatment R&D “at the right time” and tells Scrip that there is room for the Indian firm to provide competitive assets in the space. Stoeckli, an ex-Sanofi senior executive, also outlines why the upside potential of Glenmark’s BEAT antibody technology platform is “remarkable.”

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Dr Kurt Stoeckli, President and Chief Scientific Officer, Glenmark

“I just found that this is a perfect match, where I could bring complementarity and experience that I have gone through in big pharma and the portfolio is so exciting in terms of potential for the next 5-10 years,” Stoeckli told Scrip in an exclusive interview at Glenmark’s Mumbai headquarters.

Stoeckli, who took charge as Glenmark’s president and chief scientific officer (CSO) in October, believes that it is essential for Glenmark to be able to move ahead with a “core segment” of projects that it establishes on its own end-to-end capabilities and be “independent.” Glenmark is strategically focused on three core therapy areas – oncology, dermatology and respiratory.

“Should this go on in a very successful way even the core segment is rich enough to think about partnering especially in immunotherapies where lots of combination concepts are coming up. I consider this as very value-creating because some of these potential partners will have complementary assets, experience and access to markets and regions,” he said.

BISPECIFIC ANTIBODIES

Stoeckli, who also spent several years in drug discovery at Novartis/Sandoz in Switzerland, is particularly upbeat about Glenmark’s bispecific antibody portfolio based on the firm’s proprietary BEAT antibody technology platform. The Bispecific Engagement by Antibodies based on the T-cell receptor (BEAT) platform facilitates the efficient development and manufacture of antibodies with dual specificities.

For instance, Glenmark’s HER2xCD3 bispecific antibody (GBR 1302), he explained, has the potential to be highly active on tumor cells that have low to moderate level of expression of HER2, which is where the current standard of care is “just not sufficient” and has limitations with Herceptin (trastuzumab) or conjugates of Herceptin.

“So here is where we may be able to differentiate. For us it is the front runner, already in Phase I clinical trials; the molecule has an important role to play for us to demonstrate and confirm the BEAT platform utility,” Stoeckli said.

HER2, also known as HER2/neu, or receptor tyrosine-protein kinase erbB-2, is the target of the antibody cancer drugs trastuzumab, pertuzumab and trastuzumab emtansine. A Glenmark investor presentation dated Dec. 19 claimed that GBR 1302 could bring about “faster and more complete” killing of tumor cells as compared with current first- and second-line treatments. GBR 1302 is also being studied in gastric cancer. Other BEAT-based oncology biologics include GBR 1342 (a CD38xCD3 bispecific antibody) being developed for multiple myeloma and potentially other malignancies of hematopoietic origin and GBR 1372, targeting EGFR through redirected killing by T cells.

Stoeckli believes GBR1372, being developed for colorectal cancer, represents an “enormous opportunity” for the company.

“KRAS mutations are one of the most unmet needs in cancer therapy with a broad range of carcinomas. This is exactly where drugs like Erbitux (cetuximab) are not really effective enough and have limitations - where the body has by definition designed more than 10 mechanisms of resistance and where we have mechanistically a very good way to overcome the KRAS mutation problem,” he explained.

BEAT – RANGE OF POSSIBILITIES

Stoeckli suggested that Glenmark’s BEAT platform has a “competitive edge” compared with others including Roche’s CrossMAb technology invented to produce bispecific antibodies.

Glenmark’s platform, he says, is efficient in “playing with new targets” that come up and are of clinical relevance; flexibility beyond CD3-mediated engagement immunocytes is another plus that it brings, besides scalability.

“The stability and robustness of BEAT molecules is an important aspect of industrialization. The BEAT platform is designed such that you can efficiently purify what is up-scaled and can bring it rapidly to a point where you can supply the clinical studies with sufficient quantity and quality,” Stoeckli explained.

On whether Glenmark would consider an outright deal for the BEAT platform, Stoeckli said: “We do not say no to this upfront; we consider any sort of partner-
Amgen Inc. acquired the BiTE [Bispecific T cell engager] platform behind Blincyto (blinatumomab) when it snapped up Micromet Inc. in 2012 for over $1bn. In June this year, Novartis AG announced a collaboration and licensing agreement with Xencor Inc. for the development of bispecific antibodies for treating cancer; the deal includes rights to use Xencor’s antibody engineering platform to develop up to 10 additional antibodies for immuno-oncology and other diseases.

But Stoeckli clarifies that the BEAT platform could also be used for partnering on specific projects that the Indian firm has already ongoing.

“This would be a strategic partnership. And this means any sort of co-development, co-marketing – but we would partner and it’s not just a simple out-licensing. In addition, we could talk with someone who wants to have access to the technology per se for a certain number of targets they want to work on - we don’t purely exclude this; it is within the range of our thoughts.”

**COMBINATION THERAPY**

Significantly, Glenmark’s Dec. 19 investor presentation also highlighted a new type of “highly potent” OX40 agonist (GBR8383).

Glenmark’s OX40 agonist, in combination with programmed death (PD)-1 and other checkpoint inhibitors, is expected to be potentially very active in boosting the T cell response.

“We consider this as a typical example of a combination therapy in a broad sense in a variety of cancers. We have already made clear that we see great potential for the OX40 agonist to boost the effect of our CD3 engagers, but it goes beyond,” Stoeckli said.

Glenmark maintains that preclinical data on GBR8383 confirms a strong agonistic effect upon the checkpoint OX40 in comparison with other OX40 agonists currently in clinical trials. The company believes that GBR8383 has potential to enhance current immunotherapies (PD-1, PD-L1, CTLA4).

“Checkpoint inhibitors, immunotherapies require combination therapy in the future because the cancer site mechanistically predicts that you have to activate the immune system in multiple ways,” Stoeckli adds. Experts say that, theoretically, an OX40-targeted drug could be used to stimulate an immune response and it could be combined with a PD-1/PD-L1 [programmed cell death-ligand 1] inhibitor that would prevent tumor cells from evading the generated response.

**THE BIG THING**

Stoeckli also says that the big thing with immunotherapies is its potential to reach more patients; right now, even the “best of the best” immunotherapies, he says, reach only 30% response rates, at best.

“Great progress has been made and if you look at what has happened for the patients [who respond] - it has really changed their lives. They have a very different perspective. But there is huge unmet medical need for patient populations that are not responding,” he notes.

Stoeckli says that breakthroughs in cancer therapy will find the right combination that can change the response rates.

“This is what we are working on, molecules that engage and further boost, modulate in a positive way, the immune system.”

Glenmark’s new CSO also believes that some big pharma companies missed the opportunity to get on board with immunotherapy cancer treatments at the right time.

“So they are looking at partnerships to replenish their own pipelines, get access to competitive edge technologies. Nobody has, to date, been able to do everything on their own since nobody knows exactly which combinations will be most effective,” Stoeckli said, referring to J&J’s collaboration with Genentech and how Pfizer Inc. and Merck & Co. Inc. are going into combination therapy approaches either internally or via partnerships.

“There is room for Glenmark to come in and provide competitive assets,” he said.

In March 2016, Janssen Inc. and Genentech Inc., part of the Roche group, entered a clinical trial collaboration pact to initiate certain studies to determine the safety and tolerability of daratumumab (Darzalex), the first CD38-directed monoclonal antibody, in combination with atezolizumab, an investigational mAb designed to bind with a programmed cell death-ligand 1 (PD-L1). 

*Published online 23 December 2016*

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**Christmas Cheer For Cipla’s Seretide Equivalent In The UK**

Cipla’s generic version of Seretide has finally received regulatory approval in the UK, bringing much needed relief to investors and opening up more competition for GlaxoSmithKline on its home turf.

Cipla Ltd. has received final approval from the UK MHRA for its fluticasone + salmeterol metered dose inhaler (Serefio), ending several months of investor anxiety over the product’s debut on the British market.

Cipla said that its Serefio 25mcg/125mcg and 25mcg/250mcg are generic “equivalent” versions to GlaxoSmithKline PLC’s Seretide inhalers for asthma. Mylan NV, in June last year, launched the first bioequivalent alternative to GSK’s Seretide Evohaler (salmeterol xinafoate/fluticasone propionate), branded as Sirdupla in the UK.

Cipla said that it expects to launch Serefio in the UK through a partner “in the coming weeks,” but gave no specifics on the alliance.

Details on the UK MHRA website cite Fannin (UK) Ltd as the market authorization holder of Serefio and lists Cipla’s Goa unit as the manufacturing site.

Cipla did not immediately respond to email queries pertaining to the product’s MHRA approval, including aspects around substitutability with Seretide.

Industry experts tracking the development, however, suggested that Cipla’s generic product is a substitutable version of GSK’s Seretide inhaler and that the UK National Health Service (NHS) now has a cost-effective asthma therapy on hand.

Cipla had earlier launched a “cost-efficient” generic version of GlaxoSmithKline’s Advair/Seretide in several European markets.

*Published online 23 December 2016*

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**Click**

Just The Tonix: New York Biotech Has Breakthrough Drug For PTSD

Tonix Pharmaceuticals Holding Corp., founded in 2007 and based in New York, spent the first ten years of its life developing lead compound, TXN-102, for the treatment of chronic pain condition fibromyalgia syndrome (FMS). But after a setback in Phase III for this indication earlier this year and positive results in another of its earlier stage clinical trials for the same drug in post-traumatic stress disorder, Tonix decided to shift gears and put all its resources into the latter condition. Since committing to this change of direction in September this year, the company has won a breakthrough therapy designation from the US FDA on December 19, 2016 for the development of TXN-102 in PTSD – a condition currently considered an urgent unmet need in the US due to a huge spike in suicides in military veterans. CEO and principal founder of Tonix, Dr. Seth Lederman, told Scrip that the FMS program “narrowly missed” in Phase III and still has importance, but the company simply cannot afford to pursue both indications simultaneously and believes the PTSD program has the legs to get all the way to market. The FDA’s breakthrough therapy designation is intended to expedite the development and review of a drug candidate. The benefits of breakthrough therapy designation include the eligibility for priority review of the New Drug Application (NDA) within six months instead of 10 months and rolling submission of portions of the NDA, in addition to an organizational commitment involving the FDA’s senior managers contributing significant guidance to the company. jessica.merrill@informa.com, 28 Dec 2016

Clovis Transitions To Commercial Stage On Rubraca Approval

Clovis Oncology Inc. will launch its first commercial drug, Rubraca (rucaparib), this week at a wholesale acquisition cost of $13,740 for a 30-day supply, or $164,880 for a year of treatment. The company announced the FDA approval of Rubraca under an accelerated approval Dec. 19 for the treatment of patients with BRCA mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with two or more chemotherapies. CEO Patrick Mahaffy said during a same-day conference call that many factors went into the pricing decision, including the clinical benefit of the drug, the market for oncology drugs and the need for the company to reinvest in development to bring new innovative therapies to market. Patients should be selected for treatment with Rubraca based on an FDA-approved companion diagnostic developed by Foundation Medicine Inc. FDA simultaneously approved the FoundationFocus CDxBRCA companion diagnostic for use with Rubraca, the first next-generation sequencing-based companion diagnostic approved by FDA. Rubraca will be the second poly ADP-ribose polymerase (PARP) inhibitor approved for cancer, and it appears that it will have an advantage over the competition, AstraZeneca PLC’s Lynparza (olaparib), which was approved in December 2014 for advanced BRCA mutation ovarian cancer after three prior treatments. The labeling advantage for Clovis could be short-lived, however. Tesaro Inc. is also awaiting FDA approval of a PARP inhibitor, niraparib, in BRCA ovarian cancer. In the Phase III NOVA trial, niraparib, tripled progression-free survival compared to placebo in patients on maintenance therapy with platinum-based chemotherapy, and the news doubled the company’s stock price when it was announced June 29. jessica.merrill@informa.com, 19 Dec 2016
Allegan, IronwoodSeek To Divide And Conquer IBS

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Allegan PLC and Ironwood Pharmaceuticals Inc. have released promising topline Phase IIb data for two novel formulations of their irritable bowel syndrome (IBS) treatment Linzess (linaclotide) that they hope will boost the franchise for many years to come by offering better and faster pain relief in constipation-predominant patients and opening up the product for use in other IBS subtypes, and possibly even other GI disorders.

The two formulations, known as CR1 and CR2, are designed to deliver the drug at two separate locations in the gastrointestinal tract where they are expected to produce slightly different therapeutic effects for different patient subgroups.

Linaclotide is a guanylate cyclase-C (GC-C) agonist that was first approved in the US in 2012 for the treatment of adults with irritable bowel syndrome with constipation (IBS-C) or chronic idiopathic constipation (CIC). It is marketed by Ironwood and Allegan in the US as Linzess, and by Allegan in Europe as Constella where it is approved for the treatment of adults with moderate to severe IBS-C.

Based on non-clinical studies linaclotide is thought to act in two ways after binding to the GC-C receptor within the intestinal epithelium, resulting in increased intestinal fluid secretion and accelerated transit, and a decrease in the activity of pain-sensing nerves in the intestine. The companies note, however, that the clinical relevance of the effect on pain fibers has not been established.

“Our intent was to dial up or down the two components of the linaclotide mechanism of action – the effect on pain-sensing nerves and the effect on fluid secretion – by varying where the drug is delivered,” explained Dr Mark Currie, chief scientific officer and president of research and development at Ironwood.

The colonic-release 1 (CR1) formulation is designed to target delivery of linaclotide to the distal small intestine and colon, where the majority of the abdominal pain associated with IBS-C is believed to originate. The Phase II clinical trial of this formulation looked at whether CR1 could further decrease the activity of key pain-sensing nerves in the distal small intestine and colon while maintaining an effect on fluid secretion. The long-term aim is to have a version of Linzess with increased pain relief for IBS-C patients compared with the current immediate-release (IR) formulation.

The colonic-release 2 (CR2) formulation delivers the drug to the proximal ileum and colon to relieve abdominal pain without any of the diarrhea side-effects. This means it could be used to relieve pain in IBS patients without constipation as the predominant symptom, thus expanding the potential patient population for Linzess, possibly even to diseases like ulcerative colitis and diverticulitis.

Tom McCourt, Ironwood’s chief commercial officer, said: “We believe the potentially enhanced clinical profile of linaclotide CR1 could support further growth of the Linzess franchise from $1bn in US net sales by 2020 to potentially greater than $2bn in peak US net sales.” Ironwood and Allegan said they were pursuing patent protection for CR1 and CR2 that, if issued, is expected to provide patent coverage into the mid-2030s.

The data are also timely, coming shortly after Synergy Pharmaceuticals Inc. announced that it now has positive data from two Phase III trials for its rival GC-C agonist plecanatide showing an efficacy that is roughly comparable to Linzess but with a lower rate of diarrhea.

CR1 STUDY

The new topline linaclotide results are from two Phase IIb trials – one for each formulation – with the data for CR1 considered the most convincing by analysts. The companies now intend to discuss their Phase III development plans with the US FDA and expect to begin a Phase III trial in adults with IBS-C of CR1 and a further Phase IIb study of CR2 in the second half of 2017.

Topline data from the placebo-controlled, dose-ranging Phase IIb clinical trial evaluating the CR1 formulation in 532 adult IBS-C patients showed numerically greater abdominal pain improvement with CR1 300 mcg compared with placebo and with the 290 mcg IR formulation of linaclotide. The companies noted that the trial was exploratory in nature and comparisons to placebo were evaluated using nominal p-values.

The most common adverse event was mild-to-moderate diarrhea, which was reported in 10.4% of patients on CR1 300 mcg compared to 1.5% of patients on placebo and 13.6% of patients on IR 290 mcg.

Analysts thought the data encouraging. Those at Biomedtracker pointed to the comparatively earlier onset of action compared with the marketed formulation as a potential differentiator. “[The] strategy appears to work as CR1 had numerically greater abdominal pain improvement while retaining its efficacy on constipation... Linzess currently takes six weeks to improve pain symptoms so a faster onset could be clinically significant.”

Umer Raffat from Evercore ISI said he believed that the data were strong enough to make the possibility of success over the IR version at Phase III a reasonable hope.

Nevertheless, he believes that “the true upside is on CR2 formulation”, which is being positioned as a pain reliever for indications beyond IBS-C, but he noted that the data are “not super clear just yet”.

CR2 DATA

The double-blind, placebo-controlled, dose-ranging Phase IIb trial for the CR2 formulation randomized 532 adult patients with IBS-C. Again, the trial was exploratory in nature and comparisons to placebo were evaluated using nominal p-values.

“These findings support further investigation of CR2 in specific GI indications where patients experience abdominal pain but are not necessarily constipated, such as IBS-mixed, IBS with diarrhea, ulcerative colitis and diverticulitis,” the companies said.
**AbbVie Makes Further Inroads In Oncology As Humira Loss Looms**

**EMILY HAYES** emily.hayes@informa.com

New data position BCL-2 inhibitor Venetoclax, partnered with Roche, for roles in multiple myeloma and acute myeloid leukemia, among other indications beyond chronic lymphocytic leukemia.

AbbVie Inc. is making inroads in oncology, expanding the potential reach of its first approved hematological cancer drugs Imbruvica and Venclexta while advancing new pipeline candidates ahead of patent expirations for the blockbuster tumor necrosis factor inhibitor Humira.

Oncology has represented a newer, promising growth area for AbbVie, and the company has been investing heavily in the pipeline for this therapeutic area through partnerships, in-house development and ambitious expansion plans for the first approved drugs. Growth in areas new and old are important for AbbVie as the company prepares to face sales losses due to biosimilar products competing with Humira (adalimumab), the top-selling treatment for arthritis and other autoimmune conditions that generated sales of $6.43bn in this year's third quarter.

It's not clear when biosimilars for the TNF inhibitor will hit the market, even after US FDA approval in September for Amjevita (adalimumab-atto), Amgen Inc's biosimilar version of Humira. But while a patent dispute between AbbVie and Amgen will delay Amjevita's launch beyond 2017, competition clearly is nipping at Humira's heels, and AbbVie is betting big on cancer drugs to help fill the product's shoes.

Oncology is one of the company's most active areas of development. Some 13 drugs are in clinical development for 22 different indications, including hematological malignancies and solid tumors.

AbbVie's BTK inhibitor Imbruvica (ibrutinib), which is partnered with Johnson & Johnson unit Janssen Biotech Inc., has proven to be a big success, with approvals in chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), Waldenström's macroglobulinemia, and many more indications on the way.

The partners presented impressive long-term data for Imbruvica in CLL during the American Society of Hematology (ASH) annual meeting from Dec. 3-6 in San Diego, as well as Phase I/II data showing a 67% objective response rate in graft-versus-host disease, a condition that may occur if donor cells attack the body after stem cell and bone marrow transplants.

AbbVie reported sales of $659m for Imbruvica in 2015 and partner J&J reported $689m. Each of seven new filings in coming years will bring another $500m in revenue, Abbvie estimates.

Imbruvica is under FDA review for marginal zone lymphoma; in addition to graft-versus-host disease, it is in Phase III for indolent non-Hodgkin lymphoma (INHL), follicular lymphoma (FL), B-cell NHL and diffuse large B-cell lymphoma (DLBCL).

AbbVie also is in Phase II for acute myeloid leukemia (AML) and multiple myeloma.

**VENCLEXTA’S PROMISE IN MYELOMA**

AbbVie also has high hopes for its BCL-2 inhibitor venetoclax, partnered with Genentech Inc., which was approved for second-line CLL with 17p deletions in April in the US, where it is marketed as Venclexta.

Venetoclax was approved this month in Europe, where is branded as Venclyxto, for second-line treatment of CLL with 17p deletions. Only about 10% of treatment naïve CLL patients have 17p deletions, but the indication is a gateway into much broader use, although it's dominated by Imbruvica.

Chief financial officer Bill Chase acknowledged during AbbVie's third quarter earnings call Oct. 28 that the market for relapsed/refractory CLL with the 17p deletions was small — worth about $300m in sales — and Imbruvica has a strong leadership position with more than a 50% share of that market.

Furthermore, new late-stage competitors in CLL are on the near horizon — AstraZeneca PLC/Merck & Co. Inc/Acerta Pharma BV's BTK inhibitor acalabrutinib and TG Therapeutics Inc's anti-CD20 ublituximab.

Chase described venetoclax as an asset that offers significant growth potential over the longer term, with expansion into earlier lines of therapy and other hematologic malignancies. For instance, AbbVie is looking forward to results from the MURANO study, which tests venetoclax with Roche's Rituxan (rituximab) in second-line CLL in the first half of 2017 to support broader labeling.

Data for venetoclax in multiple myeloma generated buzz at the ASH annual meeting. In a Phase I study of relapsed/refractory myeloma with the t(11;14) translocation, the most common chromosomal translocation in multiple myeloma, the objective response rate with Venclexta as a single agent was 40%, almost twice as high as the response in the overall population.

Gary Gordon, vice president of oncology development at AbbVie, said in an interview that this could be one of the first applications of biomarkers in selecting multiple myeloma patients for treatment.

"These results are particularly strong given that patients in this study were heavily pre-treated with a median of five prior therapies. Subsequent biomarker analysis further revealed that patients in this subpopulation with high BCL-2 to BCL-XL ratio had the highest response rates. This is significant in that it essentially identifies a subset of multiple myeloma patients that would most benefit from Venclexta mono-therapy," Biomonitor analyst Dustin Phan said.

In a separate Phase Ib study of Venclexta with Takeda Pharmaceutical Co. Ltd's flagship proteasome inhibitor Velcade (bortezomib) and dexamethasone in relapsed or refractory myeloma, which also was presented at the ASH meeting, the objective response rate was 38% for those who were refractory to bortezomib and 89% in patients who were not refractory to bortezomib and had previ
Capina, Essentialis Merger To Create Rare Disease Firm

The combined company would advance a diazoxide choline controlled-release daily pill for treating patients with Prader-Willi syndrome through pivotal Phase II/III clinical trial.

Nasdaq-listed Capnia Inc. plans to acquire privately held Essentialis Inc. through a merger designed to create a combined developer of rare disease treatments.

Under the deal’s terms announced Dec. 27, Capnia will issue common stock priced at $0.96 per share to a syndicate comprised of current and new investors, raising gross proceeds of $8m for use in advancing Essentialis’ diazoxide choline controlled release (DCCR) tablet for treating the rare disorder Prader-Willi syndrome (PWS) which causes constant hunger and various metabolic, endocrine, cognitive and behavioral symptoms, and for which there currently are “no effective treatments,” Capnia’s chief executive officer Anish Bhatnagar said in a statement.

A pivotal Phase II/III clinical trial for the drug, which was given orphan drug designation for the treatment of PWS by the FDA in May 2014, would start in the second half of 2017. The combined California-based company also envisions developing DCCR for other unspecified orphan indications.

The planned merger represents a big change for Capnia, a diversified healthcare group which develops diagnostics and therapeutics (drug-device combinations) based on a precision gas flow metering technology. The company’s first product, CoSense, is used to diagnose hemolysis in newborns. Capnia said it would evaluate alternatives for its legacy products and product candidates.

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VELOPARIB PROVIDES SOLID TUMOR OPPORTUNITY

AbbVie presented mid-stage data for another asset now in Phase III – the PARP inhibitor veliparib – at the San Antonio Breast Cancer Symposium on December 7.

The Phase II study tested veliparib in combination with different kinds of chemotherapy in 290 breast cancer patients with BRCA1 and BRCA2 mutations. Although patients taking veliparib with carboplatin and paclitaxel chemotherapy had a significantly better response rate compared to those taking carboplatin and paclitaxel with placebo (77.8% vs. 61.3%), progression-free survival and overall survival were not significantly improved compared to the control group. However, toxicity was also not significantly increased in the arm that included veliparib as part of combination therapy.

AbbVie notes that the study was not powered well enough to show a difference in progression-free survival and the company is now running the Phase III BROCADE study, which tests veliparib with carboplatin and paclitaxel in HER2-negative metastatic BRCA-associated breast cancer.

AbbVie is planning to differentiate veliparib from other PARP inhibitors on the basis that it is a potent inhibitor of PARP, it combines well with multiple chemotherapies – particularly platinum chemotherapies – without dramatic increases in toxicity, and it penetrates the central nervous system, Gordon said.

Veliparib also is in Phase III for squamous non-small cell lung cancer (NSCLC), non-squamous NSCLC, triple-negative breast cancer and ovarian cancer.

Published online 21 December 2016
The CRO View: Sharing Opportunity Vs Risk

Premier Research’s chief commercial officer, Sean Russell, describes how the CRO has turned risk-sharing negotiations from a black art to a predictable process.

SEAN RUSSELL

We hear a lot about risk sharing in drug development these days, and it’s a healthy trend in an industry often defined by high costs and the pressure of project deadlines. Drug development thrives on cost and schedule adherence, and the inextricable link between the two leads increasingly to risk-reward arrangements between drug makers and their clinical research providers.

Having been involved in many of these, I like to avoid “risk sharing” and other terms that can cast these agreements in a negative light. When we look at clinical development, I prefer to focus on opportunity sharing — not so much avoiding failure as improving clinical trial productivity and efficiency.

After all, if you start a clinical development program assuming you’re going to fail, you’d better find something else to do.

FIRST, A DEFINITION

Risk- and opportunity-sharing is still a pretty new concept, and there are different types of these arrangements. In this article, I’m describing agreements between drug makers and clinical research organizations under which CROs are rewarded, or penalized, based on their performance versus contract terms and milestones.

As CROs increasingly assume the role of professional adviser as opposed to service provider, sponsors expect us to have some skin in the game by connecting performance and reward. And the basis of a well-designed incentive arrangement is this: sponsors want their CROs to succeed because successful clinical trials are essential to getting new drugs to market. No risk-reward deal set up as a trip wire — “you missed these deadlines and now we’re going to extract our penalty” — has any chance of succeeding.

THE CARROT, NOT THE STICK

So with growing frequency, we’re using a performance-based pricing model as a tool for negotiating and managing opportunity-sharing agreements. Sponsors pursue these deals hoping we reach those incentive milestones and happily pay for performance that meets or exceeds targets. We share these payments as project team bonuses to motivate our employees, recognizing that happy employees are engaged and stick around — even in the clinical research business, which is famous for rapid employee turnover.

Of course, bonus payments alone cannot provide the impetus needed to motivate our teams to the level of performance we aim for. Many factors drive high-functioning teams, such as the satisfaction of collaborating with talented colleagues and teaming with sponsors on work that has the potential to advance science and improve lives. But bonuses can be an important part of the mix in improving employee retention.

We’ve come a long way in evolving toward this ideal in the past couple of years, leaving in the wake of risk-sharing’s checkered past some classic non-starter ideas. They include penalties without corresponding rewards (an unthinkable bad deal) and CROs signing up for royalties from future drug sales (a long wait for a very uncertain return).

OPPORTUNITY-SHARING MILESTONES

These arrangements began as a sort of afterthought in the contract negotiation process, offered by sponsors as a way to help close the deal. Recognizing the potential for mutual benefit, we developed a template outlining the sorts of terms we’ll consider for inclusion. We’ll typically put a percentage of the total contract value — or alternatively, our project management fee — at stake, tied to milestones such as:

- Time from contract award to opening of the firststudy site.
- Time from contract award to first patient screened.
- Date of database lock relative to last patient last visit (incentive rises for every week that lock date precedes LPLV).
- Percentage of sites activated within a prescribed period.

To cite a recent example, a double-blind trial of a treatment for major depressive disorder tied incentives and penalties to five factors: US patient enrollment (40%), enrollment in two other countries (7.5% each), database lock (30%), and first patient screened (10%).

ASSESSING THE LEVEL OF RISK

For a successful negotiation, the CRO and sponsor must agree on several fundamentals to ensure that both parties share equally in the financial and performance benefits and risks. We’ll assume risk only at a level commensurate with the control we’re allowed over the study’s execution — things like:

- Protocol design and site selection, which have a significant bearing on patient recruitment, retention, and compliance.
- Appropriate level of feasibility assessments to be performed.
- Operational strategy, such as recruitment plans, monitoring, strategy, data management platform and process, and statistical analysis planning.

In creating this structured approach, we have advanced risk-reward negotiation from a black art to a process that’s straightforward, predictable and repeatable. And we’ve witnessed compelling results — for example, greatly improving performance in a recent Eastern European study to evaluate an adult schizophrenia drug for a biopharmaceutical customer. Our incentivized team moved up the timeline for the 400-person study and, to a person, remained for its full 22-month duration. Published online 29 December 2016
Allergan Adds Accretive Aesthetics Assets In $2.9bn LifeCell Acquisition

MANDY JACKSON mandy.jackson@informausa.com

Allergan will pay $2.9bn in cash for LifeCell, a division of Acelity, adding its first regenerative medicine portfolio and marking its first commercial-stage deal in more than a year. The company hopes to exploit the surgical products for aesthetic uses beyond breast reconstruction.

Allergan PLC will pay Acelity LP Inc. $2.9bn to buy the LifeCell Corp. portfolio of aesthetic and surgical products, marking Allergan’s first regenerative medicine transaction and its first acquisition of a firm with commercial-stage assets since the company bought Kythera Biopharmaceuticals Inc. last year.

Investors have punished Allergan for its development-stage acquisitions this year, sending the company’s stock below $200 per share for the first time this year after Allergan closed the acquisition of Tobira Therapeutics Inc, a deal worth about $615m up front and up to $1.7bn including milestone fees, for what currently is a late Phase II liver disease program. However, the LifeCell purchase gives Allergan a suite of commercial products for what chief commercial officer William Meury describes as the company’s “most important customer” – plastic surgeons.

“AllIcure is the only clinically-validated and scalable platform to confirm medication ingestion on mobile devices. Changing patient behavior and ensuring accurate data on a dose by dose basis has the potential to transform and streamline the clinical trial process. We are very grateful to the Scrip judges for recognizing our company as best in class.”

Adam Hanina, CEO and Chairman of AiCure

The platform was developed to automate directly observed therapy, the gold standard in monitoring and maximizing adherence, by visually identifying the patient, the drug, and the act of ingestion.

A COMMERCIAL PRESENCE RIGHT FROM THE START

Evercore ISI analyst Umer Raffat said in a Dec. 20 report that he heard three types of investor reactions to Allergan’s LifeCell acquisition news that same morning: gratitude that the assets would be immediately accretive to the company’s earning, satisfaction with LifeCell’s aesthetic portfolio given Allergan’s strong presence in that market, and concern that the company sold for $1.2bn less eight years ago.

Acelity (formerly Kinetic Concepts Inc.) acquired LifeCell for $1.7bn in 2008, but Raffat pointed out that the business is expected to generate $450m in 2016 revenue – representing year-over-year growth in the mid-single digits – versus $191m in 2007 revenue.

Published online 21 December 2016

Scrip Awards Winner » 2016

Best Technological Development in Clinical Trials

AiCure’s technology is a new approach to artificial intelligence that uses AI to visually confirm medication ingestion on smartphones.

“...The platform was developed to automate directly observed therapy, the gold standard in monitoring and maximizing adherence, by visually identifying the patient, the drug, and the act of ingestion.

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Published online 21 December 2016
Scrip’s weekly **Pipeline Watch** tabulates the most recently reported late-stage clinical trial and regulatory developments from the more than 10,000 drug candidates currently under active research worldwide.

### Selected clinical trial developments for the week 16–29 December 2016

#### Phase III Results Published

<table>
<thead>
<tr>
<th>LEAD COMPANY/PARTNER</th>
<th>COMPOUND</th>
<th>INDICATION</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mylan NV/Biocon Ltd.</td>
<td>biosimilar trastuzumab</td>
<td>breast cancer</td>
<td>HERITAGE; published in JAMA online Dec. 1.</td>
</tr>
<tr>
<td>Roche/Biogen</td>
<td>Ocrevus (ocrelizumab), anti-CD20 MAb</td>
<td>primary progressive multiple sclerosis, relapsing MS</td>
<td>ORATORIO, OPERA I, II; NEJM online on Dec. 21.</td>
</tr>
</tbody>
</table>

#### Phase III Interim/Top-line Results

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<tr>
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<th>COMPOUND</th>
<th>INDICATION</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roche/Chugai Pharmaceutical Co. Ltd.</td>
<td>emicizumab (a bispecific MAb)</td>
<td>haemophilia A with Factor VIII inhibitors</td>
<td>HAVEN 1; met primary endpoint, reduced bleeds when used prophylactically.</td>
</tr>
<tr>
<td>Synergy Pharmaceuticals Inc.</td>
<td>ppecanatide</td>
<td>irritable bowel syndrome with constipation</td>
<td>IBS-C (Study 2); met primary endpoint.</td>
</tr>
<tr>
<td>Alexion Pharmaceuticals Inc.</td>
<td>Soliris (eculizumab)</td>
<td>delayed graft function after kidney transplant</td>
<td>PROTECT; missed primary endpoint in potential new indication.</td>
</tr>
<tr>
<td>Sanofi/Lexicon Pharmaceuticals Inc.</td>
<td>sotaglitiflox</td>
<td>type 1 diabetes</td>
<td>Tandem2; met primary endpoint in second pivotal study.</td>
</tr>
<tr>
<td>ViiV Healthcare</td>
<td>dolutegravir plus rilpivirine</td>
<td>HIV maintenance</td>
<td>SWORD-1, -2; met primary endpoint, non-inferior to three- or four-drug regimens.</td>
</tr>
<tr>
<td>Ionis Pharmaceuticals Inc./Akcea</td>
<td>volanesorsen, an antisense drug</td>
<td>familial partial lipodystrophy, familial chylomicronemia syndrome</td>
<td>COMPASS; met primary endpoint, reduced triglycerides.</td>
</tr>
<tr>
<td>Anthera Pharmaceuticals Inc.</td>
<td>Sollpura (liprotamase)</td>
<td>cystic fibrosis</td>
<td>SOLUTION; Narrowly missed primary endpoint of non-inferiority to Pancreaze</td>
</tr>
</tbody>
</table>

#### Phase III Initiated

<table>
<thead>
<tr>
<th>LEAD COMPANY/PARTNER</th>
<th>COMPOUND</th>
<th>INDICATION</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ViiV Healthcare</td>
<td>cabotegravir</td>
<td>HIV prevention</td>
<td>HPTN-083; a long-acting injectable agent.</td>
</tr>
<tr>
<td>GlaxoSmithKline PLC/Innoviva Inc.</td>
<td>fluticasone furoate, umecclidinium, vilanterol</td>
<td>asthma</td>
<td>CAPTAIN; a once-daily triple combination dry powder inhaler.</td>
</tr>
<tr>
<td>Sancilio Pharmaceuticals Co. Inc.</td>
<td>SC411</td>
<td>sickle cell anemia</td>
<td>A reformulation of docosahexenoic acid.</td>
</tr>
<tr>
<td>Flamel Technologies SA</td>
<td>FT218 (sodium oxybate) once-nightly formulation</td>
<td>daytime sleepiness and cataplexy</td>
<td>REST-ON; in patients with narcolepsy.</td>
</tr>
<tr>
<td>AbbVie Inc./Roche</td>
<td>Venclexta (venetoclax)</td>
<td>acute myeloid leukemia</td>
<td>Combined with azacitidine in elderly patients.</td>
</tr>
<tr>
<td>ChemoCentryx Inc./Galenica Group</td>
<td>CCX168 (avacopan)</td>
<td>antineutrophil cytoplasmic antibodies associated vasculitis</td>
<td>To induce and sustain remission versus prednisone.</td>
</tr>
<tr>
<td>Esperion Therapeutics Inc.</td>
<td>ETC-1002</td>
<td>dyslipidemia</td>
<td>CLEAR Tranquility: as an add-on to ezetimibe therapy.</td>
</tr>
<tr>
<td>Strongbridge Biopharma PLC</td>
<td>COR-003 (levoketoconazole)</td>
<td>Cushing's syndrome</td>
<td>LOGICS; A second Phase III study.</td>
</tr>
</tbody>
</table>

#### Phase III Announced

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Gilead Sciences Inc.</td>
<td>Vemlidy (tenofovir alafenamide fumarate)</td>
<td>hepatitis B</td>
<td>Switching from tenofovir disoproxil fumarate.</td>
</tr>
</tbody>
</table>
### PIPELINE WATCH

#### Phase II Suspended

<table>
<thead>
<tr>
<th>Company</th>
<th>Compound</th>
<th>Phase</th>
<th>Disease/Indication</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hansa Medical AB</td>
<td>IdeS (IgG antibody degrading enzyme)</td>
<td>Phase II</td>
<td>acquired thrombotic thrombocytopenic purpura</td>
<td>No positive effect, studies continue in other indications.</td>
</tr>
</tbody>
</table>

#### Phase II Results

<table>
<thead>
<tr>
<th>Company</th>
<th>Compound</th>
<th>Phase</th>
<th>Disease/Indication</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orion Corp.</td>
<td>salmeterol plus fluticasone dry powder <em>Easyhaler</em></td>
<td>Phase II</td>
<td>asthma, chronic obstructive pulmonary disease</td>
<td>A generic version of GlaxoSmithKline’s Seretide, filing expected first half of 2017, in Europe.</td>
</tr>
<tr>
<td>GenSight Biologics SA</td>
<td>GS010 (gene therapy)</td>
<td>Phase II</td>
<td>Leber’s hereditary optic neuropathy</td>
<td>Mixed but promising results after 78 weeks of follow-up.</td>
</tr>
</tbody>
</table>

#### Phase II Completed

<table>
<thead>
<tr>
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<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adocia SAS/Eli Lilly &amp; Co.</td>
<td>BioChaperone Lispro (insulin lispro)</td>
<td>Phase II</td>
<td>type 1 diabetes</td>
<td>Safe and effective in an insulin pump versus Humalog.</td>
</tr>
</tbody>
</table>

#### Phase II Interim/Top-line Results

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<tr>
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<th>Compound</th>
<th>Phase</th>
<th>Disease/Indication</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ironwood Pharmaceuticals Inc./Allergan PLC</td>
<td>linacotide colonic release formulations</td>
<td>Phase II</td>
<td>irritable bowel disease with constipation</td>
<td>Extending the use of linacotide with new formulations.</td>
</tr>
<tr>
<td>Galapagos NV/AbbVie Inc.</td>
<td>GLPG1837 (cystic fibrosis)</td>
<td>Phase II</td>
<td>cystic fibrosis</td>
<td>SAPHIRA 1; promising efficacy, well tolerated.</td>
</tr>
<tr>
<td>Acadia Pharmaceuticals Inc.</td>
<td>Nuplazid (pimavanserin)</td>
<td>Phase II</td>
<td>Alzheimer’s disease psychosis</td>
<td>Met primary endpoint against psychosis but mixed results on other endpoints.</td>
</tr>
<tr>
<td>RespireRx Pharmaceuticals Inc.</td>
<td>dronabinol</td>
<td>Phase II</td>
<td>obstructive sleep apnea</td>
<td>PACE; improved sleepiness symptoms.</td>
</tr>
</tbody>
</table>

#### Phase II Initiation

<table>
<thead>
<tr>
<th>Company</th>
<th>Compound</th>
<th>Phase</th>
<th>Disease/Indication</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concert Pharmaceuticals Inc.</td>
<td>CTP-656 (deuterated ivacaftor)</td>
<td>Phase II</td>
<td>cystic fibrosis</td>
<td>A potential next generation CFTR potentiator.</td>
</tr>
<tr>
<td>SAGE Therapeutics Inc.</td>
<td>SAGE-217 (major depressive and mood disorders)</td>
<td>Phase II</td>
<td>major depressive and mood disorders</td>
<td>Four programs now underway.</td>
</tr>
<tr>
<td>Portage Biotech Inc.</td>
<td>BHV-4157 (spinocerebellar ataxia)</td>
<td>Phase II</td>
<td>cystic fibrosis</td>
<td>In adult patients.</td>
</tr>
<tr>
<td>AOBiome</td>
<td>B244 (ammonia-oxidizing bacteria)</td>
<td>Phase II</td>
<td>hypertension</td>
<td>Also being evaluated in acne.</td>
</tr>
<tr>
<td>NovaBiotics Ltd.</td>
<td>Lynovex (cysteamine), oral</td>
<td>Phase II</td>
<td>cystic fibrosis</td>
<td>For exacerbations of lung disease.</td>
</tr>
<tr>
<td>Neothetics Inc.</td>
<td>LIPO-202 (salmeterol) injectable</td>
<td>Phase II</td>
<td>submental fat reduction</td>
<td>A proof of concept study.</td>
</tr>
<tr>
<td>Acceleron Pharma Inc.</td>
<td>ACE-083 (facioscapulohumeral muscular dystrophy)</td>
<td>Phase II</td>
<td>cystic fibrosis</td>
<td>A locally acting muscle agent.</td>
</tr>
<tr>
<td>Immunomedics Inc.</td>
<td>sacituzumab govitecan (IMMU-132)</td>
<td>Phase II</td>
<td>triple-negative breast cancer</td>
<td>In patients with metastatic disease and more than one prior therapy.</td>
</tr>
</tbody>
</table>

*Source: Biomedtracker*
2017, Year Of The Dog

ANDY SMITH

News in the life sciences sector over the holiday period was peppered with clinical and regulatory failures at Acadia, Anthera, Opko and Cempra, and a drug pricing controversy from Biogen. Following underperformance in 2016 and with that sort of run-up, 2017 already looks likely to be another lost one.

The biotech sector moves in cycles and the momentum that builds up the peaks is driven by the generalist investor. Generalists are attracted by rising stock prices, cheap valuations, increased M&A and high-profile drug approvals. In 2016, the year-long 22% decline for the NASDAQ Biotech Index – as compared with the S&P 500’s near 10% rise – and fewer approvals by the FDA spurred on the departure of the generalist from biotech. In the 12-year cycle of the Chinese calendar the year of the dog is not until 2018. In biotech, however, without the generalist, 2017 looks likely to be an early dog.

Acadia Pharmaceuticals Inc. got the holiday bad news ball rolling when it reported “positive” top-line results from the placebo-controlled Phase II study of pimavanserin in 181 Alzheimer’s disease patients with psychosis. With so few analysts in the market on Dec. 20 it was left to social media commentators to pronounce on the trial results. Those pronouncements focused on the primary endpoint of the study listed on clinicaltrials.gov measured at 12 weeks not being significant. Acadia’s announcement focused on the measurement at six weeks as the primary endpoint and just scraped significance with a p-value of 0.0451. While Acadia will be barreling into Phase III on the basis of the exploratory Phase II study, I liked the analogy quoted on social media about the ice being very thin around p=0.05 in both directions. From the day of Acadia’s announcement until the last trading day of the year, the firm’s stock price managed a 5% increase – lackluster, maybe, but then again, the study didn’t demonstrate anything conclusive. In any event, Acadia is likely to have bigger problems in 2017. With fourth-quarter earnings season just around the corner, the sales of Acadia’s first drug Nuplazid (also pimavanserin) in its second full quarter on the market will be closely watched. After a checkered Phase III program in psychosis associated with Parkinson’s disease – an indication I have always regarded as made up to fit the drug in the absence of patients – Nuplazid sales in their first full quarter were only $5.3m. Bearing in mind that it took 15 quarters from the launch of Provenge (sipuleucel-T) before Dendreon Corp. concluded that the product was unviable and filed for bankruptcy, Acadia may have some time yet before succumbing to a similar fate.

SOLLPURA FAILURE

A week after Acadia’s “positive” clinical trial there was an attempt to sugar-coat Anthera Pharmaceuticals Inc.’s announcement on the Phase III failure of Sollpura (liprotamase) in the SOLUTION study of 126 cystic fibrosis patients with exocrine pancreatic insufficiency by including the word “encouraging” in the title of the announcement. Investors were not fooled and the Anthera share price finished the last week of 2016 down by more than 66%. Many investors probably didn’t realize that Sollpura had already failed more than once at Altus Pharmaceuticals Inc., forcing Altus’ bankruptcy. Sollpura then passed through the hands of the Cystic Fibrosis Foundation, Alnara Pharmaceuticals Inc., Eli Lilly & Co. and finally to Anthera where it may have another Phase III failure to go through before the product again supports a different company’s IPO.

SOLITHERA REJECTION

Other clinical trial failures that punctuated the holiday period included the Phase III failure of Opko Health Inc.’s long-acting human growth hormone. The FDA’s rejection of Cempra Inc.’s antibiotic Solithera (solithromycin) for the treatment of community-acquired pneumonia had wider implications for the sector.

The narrative accompanying the later stages of Solithera’s development had been bathed in assurances of the need for new antibiotics and the global implications of antibiotic resistance that help include incentives in the recent 21st Century Cures Act. Cempra investors probably believed that all this hullabaloo would result in a free pass for any antibiotic in any indication. Unlike Sarepta Therapeutics Inc.’s Exondys 51 (etepliren), in which approval was helped by advocate and patient pressures, Solithera’s efficacy was not in doubt. Rather, the product’s approval was thwarted by the macrolide class’s hepatotoxicity and the withdrawal of another equally efficacious antibiotic, Trovan (trovafloxacin), after fatal liver toxicity emerged from an on-market and clinical trial safety database that was nearly 3,000 times that of Solithera’s 920 patients.

SPINRAZA HANGOVER

The celebration of the approval of Biogen Inc.’s antisense drug Spinraza (nusinersen) for the treatment of the rare disease spinal muscular atrophy (SMA) is likely to result in a hangover that will last throughout 2017. Spinraza’s approval was met with a rise of about 4% in Biogen’s share price that then all but dissipated over the last trading week of the year. The reason for investors’ reticence to embrace Spinraza’s commercial potential is probably related to the small number of SMA patients that can tolerate an injection into their cerebrospinal fluid and the implied pricing needed to move the needle in a company with a $62bn market capitalization. The analysts from Leerink Partners started to catch this mood when they described the $750,000 first year loading dose price as “likely to invite a storm of criticism” although this probably underplays the future price increases for Spinraza by a company that is known to regularly poke the hornet’s nest of drug pricing and whose sales growth last quarter was primarily due to price increases and channel stuffing.

The justification of value is likely to be the big cloud that hangs over the whole sector in 2017. For Acadia, the demonstration of the value of pimavanserin, which generates a barely significant p-value after six weeks and declines into insignificance by week 12, will be at least challenging and probably impossible.

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Andy Smith gives an investor’s view on life science companies. He has been lead fund manager for four life science-specific funds, including 3i Bioscience, International Biotechnology and the AXA Framlington Biotech Fund, and was awarded the techMark Technology Fund Manager of the year for 2007.
Robert Waters, Astellas Inc’s former global regulatory lead, has joined the Oxford-based retinal company, Oxular Ltd., as vice president of regulatory affairs. Previously, Waters held various key European regulatory roles including head of ophthalmology and head of regulatory development at Allergan plc.

Steve Bates, CEO of the UK BioIndustry Association, was made an OBE in the Queen’s New Year honours list, for services to innovation. Others in the life sciences area honoured include Shankar Balasubramanian, professor of medicinal chemistry at the University of Cambridge, who was knighted; Balasubramanian co-invented next-generation DNA sequencing. And Jim Smith, a developmental biology professor, who was knighted for his role in the formation of the Francis Crick Institute; he is currently director of science at the Wellcome Trust, and a group research leader at the Institute.

Shire Plc. has appointed Ian Clark non-executive director of the company – effective Jan. 3, 2017. Until December 2016, Clark was CEO and director of Genentech Inc., (Roche Group) and head of North American commercial operations for Roche. Before this, Clark held various senior operational, sales and marketing roles in other pharma and healthcare companies. Currently, he is non-executive director of TerraVia Holdings Inc. where he is chair of the compensation committee and member of the nominating and corporate governance committee.

Debra Flores has joined Astellas as director, state government affairs, in the Midwest region. With 20 years experience in government affairs and the healthcare industry, Flores was most recently director of state government affairs for Boehringer-Ingelheim. Before this, she was director of government affairs at New Century Financial Corporation.

Alzheon Inc., a clinical-stage biopharma company focused on Alzheimer’s disease and other neurological and psychiatric disorders, has appointed Stanley B. Prusiner chair of its scientific advisory board. Dr Prusiner received the Nobel Prize in physiology and medicine in 1997 and the Albert Lasker Award for Basic Medical Research in 1994. He is the director of the Institute for Neurodegenerative Diseases and a professor, who was knighted for his role in the formation of the Francis Crick Institute; he is currently director of science at the Wellcome Trust, and a group research leader at the Institute.

Alynlam Pharmaceuticals Inc.’s senior vice president and chief business officer, David Alexandre, is resigning from the company for personal reasons – effective Jan. 6, 2017. Alynlam has also promoted its current senior vice president, clinical development, Pushkal Garg, to the role of chief medical officer. Garg carries over 15 years of experience acquired from working at various companies including Bristol-Myers Squibb and Millennium Pharmaceuticals and joined Alynlam in 2014.

Alessandro Riva, Novartis Oncology's former head, global oncology development, has joined Gilead Sciences as senior vice president, hematology and oncology therapeutic area head. Riva will also be joining the company’s executive committee. Previously, she was a member of the Novartis Oncology Division executive committee, development committee, translational and early development committee and innovation management board. Before Novartis, Riva co-founded the Breast Cancer International Research Group (BIRG) and Cancer International Research Group (CIRG), for which she served as CEO and chief medical officer.
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- Trialtrove