Bial Trial Tragedy: No Safety Clue From Similar Products

It is now officially confirmed that the fatty acid amide hydrolase inhibitor at the center of the Bial clinical trial disaster is BIA 10-2474, which was in Phase I development for the treatment of "neurological and psychiatric pathologies." But there were few clues to its potential toxicity from previous products with this mechanism of action investigated, and dropped from development.

BIA 10-2474 is one of six products listed by Bial as being in its development pipeline, and one of two at the Phase I stage. Bial's pipeline is dominated by projects for CNS conditions (epilepsy and Parkinson's disease) plus pulmonary arterial hypertension, inflammation and respiratory.

Fatty acid amide hydrolase (FAAH) is responsible for hydrolysis of endocannabinoid, anandamide (AEA), and N-acyl ethanolamines such as palmitoylethanolamine (PEA) and N-oleylethanolamide (OEA). Inhibition of the enzyme increases levels of anandamide, a naturally occurring cannabinoid in humans that plays a role in the modulation of pain and other neurodegenerative disorders. The FAAH enzyme has two forms, and the FAAH class has several subclasses of covalent and non-covalent inhibitors, that are reversible and non-reversible. Previous research by Merck & Co scientists on FAAH inhibitors published last year in ACS Medicinal Chemistry Letters mentions theoretical concerns over long acting inhibitors, and there is speculation that the Bial product is irreversible.

As a mechanism, fatty acid amide hydrolase inhibitors have historically not...

World-Top Scientist Busted For Stealing GSK Secrets

US prosecutors have laid out yet another case where very intelligent people made the stupid mistake of thinking they were too smart to get caught. They did.

In a 43-count indictment, US prosecutors in Philadelphia on Jan. 20 described how a GlaxoSmithKline PLC senior-level manager went from being regarded as one of the world's top protein biochemists to a becoming a thief – scheming with one of her co-workers to steal trade secrets from the London-based drug and vaccine maker in a plot to market and sell the lifted information through a US company and its Chinese affiliates formed with three other conspirators, all of whom are scientists.

The indictment, filed by the US Attorney's Office for the Eastern District of Pennsylvania, includes charges of conspiracy to steal trade secrets, conspiracy to commit wire fraud, conspiracy to commit money laundering, theft of trade secrets and wire fraud.

Yu "Joyce" Xue, who was fired by GSK on Jan. 6, was a project co-leader at the firm's research facility in Upper Merion, Pa., working on monoclonal antibodies designed to link to...
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Two health crises, quite different in nature, have come to prominence over the past couple of weeks. Both demand a response from the global pharma industry.

The tragic outcome of the Phase I trial in Rennes, France, in which one volunteer lost his life and others have been seriously injured, has prompted much soul-searching in industry and beyond. While the urgent need is to establish what went wrong in this particular case, in the longer run attention will inevitably turn to what general lessons must be learned, and what changes should be made to avoid such events in future.

An essential part of the drug development process, Phase I trials thankfully rarely result in catastrophic damage to human volunteers. It is imperative that the risks of serious or lasting impact on healthy volunteers are kept as close to zero as possible, and the renewed calls for greater transparency around preclinical and early clinical data will have to be given thorough consideration, not least in order to help re-establish public trust in the Phase I process.

Meanwhile, the reports of brain damage and microcephaly in newborns in Latin America that have been attributed to maternal Zika virus infection suggest that the outbreak of the usually mild mosquito-transmitted infection that began in the region in 2015 will need to be taken more seriously than had initially appeared necessary.

With the much-lamented delayed co-ordination of efforts to address the 2014-15 Ebola epidemic in West Africa still fresh in the mind, industry will want to avoid a repeat of the finger-pointing that accused it of neglecting to develop treatments and vaccines because they would not be profitable. The emerging threat to fetuses is prompting R&D-focused action in various quarters, with companies including GlaxoSmithKline, GeneOne Life Science and Inovio Pharmaceuticals recently announcing vaccine research plans.

Of course, for industry to respond effectively to any emerging public health challenge, robust monitoring and alert systems need to be in place. It is to be hoped that the reforms being set in motion at the World Health Organization in the wake of Ebola will, among other things, help facilitate prompt and effective interventions by research-based pharma companies.
Bristol-Myers Squibb’s PD-1 inhibitor Opdivo (nivolumab) has won a recommendation from NICE, the health technology appraisal institute for England and Wales, for use on the NHS as a monotherapy for melanoma. The drug went straight to the final stages of the appraisal process and will compete against Merck & Co’s own PD-1 inhibitor Keytruda (pembrolizumab). Meanwhile, research and patient organizations have expressed relief that NICE has okayed another “exciting” new immunotherapy for cancer.

On 22 January, NICE published its final appraisal determination recommending Opdivo in line with its licensed indications as a monotherapy for treating advanced (unresectable or metastatic) melanoma in adults. BMS has welcomed the news, but at the same time expressed concern that the institute was poised to say no to the drug for lung cancer.

Elsewhere, others applauded the swift adoption of an effective immunotherapy. “It’s positive that NICE has approved this at the first time of asking. It’s vital that we get novel and exciting cancer treatments to patients as quickly as possible, and avoid the tortuous back and forths we have seen with other recent appraisals,” said Paul Workman, chief executive of The Institute of Cancer Research.

Gill Nuttall, founder of Melanoma UK was also pleased with this news and highlighted the importance of immunotherapies, which she said are changing survival expectations in cancer. “We need to do more to bring patient access to these potentially life-extending cancer medicines as quickly as possible,” she said.

Opdivo, like Keytruda, won approval from the UK’s medicines regulator, the MHRA, to enter the Early Access to Medicines Scheme (EAMS), which aims to allow early availability of promising new unlicensed drugs for patients with a high unmet medical need. This meant Opdivo was made available in the UK, free of charge to the NHS, on May 30, less than a month before it won EU approval on June 19. Approval under EAMS also means the NHS is obliged to make funding available for the drug earlier following positive NICE guidance. Usually local authorities have 90 days to fund a product recommended by NICE, but this time line falls to 30 days for EAMS-approved drugs.

According to NICE, the decision to dispense with preliminary draft guidance had nothing to do with the Early Access to Medicines Scheme. NICE was able to recommend the drug for the full licensed indication based on the available evidence, for this reason there was no need for additional consultations, it said.

Opdivo costs £439 per 4 ml vial and £1,097 per 10 ml vial, excluding VAT and any local procurement discounts. NICE’s appraisal committee decided that the incremental cost effectiveness ratio for the drug, compared with BMS’ Yervoy (ipilimumab), Roche’s Zelboraf (vemurafenib) and Novartis’ Tafinlar (dabrafenib), would be less than £30,000 per quality adjusted life year gained. This meant the drug was cost-effective. This estimation included confidential discounts applied to the three drugs.

NICE also agreed the drug could be evaluated under its end-of-life criteria, giving it scope to accept more expensive medicines. In November 2015, NICE published guidance recommending Keytruda as an option for treating advanced melanoma that has not been previously treated with Yervoy. The recommendation depends on a confidential discount.

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PRE-CONFERENCE INTERACTIVE US MASTER CLASS
27 APRIL 2016
2015 was a busy year for both the US FDA and the EMA, with both agencies reporting a substantial uptick in the numbers of novel products they approved, but what product approval decisions are due in 2016? Here Scrip looks at 10 of the more interesting approval decisions to look out for in 2016, in rough order of when they are expected. It is perhaps telling that each of the 10 applications is due to be decided upon first in the US, and so the list is in approximate order of their Prescription Drug User Fee Act (PDUFA) action dates (where known). However, it should be noted that last year many oncology drugs were approved well ahead of their PDUFA dates, a trend that could well continue.

BioMarin’s Kyndrisa, Sarepta’s Eteplirsen For DMD
US approval decision: January 2016
EU approval decision due: drisapersen Q3 2016
US approval decision due: eteplirsen February 2016
EU approval decision due: eteplirsen not yet filed

Regulatory decisions are finally expected for two investigational treatments for the orphan disease Duchenne muscular dystrophy (DMD) this year. The FDA has just given its negative verdict on BioMarin’s drisapersen (Kyndrissa) which came as no surprise following an FDA panel in November that was highly skeptical of the company’s data for the product, both for efficacy and safety. In its Complete Response Letter, the agency said it wants another Phase III trial, kicking drisapersen into the long grass. Its future will likely depend on how the EU’s CHMP responds to the product (a decision is due in the first half), and on how Sarepta’s rival product eteplirsen fares at its own panel meeting on Jan. 22. Eteplirsen has a PDUFA action date of Feb. 26. Both drugs are seeking the approval to treat patients with DMD amenable to exon 51 skipping. Duchenne is the most common fatal genetic disorder diagnosed in childhood – affecting about 1 in every 3,500 live male births, with about 20,000 new cases diagnosed globally each year. Also eteplirsen and drisapersen both won the FDA’s rare pediatric disease designation, which means they are eligible for a priority review voucher (PRV) on approval. Sarepta has yet to file eteplirsen in the EU.

Eli Lilly’s Ixekizumab For Psoriasis
US approval decision due: first quarter 2016
EU approval decision due: second half 2016

If the regulators are willing, Lilly’s offering in the new anti-IL17 class is set to challenge Novartis’s frontrunner Cosentyx (secukinumab) which reached the market last year for moderate to severe plaque psoriasis (the first of a number of potential anti-inflammatory conditions). Together these products are pushing back the treatment frontiers in this disease, raising the bar for their followers. So much so that AstraZeneca transferred its IL17 product brodalumab to Valeant after its partner Amgen pulled out of their co-development deal after suicidal ideation adverse events came to light during clinical trials. Ixekizumab and secukinumab may be snipping at the heels of the current standard of care Johnson & Johnson’s Stelara (ustekinumab), which superseded the older anti-TNFs in moderate to severe psoriasis, but other products are on the way: a number of anti-IL23 agents are in late-stage development by Boehringer Ingelheim, Merck & Co and J&J.

Datamonitor 7MM sales forecast 2023 $297m

Clovis Oncology’s Rociletinib For NSCLC
US approval decision due: March 2016
EU approval decision due: mid-2016

Clovis shocked investors in November when it released response rate data for rociletinib in non-small-cell lung cancer (NSCLC) that were lower than the firm had previously reported. What’s more, the data submitted to the FDA could delay any approval, with the PDUFA action date likely being pushed past the currently scheduled Mar. 30. The rolling filing was for the treatment of patients with mutant epidermal growth factor receptor (EGFR) non-small cell lung cancer who have been previously treated with an EGFR-targeted therapy and have the EGFR T790M mutation as detected by an FDA approved test. Analysts had hoped that the product would sail to market, like AstraZeneca’s similar product Tagrisso (osimertinib) did in the same indication, in November, well ahead of its PDUFA action date of Feb. 6, 2016. Now they expect a decision in the middle of the year at the earliest; with a worst-case scenario being that the FDA requires data from the TIGER-3 trial which would push approval back until 2017. Clovis can at least take some comfort in the progress of its other offering rucaparib. Its NDA submission timeline has been brought forward to Q1 2017, and the company is eyeing a potential US launch for advanced ovarian cancer by the end of 2016.

Teva’s Cinqair For Asthma
US approval decision due: March 2016
EU approval decision due: second half 2016

This is Teva’s answer to GlaxoSmithKline’s newly approved Nucala (mepolizumab), which last year became the first product licensed in this new class of anti-IL-5 products for severe asthma with an eosinophilic phenotype – a very difficult to treat population, which makes up about 3% of the 25 million people with asthma in the US. Teva is seeking to market iv reslizumab (Cinqair) to reduce exacerbation, relieve symptoms and improve lung function in adults and adolescents 12 years or above with asthma with elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids. And it looks set for approval in at least some patients: the FDA’s Pulmonary-Allergy Drugs Advisory Committee on Dec. 9 lent its support to reslizumab as a treatment for adults with severe asthma, but said there were not enough data about whether the drug is safe and effective in adolescents 12-17 years. However, a similar verdict from the same committee for Nucala was ignored by the FDA which later approved Nucala for patients 12 years or older – might it do the same for Cinqair?

Datamonitor 7MM sales forecast 2024: $815m

AbbVie/Roche’s Venetoclax For CLL
US approval decision due: April 2016
EU approval decision due: November 2016 – May 2017

AbbVie and Roche’s B-cell lymphoma-2 (BCL-2) inhibitor has been filed for US and EU approval on the basis of Phase II data in which a clinically meaningful proportion of relapsed, refractory and previously untreated chronic lymphatic leukemia (CLL) patients with a 17p deletion achieved an objective response. Another Breakthrough Therapy designate, Venetoclax selectively inhibits the BCL-2 protein, which prevents apoptosis in some cells, including lymphocytes. It is thought the drug’s mechanism “may help restore the natural process that allows these leukemic cells to self-destruct,” representing a new way to treat CLL patients with a 17p deletion – a group with few effective treatment options. Up to 10% of newly diagnosed CLL patients each year have a 17p deletion, and about 30%
to 50% of relapsed and refractory CLL patients have a 17p deletion.

The product will have to muscle into an increasingly crowded field, however. AbbVie’s own Bruton’s tyrosine kinase inhibitor Imbruvica (ibrutinib) and Gilead’s PI3K delta inhibitor Zydelig (idelalisib) are other options available and analysts say the key question, if approved, is where this product will fit into the therapeutic sequence. Then again, there is also the option to combine it with Imbruvica, further bolstering AbbVie’s oncology portfolio.

AbbVie’s NDA was granted a priority review, meaning that its approval should come in the last week of April. An EU decision is expected between November 2016 and May 2017.

Acadia’s Nuplazid For Parkinson’s
US approval decision due: end of April 2016
EU approval decision due: not yet filed

Nuplazid’s development has been characterized by delay after delay, but September finally saw Acadia file an NDA for Parkinson’s disease psychosis after new CEO Steve Davis took the helm. If approved, Nuplazid (pimavanserin) would represent a new and distinctly different pharmaceutical approach to treating psychosis and would be the first drug approved in the US for psychosis associated with Parkinson’s disease. In a Phase III clinical trial, Parkinson’s patients treated with the selective serotonin inverse agonist (SSIA) that preferentially targets 5-HT2A receptors had twice the improvement in psychosis as individuals who received a placebo. Patients benefited from the drug without side effects associated with antipsychotic medicines that often are prescribed off-label to people with Parkinson’s disease psychosis. Nuplazid has Breakthrough Therapy designation and priority review status, with a PDUFA data of May 1 (which falls on a Sunday, so the decision is expected the Friday before). An MAA filing is planned between March and June this year. About 40% of Parkinson’s patients experience psychosis characterized by hallucinations and delusions.

BMT worldwide sales forecast $487.5m in 2025

Portola’s Anticoagulant Antidote
US approval decision due: August 2016
EU approval decision due: not yet filed

Filed in the US in November, this is the second of two anticoagulant antidotes approaching the market which, it is hoped, will boost sales of the new generation of blood thinners (the other one being Boehringer Ingelheim’s idarucizumab, which was approved late last year in the US and EU). The newer oral anticoagulants products were a welcome alternative to warfarin in reducing the risk of blood clots that can cause heart attacks and strokes in a variety of clinical settings, but doctors sometimes need urgently to reverse their effects in cases of hemorrhage or when emergency surgery is indicated. The lack of antidotes to these products (as compared with warfarin, for which vitamin K is used), has left prescribers cautious and uptake has been slower than hoped. While Bi’s idarucizumab was developed for use with its direct thrombin inhibitor dabigatran, Portola’s product is aimed at use against the range of Factor Xa inhibitor products, including apixaban (BMS/Pfizer’s Eliquis), and rivaroxaban (Bayer/J&J’s Xarelto). Andexanet alfa is due to be filed in the EU this quarter.

Andexanet alfa was designated a Breakthrough Therapy by the FDA and if approved will be the first universal antidote for Factor Xa inhibitor anticoagulants. The FDA assigned a PDUFA date of Aug. 17, 2016 under an Accelerated Approval pathway, and all being well launch is expected later this year.

Amgen’s Etelcalcetide For SHPT
US approval decision due: August 2016
EU approval decision due: August 2016 – February 2017

This product is being positioned as the follow-on to Amgen’s blockbuster Sensipar (cinacalcet) which is due to go off patent in 2018. Secondary hyperparathyroidism (SHPT) affects about two million people who are currently on dialysis and is caused by an increase in parathyroid hormone as kidney function declines. Etelcalcetide’s main benefit appears to be its dosing: it is given iv three times a week at the end of each dialysis session, compared with once daily oral dosing with Sensipar which can involve many tablets per day to normalize serum calcium levels. Also known as AMG 416, etelcalcetide is a calcimimetic agent that binds to the calcium channels and decreases the production of the hormone. It was filed for US approval last autumn and with a standard review has a PDUFA date of Aug. 24. Amgen announced its MAA filing for the treatment of SHPT in adult patients with chronic kidney disease on hemodialysis therapy using the centralized procedure in early September.

CTI/Baxalta’s Pacitinib For Myelofibrosis
US approval decision due: September – November 2016
EU approval decision due: not yet filed

Pacitinib is an investigational oral kinase inhibitor with specificity for JAK2, FLT3, IRAK1 and CSF1R, currently under US review as a treatment for patients with intermediate and high-risk myelofibrosis with low platelet counts of less than 50,000 per microliter (<50,000/μL).

The disease is a rare and serious chronic blood cancer that can affect patients of all ages with a median age of 65 years, with an estimated prevalence in the US of about 18,000 patients. The only product specifically approved for myelofibrosis is Novartis’s JAK1 and 2 inhibitor Jakafi (ruxolitinib), which was approved in 2011 for the treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis or post-polycythemia vera myelofibrosis or post-essential thrombocytemia myelofibrosis. The pacitinib NDA was based mainly on CTI BioPharma’s randomized, open-label, multicenter PERSIST-1 Phase III trial, which compared the product with best supportive care (not including a JAK inhibitor) and showed consistent rates of spleen volume reduction and control of disease-related symptoms across all intermediate or high-risk myelofibrosis subgroups. The rolling NDA was initiated in November 2015 and completed earlier this month and so BMT expects a decision between Sept. 23 and Nov. 5, 2016, assuming an accelerated review time. An EU filing is due early this year.

Sanoﬁ/Regeneron’s Sarilumab For RA
US approval decision due: October 2016
EU approval decision due: not yet filed

The highly competitive anti-inflammatory segment saw another novel offering filed last year, a product of the R&D alliance between the French giant Sanoﬁ and Regeneron Pharmaceuticals. Like Roche’s marketed blockbuster arthritis treatment Actemra (tocilizumab, currently the only IL inhibitor licensed for Rheumatoid Arthritis; RA), sarilumab inhibits the interleukin-6 receptor, but it is a fully human monoclonal antibody, rather than being humanized. It seems its fate on the market will rest on how well it can differentiate itself not only from Actemra, but also from Johnson & Johnson/ GlaxoSmithKline’s fully human anti-IL-6 antibody sirukumab in Phase III for rheumatoid arthritis (positive top-line results in moderate to severe disease were reported in December). Moreover, the arrival on the market of biosimilar anti-TNFs is expected to have a more profound impact of the RA market. Their anticipated lower price compared with the branded agents will drive uptake, with payers heavily influencing prescribing decisions. The BLA filing was accepted for review for the treatment of patients with active, moderate to severe rheumatoid arthritis; the PDUFA date is set for Oct. 30, 2016 (as this date falls on a Sunday, a decision is expected on Friday, Oct. 28). An EU submission, however, is not expected until late 2016.
Where Will Technology Take Pharma In 2016?

Non-traditional healthcare partnerships are on the increase, including collaborative deals between big phamas and technology giants such as Apple Inc. and Google. But what changes could these business partnerships – which have increased over the past few years – have in the long-term on the pharmaceutical and biotech industry?

A new series of reports from Sagient Researcher’s BioMedTracker (BMT), an affiliate of Scrip, look specifically at this question, conducting some future-gazing to speculate on how the industry might change as crossovers between technology and healthcare increase, particularly in the life sciences sector.

In the reports, Intersection Between Tech And Pharma, (of which two of three have been published so far) it is noted that 40% of Fortune 50 companies pursued healthcare related partnerships in 2014.

Lead author of the report Armando Uribe told Scrip that in his opinion healthcare and technology partnerships, if they continue in growth and volume, could really help enhance the understanding of many diseases through better research.

“The future of health research is going to be in better comprehending why our bodies do the things they do. If researchers start to get a better understanding of that, then they can begin helping people prevent chronic diseases like type 2 diabetes, obesity, heart disease and more, instead of focusing on treatments to manage them,” Uribe said. However, he noted that collaboration or “intersection” between pharma and technology “is still at a very early stage.”

One of the major players to make a move towards healthcare is Google, which under its new parent company, Alphabet, has its own internal life science unit – what used to be known as the mysterious and shrouded Google[x] and has now been spun out under the header Verily.

Verily’s first pharma relationship was announced in July 2014, a deal which would see the company team up with Novartis AG’s Alcon business for the development of a smart contact lens. Following that announcement, in 2015 Verily secured deals with the likes of Biogen, Sanofi, Johnson & Johnson, and Dexcom. These partnerships cover a wide range of diseases such as multiple sclerosis, heart disease and diabetes and Verily’s partnership with Johnson & Johnson is for research into the advancement of surgical robots.

Google and Novartis’s deal remains the most advanced prospect though and the two companies expect to initiate human testing for this product in 2016. This lens prototype is for accommodative vision correction in people with presbyopia, or age-related long sightedness, who can no longer read without glasses, BMT notes.

However, despite Google’s obvious attraction to the healthcare space, BMT analysts highlighted that Andrew Conrad, head of Google[x]’s life science team, does not intend Google[x] to become a pharma company. However, “it seems that they may plan on creating a software product that they can license to others in the biotech and pharma space.”

BMT said in its report that as an eye care focused company, Alcon may be brainstorming other innovative ideas in which they can use the smart lens. Analysts noted that the partnership will also help Google understand how to combine these sensors on a lens in a way in which the eye and cornea won’t be bothered. “If successful, the life sciences team could be looking to license the technology to other big ophthalmology players in the pharma space like Allergan or Regeneron. Currently there are no other competitors in the space as other companies are focused on developing small devices attached to the body that connect to a separate device that reads and transfers patient information,” BMT said.

BMT did point out though, that as in this case, a trend is appearing among these tech and pharma partnerships – there is very little information about these arrangements made public.

For example, while Novartis CEO Joe Jimenez has publically stated that it will be around five years before a smart lens type product reaches the market, what remains unclear is the level of involvement both parties have in one another’s projects. “Novartis has not mentioned any development of the smart lens for glucose monitoring and Google[x] has not mentioned any development in patients with presbyopia,” BMT said in its report. “With the information provided we can speculate that Novartis’s product, if approved, would be sold direct-to-consumer by prescription.”

Also Scrip recently spoke to Apple for insight into the company’s recent mobile app development deal and how it views the future for Apple and pharma; however Apple said it is not its practice to talk about future products in any sectors. The company did note it expected to provide a public briefing on its goals for the healthcare sector in the near future.

More From Apps

Urbe nominated “mobile health and mobile app development” as the most interesting area for tech and pharma firms to collaborate in at this time. “Our smartphones have the technology to tell us a lot of different information and the more quality information that can be gathered will help an individual stay engaged and make better educated decisions about their behavior,” he said. BMT’s report highlights Apple’s recent partnerships with Epic systems, for information transfer to EHRs (electronic health records), and with IBM for apps that aim to cut down the hospital inefficiencies.

He noted that one area where we could see an increase in app development from pharma or biotech firms would be orphan diseases. “Since orphan disease patients are usually found in small groups all over the world, I think it’s an area where having mobile apps for research can really help with the understanding of these diseases,” he said.

What’s Next?

Novartis and a handful of other healthcare firms aside, Uribe said the thing that has surprised him most in watching the growing health/tech space is how reluctant pharma still seems to be when it comes to collaborating with tech.

“There was even an interview where the CEO of Roche said the tech companies were simply IT companies in the healthcare space and they lack the medical knowledge. Overall, there has only been a small number of big phama companies involved in partnerships with tech to date,” Uribe said.

However, Uribe does see the push for collaboration continuing from the technology side. “Tech firms have had a growing interest in healthcare because of how inefficient it is,” he said. “Whether it’s helping to gather and analyze results from a clinical trial or general patient care, it is very clear that the way things are done in healthcare hasn’t changed in a very long time. Tech companies really see an opportunity in that, especially given how much our technology has advanced in the last 10 years.”

And in his opinion there is space for better technology everywhere in healthcare, “whether it is collaborations for surgical robotics, mobile health apps, EHRs, or data analytics software.”

To download BMT’s The Intersection Between Tech and Pharma special reports go to: www.biomedtracker.com
JPM: Biotech Values Dive, Industry Remains Optimistic

Most of the time when biopharma CEOs and healthcare-focused investment bankers descend on San Francisco’s Union Square in mid-January to assess the industry’s status for the months ahead, biotech stocks rise as companies announce deals and data, but that’s not what happened this year.

Investor sentiment for the biopharma industry seesawed dramatically during the 34th Annual JP Morgan Healthcare Conference from Jan. 11 to 14. The Nasdaq Biotech Index (NBI) closed down on two of the four days and up on the other two days, ending the conference 10% below the prior week. But when you talk to big pharma or small biotech executives and long-time biopharma investors, they believe that the industry is generating incredible science with the power to help a lot of patients.

Admittedly, though, the industry has to retain some eternal optimism or else no one would stay in a business with a high failure rate historically and limited successes – although some of those successes are multibillion-dollar drugs.

BD Optimism Runs High

“We’re building better drug candidates and they’re getting better so much faster than I thought,” James Sabry, senior vice president and global head of Genentech partnering, told Scrip.

But while Sabry is optimistic, he notes that the declining value of biotech stocks and the increasing difficulty of initial public offerings for pre-commercial companies has early-stage executives running scared, so much so that deal values already are being affected.

“I feel more urgency on the part of biotech companies, because it feels as if there’s less time to raise money,” he said, with companies fearing that drug development financing is about to dry up.

The net effect of the NBI falling 26.3% from its 2015 peak, reached on July 20, is that biotech companies have become less aggressive about how much control they want to maintain in partnership agreements and there’s more room to negotiate prices in licensing deals. But since big pharma and large biotech companies like Genentech need to fill research and development pipelines with the next wave of game-changing treatments, Sabry is optimistic that the volume of dealmaking won’t slow down in 2016.

“I think there are going to be some great deals in the next year,” he said, and not just because Genentech and its peers may get a discount relative to the last few years. There could be more deals than 2015, he notes, because any decline in values gives bigger companies better access to drug candidates from smaller firms.

“Innovation, more and more, comes from small companies,” Sabry said, noting that half of Genentech’s therapeutic candidates come from outside of the Roche company.

Roche’s big pharma peer Eli Lilly & Co. takes a similar approach to filling its R&D pipeline. About 60% of Lilly’s drug candidates come from internal R&D, but the other 40% comes from licensing and acquisitions with a preference for early-stage assets, CEO John Lechleiter told Scrip.

Small Firms Positioned For Deals

Luckily for four-year-old Cambridge, Massachusetts-based RaNA Therapeutics, the biotech firm closed a $55m series B venture capital round in July, before biotech stock values began to plunge and a few months before the IPO market appeared to shut down for drug developers.

The financing allows RaNA to focus on business development rather than fundraising while the company prepares to begin its first clinical trials. RaNA is developing drug candidates that target long non-coding RNA with the goal of upregulating genes specific to certain diseases – initially spinal muscular atrophy (SMA) and Friedreich’s ataxia.

“We’re very comfortable with our balance sheet today,” RaNA CEO Ron Renaud told Scrip. “But as we take more from the bench into the clinic, we will focus more on fundraising.”

For now, the company is talking to potential partners about programs that could help RaNA test the possibilities of its technology platform, and it’s focused on taking its first candidates into the clinic, because “if you have good data, that always attracts capital,” Renaud said.

The CEO knows well that by keeping data front and center, despite valuation fluctuations and other challenges, a lot of value will be created. Renaud was CEO of Idenix Pharmaceuticals when Merck & Co. Inc. paid $3.85bn for the publicly-traded hepatitis C-focused company in 2014 after Idenix recovered from clinical holds on some of its programs.

Based on his experience as a public company CEO, Renaud is happy to be leading a private company that doesn’t have to answer to shareholders during a period of declining biotech stock values, but he doesn’t think that recent public investor sentiment will send the industry into hibernation.

“We’re seeing a lot of terrific science being valued in a way that’s appropriate for the industry right now,” Renaud said.

Investors Reassess Values

Nina Kjellson, a general partner at the venture capital firm Canaan Partners, said in an interview that VC investors are reviewing their portfolios in the wake of stock price declines and the likelihood that some private companies won’t be able to launch planned IPOs in the near term.

Just how far values will fall in the eyes of stock market investors, who can be fickle, is unknown. However, the mindset of investors that focus entirely on the life science sector is to bet on technology with good scientific potential based on the industry’s growing genomic knowledge and other advances.

“There’s no change in the view of the industry,” Kjellson said. “The science has evolved and pharma still wants to partner with early-stage companies.”

For venture capital investors, returns usually are larger when biotech firms are purchased compared with when companies launch IPOs. Canaan tries to build biotechs that will be targeted for acquisitions, rather than position startups as IPO candidates due to the fickle nature of the stock market.

Under that strategy, Kjellson believes that early-stage companies still will be able to find capital even if the IPO market dries up and if mezzanine capital, which often is used to span the period between venture funding and an acquisition or public offering, becomes harder to find.

“You will just see bigger series A rounds, since you can raise enough money now to get to Phase II,” she said.

Dennis Purcell, founder and senior adviser at Aisling Capital, also believes that funding won’t dry up. There are a lot of new investors that are investing in biotech, but they aren’t necessarily buying and selling stocks: health care systems that have their own VC funds, sovereign wealth funds, pension funds that want to invest directly in venture capital, and other private investors, Purcell said during a Jan. 12 panel discussion about the status of the industry at the Biotech Showcase, an event that runs concurrently with the J.P. Morgan conference in San Francisco.

So will private biotech firms benefit from investors that want to put cash into the industry, but who are wary of the wavering values of public drug development companies? That remains to be seen, but specialty pharma stock values may continue to be in limbo this year, according to analysts at the investment bank Leerink.

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Bial Trial Tragedy: No Safety Clue From Similar Products (Continued from page 1)

J&J voluntarily suspended dosing in a Phase II trial for anxiety and major depressive disorder comparing 25 mg po once daily with placebo in a planned 140 patients which began in October 2015 and was due to report in 2017 (see p13).

Another compound, IPI-940, is in development by the private Canadian firm FAAH Pharma and in 2014 was due to enter Phase IIa for neuropathic pain, with post-herpetic neuralgia being the primary focus. The compound was originally discovered and developed by Infinity Pharmaceuticals, Inc. but FAAH Pharma received venture funding from Montreal-based venture capitalists TVM Life Sciences to continue its clinical development.

Pfizer discontinued PF-04457845, which was in Phase II for post-traumatic stress disorder last year, for lack of efficacy as it did not meet its primary endpoint, with no safety issues reported. It had previously been tested in a Phase Ila trial for osteoarthritis of the knee, but no results for this study have been posted on clinicaltrials.gov.

Sanofi had SSR-411298, which reached Phase II in cancer pain but was discontinued for strategic reasons in 2012; again no safety issues were reported. It has previously been discontinued for anxiety and depression because Phase II results did not support progression into Phase III.

Vernalis’s V-158866 was discontinued last year after a Phase II proof-of-concept study for neuropathic pain showed that it failed to meet its pain-reduction primary endpoint. At the time, Vernalis claimed that consistent with its strategy of becoming a commercial business, it would not make any further investment in V-158866, but would partner the product if the opportunity arose.

Of the remaining FAAH inhibitors that have got lost along the way, little is known of their fates (see table below).

Little is known of the fate of some other FAAH inhibitors

Another small firm, the Indian company Advinus, is looking at a FAAH inhibitor at the preclinical stage for chemotherapy-induced neuropathic pain.

No Safety Hints

Of those products that have been discontinued, the reasons behind the terminations do not appear to be due to safety concerns.

Other FAAH Products No Longer In Active Development

<table>
<thead>
<tr>
<th>Compound</th>
<th>Company</th>
<th>Indication</th>
<th>Highest Development Phase Reached</th>
<th>Other Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>IW-6118</td>
<td>Ironwood Pharmaceuticals</td>
<td>pain and inflammation</td>
<td>Phase II</td>
<td>A small-molecule FAAH inhibitor which completed a Phase II trial in 90 patients undergoing third molar extraction in the US in 2010. No results have yet been posted on clinicaltrials.gov.</td>
</tr>
<tr>
<td>MK-4409</td>
<td>Merck &amp; Co</td>
<td>general pain</td>
<td>Phase I</td>
<td>Phase I trials were conducted in 2009</td>
</tr>
<tr>
<td>SSR-101010</td>
<td>Sanofi</td>
<td>depression and anxiety</td>
<td>Phase I</td>
<td>It was in Phase I in 2007.</td>
</tr>
<tr>
<td>KDS-4103 (URB-597)</td>
<td>Organon (now Merck &amp; Co)</td>
<td>nociceptive pain</td>
<td>Preclinical/Phase I</td>
<td>It was originally under development by Kadmus Pharmaceuticals; however, Kadmus licensed all rights and assets to its FAAH inhibitors to Organon. It was ready for Phase I trials in 2007.</td>
</tr>
<tr>
<td>RN-450 29</td>
<td>Evotec (Renovis before the acquisition)</td>
<td>chronic pain, anxiety and depression</td>
<td>Preclinical</td>
<td>One of a series a tetrahydropyrdopyridine inhibitors of FAAH, which reached the hit-to-lead stage of development in 2011</td>
</tr>
<tr>
<td>Org-231296</td>
<td>Organon (Schering-Plough (now Merck &amp; Co))</td>
<td>general pain</td>
<td>Preclinical</td>
<td>It was in preclinical development in 2007.</td>
</tr>
<tr>
<td>VER-156084</td>
<td>Vernalis</td>
<td>inflammatory and neuropathic pain</td>
<td>Preclinical</td>
<td>A selective FAAH inhibitor.</td>
</tr>
<tr>
<td>FAAH inhibitor</td>
<td>LG Life Sciences</td>
<td>pain associated with rheumatoid arthritis and peripheral neuropathic pain</td>
<td>Preclinical</td>
<td>It was in the research phase in 2010.</td>
</tr>
<tr>
<td>URB-937</td>
<td>Italian Institute of Technology (IT)</td>
<td>pain associated with rheumatoid arthritis and peripheral neuropathic pain</td>
<td>Preclinical</td>
<td>A second-generation inhibitor of FAAH, which was under development for the treatment of pain without causing side effects. Clinical trials had been expected in 2012.</td>
</tr>
<tr>
<td>PF-04862853</td>
<td>Pfizer</td>
<td>general pain</td>
<td>preclinical</td>
<td>FAAH inhibitor series with novel spirocyclic cores. No development reported since 2011.</td>
</tr>
<tr>
<td>MAK-5206</td>
<td>MAKScientific</td>
<td>multiple sclerosis</td>
<td>preclinical</td>
<td>It was in vivo proof-of-concept in 2013. AM-374 and AM-404 were other compounds under investigation</td>
</tr>
<tr>
<td>ST-4070</td>
<td>Sigma-Tau</td>
<td>neuropathic pain</td>
<td>preclinical</td>
<td>A reversible FAAH inhibitor in preclinical development in 2012.</td>
</tr>
</tbody>
</table>

Source: Citeline’s Pharmaprojects
An Uncertain Future For Alkermes After Failed Trials

Alkermes efforts to create its own line of wholly-owned products beyond its side business as a formulation expert have not been the most successful so far. In fact, data released Jan. 21 could sideline one of its most promising efforts.

The biotech announced results from closely-watched Phase III trials of major depressive disorder therapy ALKS-5461. Both the FORWARD-3 trial and the FORWARD-4 trial, which both tested the MDD drug versus a placebo, failed to meet their primary efficacy endpoints. There is still one FORWARD trial ongoing.

Alkermes was depending on these two trials to be the backbone of their regulatory submission to FDA and expected the drug to have an accelerated timeline. Alkermes CEO Richard Pops told the J.P. Morgan Healthcare Conference earlier in the month that the biotech had confidence in the development program and that it was expecting positive results from these two trials based on earlier efficacy. Pops also said that two of the three last FORWARD studies are needed to show that ALKS 5461 is more effective in treating patients who haven’t succeeded on other antidepressants to submit an NDA.

**Blockbuster drugs only work in a fraction of patients**

Depression is an incredibly tricky development area. Even drugs that have become blockbusters only work in a fraction of patients and most patients have to try several drugs before they find one that helps them. FORWARD-4 tested two dose levels of ALKS-5461, 2mg and 0.5mg, in 385 patients. Alkermes claims that there was a positive trend toward efficacy in the higher dose and that this could potentially be used in an NDA filing.

Meanwhile, FORWARD-3 tested the 2mg dose in 429 patients. No treatment effect was observed and Alkermes claims this is because of a greater than expected placebo effect. FORWARD-5 is still ongoing and includes two dose levels, 2mg and 1mg. Based on these negative results, Alkermes is increasing the enrollment in the trial and said it will update investors on timing of that trial later in the quarter.

The most common adverse events were headache, dizziness, fatigue and nausea. These events were in line with what was seen in the previous Phase # study, as well as the Phase II studies.

This is a major blow to the biotech, which has been struggling with its wholly-owned products. Alkermes has expected ALKS-5461 to be its first blockbuster. The company already has two of its own drugs on the market – the schizophrenia drug Aristada and the drug addiction treatment Vivitrol. Neither has shown much promise as of yet, but Aristada was just recently approved. The company also collects royalties on several products from Johnson & Johnson and other companies that used Alkermes long-acting technology to create long-acting formulations of their products.

**Policy & Regulation Briefs**

**JPM: Pharma Must Change Message On Pricing**

When biopharma executives were asked during the 34th Annual J.P. Morgan Healthcare Conference what they thought of public concerns about prescription drug pricing, some dismissed it as a political issue and others offered the same old explanations about recovering the cost of developing innovative medicines, yet the industry appears dismayed about the ongoing uproar. Rather than explain, once again, that its costs a lot of money and takes a lot of time to produce new therapies or place blame on other parts of the US health care system, maybe the industry should come up with different answers and perhaps offer some options that could help reduce the cost of life-saving or even curative medicines. After all, it’s not just politicians and payers that have a hard time with drug pricing; doctors and patients also have raised red flags.

**Fauci: Rules Of Clinical Trials Must Not Slip In Outbreaks**

In the midst of a crisis like the recent Ebola outbreak that swept through Guinea, Liberia and Sierra Leone, killing more than 11,300 people and sickening nearly 29,000, it’s tempting to just throw everything the medical community has to offer at it in an attempt to save lives – something drug and vaccine makers and others conducting clinical trials often are under public pressure to do in desperate situations. But if the principles and rules of science and ethics are not followed, biopharmaceutical companies and researchers engaged in medical product studies could come to the end of an epidemic or other health crisis and be left without any knowledge that could help them the next time around – wasting everyone’s time and resources, said Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH).

**French Trial Tragedy: Investigations Begin**

A French Senate committee has intervened in the debate over the Phase I study of a new drug that caused the death of one volunteer and left a number of others hospitalized, saying that it plans to meet with the government inspectors who visited the site in Rennes to discuss their findings, with a view to looking afresh at the legislation governing clinical trials. Whether the legislation might need to change, and in what way, is hard to say, given that we still don’t know what happened to cause the injuries to the trial volunteers, beyond the fact that they had taken multiple doses of the drug from Portuguese company Bial, BIA 10-2474, a substance for the treatment of “neurological and psychiatric pathologies.” (See p1, 8, 12 & 13.)

**Industry’s Pledges, Government Cash Enough For Davos?**

For the first time, the drugs and diagnostics industries have banded together to produce a joint declaration on tackling antimicrobial resistance, which they are heralding as a great step forward in tackling the problem and launching during the World Economic Forum in Davos, Switzerland. The pledges are, however, vague and include no specific financial commitments. The declaration calls on governments to front up the cash. The declaration was drafted and signed by 85 companies and nine industry associations from 18 countries. It lays out a common set of principles on antibiotic conservation and supporting research, and calls on governments worldwide to work with industry to support R&D into new antibiotics, diagnostics and vaccines.
World-Top Scientist Busted For Stealing GSK Secrets  (Continued from page 1)

HER2 receptors on human body cells. She also previously worked on structure modeling and antibody protein purification. Xue is credited with successfully humanizing and patenting at least four separate antibodies. Her latest discovery, however, may be the lesson of the cautionary tale: Crime doesn't pay. Indeed, Xue is now facing a possible prison term, fines and restitution, if convicted of the charges against her.

The case is another example of what firms struggle with in protecting their information from being stolen and sold by insider rogue employees. According to the independent bipartisan Commission on the Theft of American Intellectual Property, the US loses about $300bn annually due to trade secrets theft, which the group said is “undermining the means and the incentive for entrepreneurs to innovate, ultimately slowing the development of new inventions and industries that otherwise could be further expanding the world economy and raising the prosperity and quality of life for the globe’s citizens.”

Lawmakers in the House and Senate last year introduced legislation aimed at making it harder for would-be thieves to snatch corporate trade secrets and other confidential information – the Defend Trade Secrets Act (S. 1890).

The White House also has put certain measures in place over the past few years to try to coordinate efforts between federal agencies and law enforcement intended to stop the pilfering of corporate trade secrets and other information.

Prosecutors noted that Xue, who had been with GSK since June 2006 before being terminated, had access to a wide array of GSK trade secret information.

In the indictment, Xue is accused of emailing GSK trade secret and other confidential information involving about a dozen or more products and numerous company processes from her corporate e-mail account to her personal account and then forwarding it to other schemers in the plot.

Prosecutors said she also used her GSK computer to download a "substantial" amount of trade secret information from the company’s network onto a thumb drive and other portable storage devices and sending it to her co-conspirators. Also charged was Xue’s colleague, Lucy Xi, who worked as a scientist at GSK from July 2008 until she departed the company this past November.

Xi is accused of emailing GSK trade secrets and other confidential information to her husband, Yan Mei, a medicinal chemistry scientist with a PhD from the University of Iowa. Mei co-founded Renopharma Inc., which was incorporated in the US in 2012, with Xue and Tao Li, a molecular biologist with a PhD from the University of North Carolina. They also formed two affiliates based in China – Nanjing Renopharma Ltd. and Shanghai Renopharma Ltd.

Prosecutors said the companies were created specifically to market and sell stolen trade secrets and other confidential information.

They said Renopharma “publicly touted” itself as “a leading new drug research and development company,” specializing in providing products and services to support drug discovery programs at pharmaceutical and biotech companies. Also involved in the conspiracy was Xue’s twin sister, Tian Xue.

In fact, to hide the proceeds of her crimes, Yu Xue put her ill-gotten gains under the names of her sister and other family members. Tian Xue, an immunologist with a PhD from the National Institute for Medical Research in London, set up a computer system for Renopharma and also assisted her sister with some of the scientific processes for the company. She also helped with the processes that used the stolen GSK information and trade secret procedures.

Yu Xue, Li, Mei and Xi also created Humanabio Inc. as a US subsidiary of Renopharma to hide their association with Nanjing Renopharma and Shanghai Renopharma and to facilitate the parent company’s objective of marketing, selling and profiting from the stolen GSK information, prosecutors alleged.

The indictment also details some of the back-and-forth in the emails among the co-conspirators and describes the types of GSK secrets and confidential information Xue had hijacked. For instance, one document identified a specific GSK antibody under development, while another contained information about the company’s strategy for developing an anti-HER3 monoclonal antibody and the specific candidate for clinical trials.

Among the stolen documents was a GSK report detailing the design of experiment, validation and platform method instruction and verification of analytical method for the quantitation of host cell proteins in monoclonal antibodies. Another described in very specific detail GSK’s procedures to test monoclonal antibodies, the indictment said.

Prosecutors pointed out that one stolen document – a GSK research report concerning the firm’s scientific research on specific monoclonal antibody candidates targeting the HER3 receptor – was “clearly” identified as belonging to the company and was marked “confidential” on the top of each page. The bottom of the first page also read “unauthorized copying or use of this information is prohibited.”

The document described in detail the binding capabilities and other important scientific characteristics of the antibody candidates and concluded that the scientific testing revealed that two specific candidates warranted further testing based upon the positive results achieved.

The indictment also revealed some of the disputes that went on among the schemers – disclosing that Xi complained in one email to her husband Mei that Yu Xue had been “annoying” her recently.

Mei advised Xi not to lose her temper, to which Xi replied, “I won’t … she is the queen.”

A GSK spokesperson told Scrip the company was conducting a full internal review into what occurred and would continue to enhance the “multiple layers” of data protection it already has in place.

“We take information protection very seriously,” she said, adding that GSK has been cooperating fully with the US authorities in the matter.

She said GSK did not believe the breach has had any material impact on the company’s business or research and development activities.

While she said GSK encourages appropriate sharing of information for the benefit of science, patients and the firm itself, “at the same time, we make it absolutely clear that unauthorized transfer of proprietary information outside of the company is a violation of GSK global policies, procedures and values.”

Ultimately, though, like other corporations, GSK is dependent on its employees to fulfill those obligations, the spokesperson pointed out.
Questions Arise About Latest MannKind Deal

The latest shenanigans to come out of MannKind Corp. were announced Jan. 21 when the failed biotech told investors that it has inked a collaboration with Receptor Life Sciences Inc. for use of its technology platform. According to a statement from the company, MannKind will perform initial formulation studies for Receptor, which will develop inhaled formulations of a number of undisclosed therapeutic compounds. MannKind will transfer its technology to Receptor and leave development and commercialization in its newly-formed hands. MannKind is eligible for $102.25m in development and commercialization milestones, as well as double-digit royalties on any product sales. There was no upfront payment.

Investors seem to think this is great news. MannKind’s stock is up almost 9% in midday training – although the stock still lingers well below $1 per share.

Never heard of Receptor Life Sciences? You wouldn’t be alone. The newly formed entity was only described by MannKind as a pharmaceutical company based in Seattle, Washington that “is quietly laying the foundation for groundbreaking new products in the specialty pharmaceutical market.”

Requests for comment from Receptor were not answered.

The company has an empty website that was reportedly created Jan. 10, the same day that MannKind’s former investor relations person and CFO Matthew Pfeffer took over as CEO of the company.

Despite silence from Receptor, Pfeffer responded to requests from Scrip for comment. “We have been in discussion for several months and are gratified we were able to ultimately reach agreement that is so beneficial for both companies. At this point, we have spent little and risked less in validating this possibility. Most of this work is still ahead of us,” he said. “Even then, our costs are largely confined to supporting their efforts using existing personnel, so our incremental out of pocket costs are minimal. All the risk and virtually all the cost will be borne by Receptor.”

Pfeffer noted that a substantial milestone is expected later this year from Receptor. “Receptor is a newly formed private company created by prominent individuals in the Seattle area, who for reasons of their own, prefer that their privacy be respected,” added Pfeffer.

Interesting Timing

Duane DeSisto was appointed CEO earlier in the month, but was conspicuously absent at the company’s recent conference calls and the company revealed the day after the conference that his employment offer had been withdrawn – reportedly due to a conflict of interests.

This collaboration comes at a very advantageous time for MannKind, which was promoting its “new path” at the recent J.P. Morgan Healthcare Conference in San Francisco earlier this month. The biotech’s “blueprint for 2016” included putting the new CEO in place, creating new opportunities for its failed inhaled insulin Afrezza and building the company through deals for its technology platform – the same platform that is the backbone of the newly formed deal.

Skepticism abounds – many investors have been questioning the legitimacy of Receptor as a real company, posting on both social media and investors message boards looking for answers.

All of this comes just weeks after MannKind’s big pharma partner Sanofi dumped the inhaled insulin Afrezza due to poor sales. Sales of the drug have not been broken out since it hit the market – a practice used by large pharma when a drug fails to hit a certain sales threshold.

In what many saw as a desperate move, Sanofi inked its deal with MannKind in August 2014, laying out $150m upfront and promising $775m in milestone payments should the drug hit certain sales goals. Obviously, Sanofi wasn’t as confident in the prospects for Afrezza as it claimed to be when it inked the deal – backloading the milestone payments to keep risk down.

Merck Versus Merck: Trademark Wars Hot Up

Merck & Co Inc. has filed a complaint against the company formerly known as Merck KGaA with the US District Court of New Jersey making a series allegations related to trademark infringement.

The complaint follows ‘German’ Merck’s decision to rebrand itself in the lead up to new CEO Stefan Oschmann taking up the top job in April 2016, from the incumbent Karl-Ludwig Kley, although the issue has been ongoing for years.

The latest flare-up follows Merck (of Germany) announcing in October that it was eliminating its Merck Serono and Merck Millipore brands, and would be known simply as Merck outside North America. Inside North America, where ‘US Merck’ owns the brand name, it would continue to use the EMD prefix for its businesses.

However, the complaint filed by US Merck on Jan. 15 claims “trademark infringement, trademark dilution, unfair competition, false advertising, deceptive trade practices, cybersquatting and breach of contract” in the US on the part of the other Merck. US Merck is demanding a trial by jury in the case.

Since the two companies became distinct entities almost 100 years ago, there have been regular skirmishes relating to their respective uses of Merck on the internet and in different jurisdictions.

“Certain matters were not resolved between the parties and KGaA initiated litigation against Merck and related entities in 2013 in the UK, Germany and France,” noted US Merck.

The French court ruled in December 2015 that certain activities conducted by US Merck were an infringement while others were not. Earlier this month, the English High Court issued a judgment that US Merck had infringed German Merck in certain activities in the UK.

Merck (US) has come back by filing a broad-reaching US complaint.

“KGaA has been making ubiquitous use of ‘Merck KGaA, Darmstadt, Germany’, ‘Merck KGaA’ and ‘MERCK’ as a prominent feature of its branding in the US, including use on websites which are specifically targeted to users in the US (despite KGaA claiming that its operating companies in the US today purportedly operate under the trade name ‘EMD’) as well as on social media sites that are more broadly accessible, including in the US,” it complained.

In addition, claimed US Merck, “KGaA has also recently engaged in other acts as part of a systematic pattern of behavior which is increasingly disruptive and damaging to Merck’s exclusive rights in the MERCK trademarks and trade name in the US. KGaA has taken a new direction and refocused its efforts on becoming a major player in the US market, including specifically in the immunology field where it directly competes with Merck, a well-recognized leader in that field.”

US Merck also noted in 2013, Stefan Oschmann - then head of pharmaceuticals for KGaA - stated that the US was viewed as an emerging pharma market for the German company.
French Trial Tragedy: FDA Launches ‘FAAH’ Safety Probe

US regulators on Jan. 22 said they are conducting a safety probe of fatty acid amide hydrolase (FAAH) inhibitors being developed and studied in the US after one healthy volunteer in a French Phase I trial testing a product in that class died and five other participants experienced severe adverse neurological events.

In a statement posted on the FDA’s website, the agency said it was in the process of collecting and reviewing safety information pertinent to FAAH inhibitors under investigation in the US following the tragedy in France, which involved the first known human fatality linked to an FAAH inhibitor.

FDA will ‘ensure the safety of participants in clinical studies and take regulatory action’

The FDA noted that FAAH inhibitors have been studied for their potential therapeutic use in a number of neurological disorders.

But the agency emphasized no trials of BIA 10-2474 – the product involved in the Phase I French study – currently are being conducted in the US.

BIA 10-2474 is manufactured by Bial-Portela & Ca SA, a Portuguese firm, which had hired French contract research organization Biotrial to conduct the study, which has since been suspended.

The FDA said it was conferring with the European Medicines Agency and the French National Agency for Medicines and Health Products Safety (ANSM) on what had gone wrong in the Phase I study, which was being conducted at a clinical site in Rennes, France.

French Health Minister Marisol Touraine has ordered two inspections – one by the ANSM and the other by the General Inspectorate for Social Affairs. The Public Health Department of the Paris Public Prosecutor’s Office has launched an “enquête de flagrance” inquiry intended to preserve evidence at the scene. And the French Senate’s social affairs committee is looking at whether the current legislative framework on trials needs to be tweaked.

Bial first disclosed the adverse events with BIA 10-2474 on Jan. 15, reporting to officials that six of the volunteers had been hospitalized, with one of them considered brain dead – the person who eventually died two days later at the University Hospital of Rennes. Bial reported on Jan. 19 that one of the five hospitalized BIA 10-2474 study participants already had returned home, while two other volunteers were transferred to local hospitals within their residence areas. The other two remained at the University Hospital of Rennes.

The FDA pointed out that catastrophic adverse events in Phase I studies in the US have been “extremely rare.”

But the agency said it doesn’t hesitate to put a trial on clinical hold if regulators determine participants might be exposed unnecessarily to risk of illness or injury.

In the US, study sponsors must collect “rigorous” laboratory and animal data and submit those safety data to the FDA in an investigational new drug application (IND) before any human volunteers may be enrolled in a Phase I study, regulators explained.

The firms can’t start their trials until 30 days after submitting the IND – a period the FDA said its scientists need to review the safety data and determine if the proposed study is reasonably safe to move forward.

The FDA said during its safety review of the FAAH inhibitors, it would work with sponsors to “ensure the safety of participants in clinical studies and take regulatory action as appropriate.”

The agency said it also would work with manufacturers to ensure FAAH inhibitor study participants and investigators are fully informed about the risks and potential benefits of the drugs.

Johnson & Johnson unit Janssen Research & Development LLC already has voluntarily suspended dosing “as a precaution” in its Phase II trials of its experimental FAAH inhibitor, which was being tested as a treatment for patients with mood disorders. Janssen said it had not received any reports of serious adverse events in the studies of its experimental FAAH inhibitor in patients with social anxiety disorder and in major depressive disorder with anxious distress, or in its earlier Phase I safety studies.

The firm said it would reevaluate its decision to suspend dosing in the trials when it has additional information.

A database run by Citeline, an affiliate of Scrip, showed there’s only a handful of FAAH inhibitors in active development and about a dozen others listed with no development reported – meaning there’s no evidence of continued development but neither any official confirmation the products have been dropped – while three others have been discontinued.

Senate Skips Critical Measures In ‘Cures’

While many stakeholders in the biomedical community were happy just to see the Senate Health, Education, Labor and Pensions (HELP) Committee finally unveil a plan for moving forward with legislation aimed at making changes at the FDA and the National Institutes of Health (NIH) intended to accelerate medical innovation, there also was disappointment that the step-by-step strategy proposed by Sen. Lamar Alexander (R-TN), the panel’s chair, ignored several measures, like one focused on antibiotics development, that were included in a mega-bill adopted by the House last July – the 21st Century Cures Act.

There also was disappointment that the plan Alexander laid out on Jan. 19 that one of the five hospitalized US regulators on Jan. 22 said they are conducting a safety probe of fatty acid amide hydrolase (FAAH) inhibitors being developed and studied in the US after one healthy volunteer in a French Phase I trial testing a product in that class died and five other participants experienced severe adverse neurological events.

In a statement posted on the FDA’s website, the agency said it was in the process of collecting and reviewing safety information pertinent to FAAH inhibitors under investigation in the US following the tragedy in France, which involved the first known human fatality linked to an FAAH inhibitor.

Indeed, an aide to Murray told Scrip that while the Washington lawmaker was eager to continue her efforts on the medical innovation legislation “in a bipartisan way,” the plan Alexander laid out on Jan. 19 doesn’t reflect an agreement between the two senators on a path forward beyond the first mark-up session, which is slated to take place on Feb. 9.

While Murray said she was pleased the “hard work on both sides of the aisle” is moving the HELP to hold the upcoming mark-up session next month – where the committee will consider seven bills that have implications for the FDA, NIH and the drug and device industries – she insisted there was “much more to do to get patients the safe, effective, innovative cures and treatments they are waiting for.”

The HELP will consider six more bills during a March 9 hearing. On April 6, the committee is expected to hold its third and final mark-up session and complete its action on the innovation agenda under Alexander’s plan.

Murray emphasized she wanted to see legislation that would address the burden that high drug costs impose on patients and the need for “critical mandatory investments in research and development at NIH and the FDA.”

Read the full story online at: http://bit.ly/1Szj70D

donna.young@informa.com
French Trial Tragedy: Janssen Halts FAAH Inhibitor Trial

Janssen has voluntarily suspended dosing in two Phase II studies of its experimental FAAH inhibitor JNU-42165279; the drug is in the same class as the compound at the heart of the clinical trial tragedy in France.

Janssen said it had stopped the trial as a precautionary measure. It stressed that it had not received any reports of serious adverse events in its Phase II studies with its FAAH fatty acid amide hydrolase inhibitor in patients with social anxiety disorder and in major depressive disorder with anxious distress, or in earlier, Phase I safety studies of the drug.

“We will re-evaluate our decision to suspend dosing in these clinical trials when we have additional information,” Janssen said.

While investigations continue into what happened during the Rennes study with this particular molecule (see p1 & 8), little is known as to the cause of the adverse events in the Phase I trial of Bial’s FAAH inhibitor BIA 1-2474. No safety signals were seen in other trials of products in the class, leading to speculation that the tragedy may not have been due to the pharmacological class itself but, rather, unforeseen off-target effects with this particular molecule.

The results from the first investigations by French drug and device regulatory agency ANSM and by the General Inspectorate for Social Affairs are due by the end of the month. ANSM has also decided to set up a special expert scientific committee to look at the existing data on FAAH inhibitors. Few details are yet available, other than that it is a temporary body (three months) made up of pharmacologists, toxicologists and neurologists.

In the meantime, ANSM has published the Phase I trial protocol for the Rennes study, which reveals some more facts: BIA 10-2474 (its chemical name is: (3-(1-cyclohexyl(methyl)carbamoyl)-1H-imidazol-4-yl)pyridine 1-oxide), in contrast to some speculation, was designed to act as a long-acting and reversible inhibitor of brain and peripheral FAAH “endowed with sustained inhibition of the enzyme.”

It was being developed by Bial for the treatment of medical conditions in which there is an advantage in enhancing the levels of endogenous AEA and tonically increasing the drive of the endocannabinoid system. BIA 10-2474 increases AEA levels in the central nervous system and in peripheral tissues.

According to the study protocol, treatment with BIA 10-2474 produced no signs of toxicity in mice, rats, dogs and monkeys up to the no observed adverse effect level.

In terms of its effects on humans, the protocol stated that there had been no previous experience. But it did highlight some potential flags: “Since BIA 10-2474 increases exposure to anandamide, endocannabinoid effects, such as catalepsy, hypothermia and hyperphagia, may be potentiated. Subjects should be informed about the possible occurrence of such effects and cautioned against rising rapidly after sitting or lying down ... Because of potential additive sedative effects, caution should be used when taking other CNS depressants.”

There were few other clues to potential toxicity in in vitro tests in liver cells: “In human hepatic microsomes, BIA 10-2474 (up to 30 μg/ml) produced minimal inhibition in CYP2D6 and CYP3A4 (testosterone) and is not an inhibitor of CY1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1 and CYP3A4 (midazolam) activities in vitro,” the trial protocol stated. “BIA 10-2474 (up to 30 μg/ml) is not considered to be an inducer of CYP2B and CYP3A, although further investigation with CYP1A2 may be warranted due to the effect observed in one of the donors used in this study. It has been predicted that the maximum plasma concentration of BIA 10-2474 achieved in humans is not likely to be >2 μg/ml and, therefore, it is unlikely that these inhibitions will be of clinical significance.”

Chronology Of A Trial

The French health minister, Marisol Touraine, told a press conference Jan. 15 that this was an “accident of exceptional gravity,” and gave an outline of the chronology of the trial.

She said Biotrial submitted an application to begin the trial on April 30, 2015, for a “substance intended to treat mood problems and anxiety as well as motor problems linked to neurodegenerative diseases.”

The regulatory agency ANSM gave the go-ahead for the trial on June 26, 2015, “in line with the current procedure.” The trial began on July 9, 2015.

The study was to include 128 healthy volunteers, men and women, aged 18-55. To date, 90 people had taken the product at various doses, while others received placebo. At first single doses were given, then multiple doses for several days. It was those who took repeated doses who fell victim to “serious undesirable events.”

The minister said that these volunteers took their first dose on Jan. 7, 2016, and the first symptoms appeared in one person who was hospitalized on Jan. 10. The five others were then hospitalized as well. Biotrial said it stopped the trial on Jan. 11.

Touraine expressed concern that she was only told of the incident on Jan. 14, four days after the comatose patient had been hospitalized. “A more rapid alert would have been appreciated,” she told the radio station RTL. “It is true that faced with such a serious event, we would have expected the laboratory to make it known to the health authorities more quickly.”

As for the study itself, ANSM said it was being conducted only at Biotrial's Rennes clinical centre. The substance, in question, which had “potentially analgesic effects,” acted on an endogenous neurotransmitter, the agency said.

The Phase I study comprised two initial stages in which no serious adverse events were reported. The third stage involved increasing the drive of the endocannabinoid system. BIA 10-2474 increases AEA levels in the central nervous system and in peripheral tissues.

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The Rennes university hospital centre (CHU) has issued a number of progress reports over the past few days. On Jan. 19 it confirmed that the patient who was in a coma died on Jan. 17, and on Jan. 21 it said three patients had been transferred to neurology services in hospitals near their homes following improvements in their health, while two have returned to their homes.

The Rennes CHU said that of the 84 other volunteers who took part in the trial, 28 have undergone a neurological examination and a temporary body (three months) made up of pharmacologists, toxicologists and neurologists.

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The Rennes CHU said that of the 84 other volunteers who took part in the trial, 28 have undergone a neurological examination and a cerebral MRI at Rennes and showed none of the clinical or radiological anomalies seen in the hospitalised patients.

Ian Schofield
R&D Bites

Samsung Bioepis's Etanercept To Be Rolled Out In Europe

Samsung Bioepis Co. Ltd. has received a marketing approval from the European Commission for its biosimilar version of Amgen Inc’s Enbrel (etanercept), the first etanercept biosimilar to be approved by the Commission and therefore likely the first to debut in Europe. But Sandоз is close behind – the Swiss company’s biosimilar etanercept was accepted by review by European regulators in December 2015. The latest approval paves the way for the South Korean biopharma’s biosimilar to be gradually rolled out as Benevapi (previously known as SB4) in 31 European countries - 28 EU member states as well as the European Economic Area (EEA) member states of Norway, Iceland and Liechtenstein - for the treatment of rheumatoid arthritis, psoriatic arthritis (PsA), axial spondyloarthritis (ankylosing spondylitis and non-radiographic axial spondyloarthritis) and plaque psoriasis. Aside from Europe and South Korea, the company is also undergoing a regulatory approval process for the etanercept biosimilar in Canada, she added. In accordance with a commercialization agreement signed in 2013 between Samsung Bioepis and Biogen Inc., Biogen will lead the commercialization

High Hopes For Merck/AiCuris HCMV Candidate

Chimerix Inc.’s dramatic Phase III flop of its oral antiviral brincidofovir in human cytomegalovirus (HCMV) was not a disappointment to everyone. Merck & Co. Inc. and its little-known German partner AiCuris, which have Phase III data due later this year on their oral product letermovir (AIC246), suddenly found themselves in the lead with a very promising next-generation candidate for the treatment of HCMV. Merck’s stumped up €110m upfront in 2012 for Bayer spin-off AiCuris’s then-Phase II stage letermovir. The US group also agreed to pay up to €332.5m in additional milestones, plus royalties on sales. AiCuris CEO Dr Holger Zimmermann told Scrip that AiCuris had yet to earn any of the milestone payments, but he anticipated that would change when the Phase III data become available. The trial is slated for completion in the third quarter of this year. “Enrolment went much faster than we expected,” he said. In the trial letermovir is being administered on a prophylactic basis to bone marrow recipients.

Kyprolis Wins Full Monotherapy OK

The FDA on Jan. 21 granted Amgen Inc. approval to market Kyprolis (carfilzomib) in combination with dexamethasone or with Celgene Inc.’s Revlimid (lenalidomide) plus dexamethasone as a treatment for patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy. US regulators also approved Kyprolis as a single agent for the treatment of patients with relapsed or refractory multiple myeloma who have received one or more lines of therapy – converting the accelerated approval granted in July 2012 to a full approval. The news gave shares of Amgen a 1.2% boost in after-hours trading. Kyprolis’ initial accelerated approval as a single agent was for patients with multiple myeloma who have received at least two prior therapies, including Velcade (bortezomib), a drug marketed by Takeda Pharmaceutical Inc. subsidiary Millennium Pharmaceuticals Inc., and an immunomodulatory agent, and have demonstrated disease progression on or within 60 days of completion of the last therapy. Sean Harper, Amgen’s executive vice president of research and development, pointed out that Kyprolis is the only approved therapy for relapsed multiple myeloma with proven efficacy as a single agent, doublet and triplet combination that’s offered in a variety of doses, which he said would meet individual patient needs.

NIH Resumes Indian Trials, Will Others Follow?

More than two years after it cut back on Indian clinical trials, the US National Institutes of Health (NIH), the largest public funder of biomedical research in the world, appears to have recommenced activity in the area, albeit on a cautious note. The return of the NIH, some industry experts say, could boost the confidence of several sponsors still evaluating the prospects of placing large studies in India in the backdrop of evolving trial regulations. These experts, however, add that while the worst may be over, India’s clinical research segment is not out of the woods yet and regaining lost ground will be a slow journey. The NIH told Scrip that it is aware that the Government of India has taken several steps since January 2013 regulations were published to clarify the scope and application of the rules and to provide additional information on their implementation. These steps have been helpful and have enabled a number of NIH-funded studies in India to resume enrolment of new patients. We look forward to further elaborations and guidance on the Government of India’s implementation of the rules, and to continuing important collaborations with colleagues in India for the mutual benefit of our citizens,” the NIH said. The NIH essentially funds clinical trials in other countries through grants and contracts.

Zika Virus Vaccine Hunt Begins

The pharma industry’s (and the media’s) interest in Ebola has begun to wane as more affected African countries secure disease-free status from the World Health Organization, but another tropical condition has started to capture headlines – Zika virus (ZIKV), a mosquito transferred disease reportedly responsible for approximately 4,000 child birth defects since Oct. 2015. This time the focus is on Brazil, the location for the 2016 Olympic Games, where an outbreak of ZIKV is thought to be responsible for more than 3,893 cases of suspected microcephaly in newborns since Oct. last year. This number represents a huge increase in the condition that causes children to be born with abnormally small heads and brain defects, which affected only approximately 150 babies in the whole of 2014 in Brazil. ZIKV is generally mild and only causes symptoms in one in five people and the link between ZIKV and microcephaly has not been clinically established. However, 49 babies with suspected microcephaly have died and Brazil’s health ministry says in five of these cases an infection with ZIKV was found. No other explanation for the surge in microcephaly has been suggested and the US Centers for Disease Control (CDC) has issued interim guidelines for pregnant women during this ZIKV outbreak, which include suggesting all pregnant women consider postponing travel to areas where ZIKV transmission is ongoing.

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Amgen Inc. failed to convince the US Patent & Trademark Office (US PTO) Patent Trial and Appeal Board (PTAB) to institute trials under so-called inter partes reviews (IPRs) in the company’s challenge of two patents, known as ‘157 and ‘158, held by AbbVie Inc. on its tumor necrosis factor blocker Humira (adalimumab).

In a twist, Amgen, whose own products have been the targets of biosimilar makers, is pursuing a biosimilar version of Humira – disclosing this past November it had submitted a 351(k) application to the FDA, which is expected to soon make a decision on whether to accept it.

The IPR proceedings were created under the American Invents Act of 2011 as a faster and more affordable alternative to litigation for challenging patents and whose use has grown far beyond what the US PTO anticipated. An IPR may not be instituted unless the information in the petition shows there is a reasonable likelihood the petitioner would prevail in at least one of the claims challenged. But the PTAB said it was not persuaded by Amgen.

BMO Nesbitt Burns analyst Alex Arfaei said he believed the PTAB's decision strengthens AbbVie's argument that its intellectual property and litigation strategy could protect Humira from biosimilar entry in the US until 2022.

Drug makers initially were slow to pursue IPRs. But there’s been a significant uptick in the number of petitions filed by those types of firms – particularly generic manufacturers and biosimilar companies.

Indeed, an analysis by the law firm Fish & Richardson found that of the IPR petitions filed as of Sept. 30, 2015, 9% involved biopharma patents. Over half were denied, while about 31% were granted and nearly 18% were granted in part.

With IPRs relatively inexpensive to file, biopharma firms are turning to them to “clear the deck” before pursuing litigation in the district courts, said Elaine Herrmann Blais, a partner and head of litigation at Goodwin Procter’s Boston office. Her colleague, Alexandra Lu, an associate in the litigation group at firm’s Boston office, noted that a party cannot appeal the PTAB’s decision granting or denying institution.

The Supreme Court on Jan. 15 said it planned to hear its first case on the standard used by the PTAB in deciding the validity of patents under IPR reviews and whether the board’s decision to institute those proceedings should be judicially reviewable – with the petitioner in the case, Cuozzo Speed Technologies, backed up by the large biopharmaceutical trade groups, the Pharmaceutical Research and Manufacturers of America and the Biotechnology Innovation Organization, in complaining the “broadest reasonable interpretation” used now by the US PTO’s board has resulted in unprecedented levels of patent claims being invalidated.

The fact Amgen's petitions failed at the patent board, said BMO's Arfaei, is “indicative” of the patents’ strength “or the weakness” of the company's argument. He doubted whether Amgen would be able to invalidate the '157 patent in particular at the US district court.

The watch is on to see what type of path Amgen will take in its defense under the Biologics Price Competition and Innovation Act after it hears from the FDA on its adalimumab biosimilar application, given the company currently is in the midst of legal disputes involving copycats of its biologics against Sandoz Inc., Apotex Inc. and Hospira Inc.

Dr Ge Li, chairman and CEO of WuXi PharmaTech

The judges were impressed with how Li has led WuXi’s growth, since its founding in 2000 with a single laboratory to an industry-leading open-access capability and technology platform with over 10,000 employees and global facilities. The qualifying year saw the platform enable more than 2,000 collaborations worldwide and WuXi make huge strides in strengthening its R&D pipeline.

“I am deeply honored and inspired by this award. I would like to thank our many customers and partners for their tremendous support for our efforts. It has been our great privilege to help bring some of the most innovative healthcare products closer to patients."

Dr Ge Li, chairman and CEO of WuXi PharmaTech
Business Bulletin

Acorda Picks Up Late-Stage Parkinson’s Candidate

Acorda Therapeutics Inc’s president and CEO Ron Cohen has been dropping hints for some months that he was pursuing significant business development opportunities and the EU was his preferred hunting ground. Finally, on Jan. 19, Acorda said it has agreed to acquire Biotie Therapies Corp. of Finland for around $363m. Biotie has a Parkinson’s disease drug candidate in Phase III which has a mechanism of action that has caused problems for other companies. The acquisition gives Acorda worldwide rights to tozadenant, an oral adenosine A2a receptor antagonist currently in a Phase III trial called TOZ-PD for the treatment of Parkinson’s disease. The product had been partnered with Belgium’s UCB but Biotie regained full rights in 2014 after a “portfolio re prioritization” on UCB’s part. Tozadenant was originally licensed to UCB in 2010 and UCB paid Biotie $20m to exercise its license in February 2013.

The Phase III study, initiated in July 2015, is a randomized, double-blind, placebo controlled trial evaluating tozadenant in 450 Parkinson’s patients experiencing end-of-dose wearing off episodes. Biotie reached an agreement with the US FDA on a Special Protocol Assessment of this study. Top-line data from the double-blind portion of the study are expected to be available by the end of 2017. “Tozadenant is a compelling opportunity with potential market exclusivity to 2030. The Phase II data were highly statistically significant and clinically meaningful. We are targeting an NDA filing by the end of 2018,” said Cohen.

Zafgen Optimistic, But No Clear Path For Beloranib

Zafgen investors are clinging to any bit of hope they can, pushing the stock up after the obesity drug maker announced positive clinical trial data. Yet, safety signals still linger and an FDA clinical hold remains the largest obstacle to Zafgen moving beloranib forward. The biotech’s stock jumped 78.65% or $4.42, to close at $10.04 on Jan. 20 after Zafgen announced that results of the Phase III bestPWS ZAF-311 trial were finally jumped 78.65%, or $4.42, to close at $10.04 on Jan. 20 after Zafgen announced that results of the Phase III bestPWS ZAF-311 trial were finally available. While the trial showed statistically significant efficacy on both clinical endpoints when compared with a placebo in patients with Prader-Willi syndrome (PWS), the death of two patients during the trial and concerns about pulmonary embolisms threaten to derail the program permanently. Zafgen CEO Tom Hughes expressed optimism on a call with analysts, saying he expects things to move swiftly now. Yet, the elephant in the room was the complete clinical hold that the regulatory agency imposed on Dec. 2 after a second patient taking beloranib died from a pulmonary embolism. The biotech reported the first patient death in October when a patient taking the drug in the blinded portion of the study died from blood clots in the lungs. The second patient death occurred during an open-label extension phase of the trial; two other patients also experienced non-fatal pulmonary embolisms. Patients in the open-label extension study were screened to make sure they weren’t at increased risk of developing blood clots.

ACCF ‘Open For Business’

International investment group Abingworth has closed its eleventh life sciences fund, raising $105m for its Abingworth Clinical Co-Development Fund (ACCF) which will offer a novel co-development investment approach in the life science space.

ACCF will co-invest with other Abingworth funds in late-stage therapeutic clinical programs, sourced from external pharmaceutical and biotech groups seeking to advance their assets via Abingworth’s co-development portfolio companies. Abingworth says the fact that the ACCF’s raising was oversubscribed - exceeding its target of $100m – reflects a desire by players to avoid stock market volatility and focus on promising science that is supported by substantial late-stage data and subjected to robust due diligence. Abingworth managing partner Tim Haines said “a key attraction is that, as far as we know, this business model is unique and the ACCF is the first dedicated co-development life science fund.” He said the risk profile of ACCF is different from Abingworth’s venture funds. “It offers good potential returns. It’s unrelated to public stock markets. And the timelines will be shorter because they are pre-agreed terms. We take the assets from a large pharma or biotech,” Haines explained. Abingworth’s portfolio companies – Avillion LLP and / or SFJ Pharmaceuticals – then run them through clinical studies, to pre-agreed milestones. “We can predict those timelines, and then our companies can offer the asset back to the parent or owner of the asset on pre-agreed terms.” He said the attraction offered to pharma and large biotech is the possibility to progress some R&D assets which might not otherwise get spending priority.

Italian Industry Roadshow Hits The US

The Italian pharmaceutical industry has been busy polishing up its profile abroad. Having taken part in government-sponsored “Invest in Italy” roadshows in Turkey in October 2015 and Japan in November 2015, a number of leading Italian companies recently headed to the US to explain why the Italian industry is worth investing in. The first part of the “Invest in Italy” roadshow took place on Jan. 11 in New York, followed by a second leg at the JP Morgan Annual Healthcare Conference in San Francisco. The events were organized by the Italian Trade Agency, which promotes the internationalization of Italian companies under the umbrella of the Economic Development Ministry, to allow domestic firms to meet with potential investors. The San Francisco leg included a Jan. 13 conference attended by C-suite representatives of Italian firms such as Angelini, Chiesi, Dompé, Menarini, Italfarmaco, Recordati, Rottapharm and Zambon, as well as Italian executives from Italian subsidiaries of major multinational companies. Entitled “Healthcare: Italy on the move”, the conference heard from the likes of Italy’s deputy minister of economic development, Carlo Calenda, who said his government had begun a process of reforms to support the pharmaceutical sector through the whole value chain in order to help attract and maintain investments by international players. According to slides produced by the Italian pharmaceutical industry body Farmindustria, Italy’s pharmaceutical market in terms of retail and hospital sales is the third largest in Europe, and the industry consists of some 200 companies generating €29bn in manufacturing value and investing around €2.5bn in R&D each year.

Gavi Backs Merck & Co’s Ebola Vaccine

Gavi, the global vaccine alliance, has promised Merck & Co. Inc. that it has a customer for its Ebola vaccine candidate rVSV∆G-ZEBOV-GP, the only vaccine with Phase III data for the deadly viral infection, through the signing of an ‘advance purchase commitment’. The agreement, announced at the World Economic Forum in Davos on Jan. 19, is aimed at helping Merck take the vaccine through licensure and WHO prequalification. Under the commitment, Gavi has provided $5m towards the development of Merck’s rVSV∆G-ZEBOV-GP live attenuated Ebola Zaire vaccine, on the understanding that it will be filed for approval by the end of 2017. If approved, it will likely be the world’s first licensed Ebola vaccine and Gavi would be able to begin purchasing the vaccine to create a stockpile for future outbreaks. Additionally, Merck has agreed to ensure that 300,000 doses of the vaccine are available from May 2016 for use in expanded use clinical trials and/or for emergency use as needed while vaccine development continues. Merck has already submitted an application through WHO’s Emergency Use Assessment and Listing (EUAL) procedure. If the EUAL is approved, the vaccine to be used if another Ebola outbreak occurs before the vaccine is licensed. The 2014 Ebola epidemic in West Africa claimed the lives of more than 11,300 people and infected over 28,600. It also had a devastating impact on health systems with disruptive effects on childhood immunization programs. On 14 January 2016, WHO announced that no new Ebola cases had been reported in the three worst affected countries in the preceding 42 days. However, shortly following the news, Sierra Leone reported an Ebola-related death.
Will Supreme Court Lift ‘IPR Pressure’ Off Biopharma?

The US Supreme Court on Jan. 15 said it would hear a case to decide if the US Patent & Trademark Office (US PTO) Patent Trial and Appeal Board (PTAB) is using the proper standard when it determines the validity of a patent under so-called inter partes reviews (IPRs) and if the decisions to hold those proceedings should be judicially reviewable.

While the case, known as Cuozzo Speed Technologies v. Michelle K Lee, doesn't involve biopharmaceutical companies, its outcome could have broad implications for the types of products drug makers eventually decide to pursue for investment and development, said Hans Sauer, deputy general counsel for intellectual property at Biotechnology Innovation Organization (BIO), which filed an amicus brief in support of the firm that brought the appeal against the US PTO.

At issue is whether the US Court of Appeals for the Federal Circuit erred when it ruled that, in IPR proceedings, the PTAB may construe claims in an issued patent according to the so-called “broadest reasonable interpretation” (BRI) rather than their plain and ordinary meaning – often referred to as the “Phillips” standard – which is used by district courts.

The Supreme Court also is taking a look at whether a party may bring a challenge to the Federal Circuit of a decision by the PTAB to institute an IPR – trial proceedings created under the American Invents Act (AIA) of 2011 that were intended to be a faster and more affordable alternative to litigation for challenging patents and whose use has grown far beyond what the US PTO anticipated.

If the Supreme Court decides the PTAB has been using the wrong standard, it potentially could call into question the results of a number of IPRs, William Jay, a partner at Goodwin Procter, co-chair of the firm’s appellate litigation practice and head of litigation in Washington, last fall told Scrip.

Under Pressure

The IPR challenges, which have resulted in unprecedented levels of patent claims being invalidated – with most patents, about 85%, not surviving the proceedings under the PTAB’s BRI standard – have put more pressure on biopharmaceutical firms in their corporate decision-making, BIO’s Sauer told Scrip.

“It’s the kind of pressure that we don’t think is desirable for drug and therapeutic development,” he lamented.

Sauer said BIO hears frequently from its members that the “availability of IPRs is changing the way companies decide to take which products forward into development and where to make investments.”

“By putting more pressure on patents and creating more uncertainty about whether your patent will stand up to a challenge or hold up in a real commercial dispute, you are affecting corporate decision-making in an industry where there already are so many business uncertainties,” like the probability the medicine will fail in clinical trials or be unable to attract enough investment, Sauer explained.

Piling on the uncertainty about intellectual property in the face of the growing use of IPR petitions, which could wipe away a firm’s patents, may lead to a tipping point, where a company decides “to play it safer and pursue another product that may be less innovative, but has more robust patent protection,” he said.

‘Pressure on patents and more uncertainty about whether they will stand up to a challenge affects corporate decision-making’

“That’s not something we want in biotech,” Sauer insisted. “We want companies to develop the most innovative and best drugs. If companies decide to develop only the drugs with the best patents, that’s not always the same thing as the best drug that could be developed. It creates the wrong incentives. It’s not right for the industry to be under this kind of pressure from IPRs when all you want to do is make a rational investment decision, but you have to start worrying about IPRs, which has absolutely nothing to do with whether your drug is going to work and what unmet medical need it will meet.”

Biopharmaceutical firms initially were slow to pursue IPRs. But there’s been a significant uptick in the past year in the number of petitions filed – particularly from generic manufacturers and biosimilar makers.

Indeed, an analysis by the law firm Fish & Richardson found that of the IPR petitions filed as of Sept. 30, 2015, 9% involved biopharma patents. Of those, over half were denied, while about 31% were granted and nearly 18% were granted in part.

According to the US PTO, as of Dec. 31, 2015, there’s been about 4,000 IPR petitions filed since September 2012.

Of the 403 total AIA petitions filed so far in fiscal year 2016 – IPRs, covered business methods and post-grant reviews – 16% involved biopharmaceutical companies, the agency reported.

“More than enough investment, Sauer explained. “We want companies to have enough investment, Sauer explained. “We want companies to try to take down biopharma patents. But there’s been a significant tipping point, where a company decides ‘to play it safer and pursue another product that may be less innovative, but has more robust patent protection,’ he said.

Kyle Bass, chief investment officer at Hayman Capital Management, and his self-created Coalition for Affordable Drugs, also has become notorious for using IPR petitions to try to take down biopharma patents.

BIO complained in its amicus brief that under the PTAB’s use of the BRI standard, a patent is “systematically more likely to be found invalid” than under the Phillips standard used by the district courts.

“Clearly, the PTAB is invalidating patents at an extraordinary rate,” the biotech trade group asserted.

In a relatively short time, the PTAB has “cut a remarkable swath through the ranks of issued patents with barely a light tap on the brakes by the Federal Circuit,” BIO argued.

If the Federal Circuit’s decision is left to stand, it would “introduce considerable uncertainty in the construction of patent claims, increase the risk of conflicting invalidity decisions and undercut a central reform that Congress enacted to strengthen the US patent system” – consequences that “threaten the predictability and strength of protection that the patent system provides to innovators and the public alike,” the Pharmaceutical Research and Manufacturers (PhRMA) said in a separate brief filed with the high court.

The Supreme Court’s review is necessary “to effectuate Congress’ intent that patent claims in IPR proceedings be given their ordinary and customary meaning,” PhRMA argued.

The group contended that under the Federal Circuit’s decision, a patent claim could be correctly found valid by a district court under the Phillips standard, but also correctly found invalid by the PTAB in an IPR proceeding under the BRI standard.

“That new reality clouds and diminishes patent rights to the detriment of patent holders, innovators and the public at large,” the big pharma trade group asserted. “Uncertainty regarding the scope of patent claims and their validity is costly to the inventive community and discourages innovation.”

The Cuozzo Case

The Cuozzo case stems from a PTAB decision involving the firm’s ‘074 patent, which covers certain components used in global positioning systems.

Garmin International Inc. and its subsidiary Garmin USA Inc. filed an IPR petition challenging claims 10, 14 and 17 of the Cuozzo ‘074 patent.

The PTAB determined the claims were “obvious” and invalidated them. The board also denied Cuozzo’s motion to amend the ‘074 patent by substituting new claims.

On appeal to the Federal Circuit, a three-
With the major winter storm slamming the Washington area, the FDA decided to postpone the highly anticipated Jan. 22 meeting of the agency’s Peripheral and Central Nervous System (PCNS) Drugs Advisory Committee, although regulators gave panelists, patient advocates and others planning to attend the hearing little warning ahead of time.

The FDA was convening the adcomm to seek the PCNS committee’s advice about whether Sarepta Therapeutics Inc.’s Duchenne muscular dystrophy (DMD) drug eteplirsen could be safely marketed in the US and if the experimental medicine is efficacious in treating the severely debilitating neuromuscular disease, which results from mutations, usually partial deletions, in the gene coding for dystrophin, a protein essential for normal muscular structure and function and the lack of which is at the heart of the condition.

Sarepta is seeking approval of eteplirsen, which it wants to market as Exondys, as a treatment for DMD amenable to exon 51 skipping, which makes up about 13% of the total Duchenne population.

But the snowed out meeting likely now means a delay in the FDA’s verdict for eteplirsen, whose Prescription Drug User Fee Act action date is Feb. 26.

The four-week timeframe between the PCNS panel and the drug’s PDUFA already was short, RBC Capital Markets analyst Simos Simeonidis pointed out.

He anticipated that with the postponed adcomm, the FDA likely would delay its decision for eteplirsen by at least four weeks.

But given the high-profile nature of the adcomm and the pressure and scrutiny the FDA is under to get to a decision, Simeonidis said he doubted the agency would wait longer than two-to-four weeks to hold the rescheduled PCNS meeting, although he also acknowledged the difficulty regulators may have in keeping most of the same expert scientists and clinicians who were slated to serve on the Jan. 22 panel.

While the delayed meeting translates into more “anxiety for patients, companies, investors and analysts,” it also gives patient advocacy groups more time to continue to campaign against the negative tone of the FDA’s briefing documents, he said.

Indeed, the meeting was expected to be well-attended by the muscular dystrophy patient advocacy community – one of the most active patient groups in the US – and even Janet Woodcock, the FDA’s director of the Center for Drug Evaluation and Research, planned to be there, as did Rep. Michael Fitzpatrick (R-PA), who has called on the agency to quickly approve products for DMD.

The FDA, in fact, cited high public interest when it released its main briefing documents on Jan. 15, well ahead of the Jan. 22 meeting.

The briefing documents, however, were bad news for Sarepta – whose shares took a beating on Jan. 15, plummeting 60%, before closing the day at $14.28, a loss of $17.35, or 55%.

The Jan. 22 meeting was supposed to be Sarepta’s chance to defend its drug and dispute the FDA’s negative analysis, in which regulators raised considerable doubts about eteplirsen’s effectiveness in treating DMD and called into question the medicine’s ability to increase dystrophin levels.

It was also supposed to be another chance for the DMD community to plead with the FDA to approve a drug for the patients who are desperate for a treatment – especially after BioMarin Pharmaceutical Inc.’s experimental Duchenne medicine Kyndrisa (drisapersen) was rejected last week by the FDA and by the PCNS this past November.

If the FDA rejects eteplirsen, it would mean the exon 51 DMD community would be left without a drug near-term, RBC Capital’s Simeonidis said.

The FDA’s Jan. 20 late-day notice that it was postponing the eteplirsen meeting – which came just before 5:30pm EST, after the US markets had closed – whacked Sarepta’s shares again.

Indeed, the stock, which already had experienced a rough day on the market – tumbling 10.3%, before closing at $13.26, down 18 cents, or 1.34% – fell 2.7% in after-hours trading following the FDA’s decision to ax the Jan. 22 meeting.

The first sign regulators were considering shutting down the meeting was when the remaining documents expected to be released on Jan. 20 – agenda, FDA’s questions for the PCNS and the roster of panelists – failed to post online at their anticipated timeline of 48 hours before the start of the Jan. 22 meeting. Regulators gave no hints about how soon the PCNS meeting would be rescheduled.

The agency’s postponement notice said to watch the Federal Register – the place where the US government informs the public of federal actions, including plans for public meetings – for a future meeting date.

Sauer said.

Will Supreme Court Lift ‘IPR Pressure’ Off Biopharma? (Continued from page 17)
How long will it take your sales team to reach 42,000 senior decision makers in pharma companies globally?

Let us demonstrate how we can do this and show you ROI now!

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Informa Pharma's global director of content Mike Ward and Scrip's West Coast editor Mandy Jackson moderated a roundtable discussion on Jan. 11, the opening day of the 34th Annual JP Morgan Healthcare Conference, in San Francisco during which they spoke with eight biotechnology veterans about the state of biotech going into 2016.

The executives, including an advisor and a venture capitalist, were fairly optimistic about the potential for high-quality companies to raise capital this year and to attract big pharma buyers or partners, despite declining biotech stock values – the Nasdaq Biotechnology Index (NBI) was down 11.8% versus the end of 2015 on the first day of the J.P. Morgan conference and the NBI was down 17.7% as of Jan. 22.

Portions of the edited roundtable transcript below give a glimpse of the participants’ views on biotech deals and dollars. The group included: Accera Inc. CEO Charles Stacey, Novavax president and CEO Stanley Erck, Symic CEO Ken Horne, Corbus Pharmaceuticals CEO Yuval Cohen, Triferoed president and CEO Sergi Trilla, Aisling Capital founder and senior advisor Dennis Purcell, BIND Therapeutics president and CEO Andrew Hirsch, and Alder Biopharmaceuticals chief business officer Mark Litton.

Mike Ward: What has been really interesting in recent years is the tons of money that has been raised by this industry, which I calculated at about $100bn in two years. Are we now seeing the strains and stresses and concerns about whether or not that money is going to continue to be available? And with that money that you’ve got in the bank, how does that change the dynamics in terms of the have and have-nots and also in terms of partnering?

Mandy Jackson: The market is looking pretty rough for biotechs already this year, only a week and half in. Do you think that that is emblematic of the way the rest of the year will go, or is this just a reconfiguring of expectations?

Dennis Purcell: Last year, about 900 companies raised money and notwithstanding what has happened in the last couple of days or the last week in the [stock] market, I think that one of the things that strikes me is how big the ecosystem has gotten. It used to be that if one company failed a trial then everybody’s stock went down, but that is just not the case anymore.

The industry is very well financed. Another thing about the ecosystem is that it is financed by non-traditional names. When I left Hambrecht & Quist [the original J.P. Morgan Healthcare Conference organizer] to start our firm, there were probably 10 or 15 major VC firms – Kleiner Perkins or MPM – and what I’m noticing now is that the range of people investing in this industry is very wide.

I am less concerned about the boom and bust than I was before. It was a lot of money [raised in biotech], but a lot of companies are pretty well funded and there is a lot of data coming this year, so I think we are not going to look at the day-to-day swings like we used to.

Stanley Erck: I’ve been on [initial public offering] roadshows, and Synergen or somebody went down and it stopped the industry for years for IPOs. One company would affect the IPO candidates.

Purcell: Who would have thought five years ago that Gilead had a higher market value than Pepsi? It’s one of the great American companies and Gilead has a higher market cap.

Jackson: Do you think this wobbling right now of biotech stock values has more of an impact on companies that are already public, and smaller companies, as opposed to private companies that are out there raising funds?

Purcell: There is a lot of private capital out there. If you look at the traditional [limited partners (LPs)] one of the big misnomers is that everything has to be a 10x [return]. But most of the people, like [the pension fund California Public Employees Retirement System (CALPERS)], if they can get 600 basis points better than the [Standard & Poor’s (S&P) index], they are happy. If the S&P is flat next year and we give them an 8% return or 10% return, they are ecstatic.

So I think there is a lot of capital trying to chase returns right now, because there is nowhere else to put your money. And even though everything has gone down – the [biotech exchange-traded funds (ETFs) known as the] IBB, the XBI, the NBI – they were up 10%, 11%, 12% last year. That’s better than CDs; better than Apple stock.

Ward: So thinking about the early stages, are any of you looking to raise money at the moment or would like to raise money? I know with biotech that is the idea, you have always got your hand out, but in terms of if you are looking at it, have people missed the boat?

Yuval Cohen: We are a Nasdaq company, we debuted in April. But for early-stage companies one big difference is that VCs are no longer the default financing. Our financing wasn’t done with a single VC; it was done with two hedge funds, a bunch of high net worth individuals and a patient advocacy group. I think that is really different, that never existed before.

It is always less challenging to raise money as a public company versus a private company. Raising money as a public company is a function of your share price, and if the market isn’t that great then the share price would have some sort of discount applied to it. As a private company, you just don’t have that luxury; your money is locked in.

I had a European fund manager say to me once that he would rather invest in the world’s most mediocre public company than the most exciting private company. And remember – this is a fund manager, he is not a VC – so it is a very different type of return. A functional public market is very advantageous for this industry.

A lot of our investors are long-term, but they certainly do appreciate liquidity. We are fortunate that our investors are still firmly in the black. It is not exactly a consolation, but when [your stock is] less down than your peers, there is a certain tiny amount of consolation in that.

Andrew Hirsch: But it depends on what part of the public market, because as we all know this is a really risky business. Things rarely work the first time and it takes patience. So, if your capital base is people who are looking to invest, and you’ve got a data inflection point in six months, and I am investing for that data inflection point, that is a hard thing. Because if [the data] doesn’t go the way you want, then they’re gone and then you don’t have the support.

They come in all different flavors; they come in the fast hedge funds, that are in and out [of the stock] on every little thing. They are trading around earnings; they are trading around data. They can be helpful in an IPO to bring capital on board, but they are not there to help build your company for the long term. I think the key is to really find those investors that believe in what you are doing, believe in your technology, get that it might not work the first time, and that are going to be willing to put the second and third dollar in. That is to me what is important. Those investors are there, and they have always been there and they are still there.

I think the difference now versus when we went public in September 2013 is that a lot of the generalists are gone. I think the generalists came in and drove up these valuations, because they were looking for returns that they weren’t able to get anywhere else, thanks to the large cap biotech earnings growing rapidly and those stock prices following, and that brought all the capital in. They have all gone because
the [biotech IPO] class of 2013/2014 they have used that capital, they’ve gotten data, not everything worked – surprise, surprise – and the generalists ran for the hills. They said, “Wait – this isn’t riskless?”

Now you are back to a more normal [stock market], which is healthy, where not every company that files an S1 [registration statement with the US Securities and Exchange Commission (SEC)] is going to go public and get a 40% bump on the first day of trading. That’s healthy and I think that’s a good place to be.

Ward: What I am trying to understand is, are we more confident that the industry is going to be able to raise money this year? We see it go up and up and up in terms of the amounts of money that’s been raised. Is it going to be more difficult this year and if it is what does that mean for the way that you guys are going to do your business?

Ken Horne: By raising money, I think valuations will go down, because optionality has gone down. You can’t go public as readily as you could last year. So as a consequence, the VCs will give you a haircut for sure in the crossover pools and they will shift back to doing whatever they were doing two years ago, with a few exceptions.

It’s playing musical chairs with 100 people and three chairs. There are not a lot of great places to put money in, but there is a lot of it floating around, so there is still money to deploy. I think you just have to be more cognizant of what pools of capital you look from.

We have got a couple of VCs, but mostly [our investors are] family offices. There is a bunch of China funding and we’re talking to all kinds of different people and not because I feel strongly this way, but because for a matter of circumstance we didn’t go public. I am happy from the other side of that, which is I can prepare for winter now and people aren’t going to be checking on me every quarter to see what happened.

We are going to go out and raise as much money as we can in private markets because with whatever has happened this year, I don’t think it will be as bad as 2007/2008, but it could suck the next few years. And we know to go and get as much money as we can right now, and I think there is plenty of it out there, I just think the valuations are lower, depending on the pool. VC guys, I would expect a haircut. Family offices, they are investing for the grandkids. If they like the story, I don’t think they care that much.

Charles Stacey: It’s not really the number of investors that we can raise money from in the West, but also the world isn’t that small. So I am looking at raising funds soon and I’ll be in Asia as much as I am going to be in the US. There is proactive interest. Geographically there is a lot of options for companies to raise money.

Purcell: Are you guys spending a lot of time in the Middle East?

Stacey: I am not personally, no.

Purcell: You would rather be in Asia than the Middle East?

Stacey: It is just where the interest has come from, for us.

Mark Litton: Somebody once told me, and I thought it was excellent advice, valuations have never killed a biotech company. I mean, if you think about it, it’s your clinical data that kills a company or safety.

The truth of the matter is, it’s just a valuation discussion. I think biotech and innovation will continue. Sure, you might have to take a haircut, maybe you don’t make the profit that you want to for that year. But in our field of drug development, it is many years. Even trials, Phase III takes two years. It’s a long-term play and you have to weather it.

Jackson: So you have your money and you are out looking to do deals, what is impacting you? Is this finance market impacting you? Are you seeing pharma look more at whether or not the drug can be paid for? What is it that’s impacting dealmaking right now, and is it for the better or the worse?

Horne: I think capital availability and valuations going down is actually going to foster M&A, so I expect more M&A this year. I think the biggest influence, not that it impacts me, but I would hazard to guess it is going to impact some of your mid-size companies, is the exploitive consolidation that is going on at the top, because that locks up those two companies. They could probably deal with the likes of our size, but they are not going to go and do billion dollar deals when they are merging, and it takes six months, nine months [to close a big deal] and they are out of the [dealmaking] picture. Pfizer-Allergan, Shire-Baxalta, all of these things just, the number of big buyers …

Ward: We have to remember there aren’t that many of them anyway who could ever be a big buyer. Just think about how many big partners who you would actually be able to sell your assets to.

Purcell: You are saying it’s the last of them now?

Ward: Yes, there is a lot fewer companies.

Horne: But the companies in the top 10 to 50 are bigger, so that helps, but the top 1 to 10 companies are now the top 1 to 5.

Purcell: In the last few years we have tripled the number of billion-dollar companies by 3x, so I am not so sure I agree with you.

Ward: Are we going to see a depression in terms of the deals that biotechs can do? Will we see a shift away from it being the pharma guys having to pay top dollar?

Purcell: I don’t have the math with me, but if you assume your drug is going to be a $2bn drug and let’s say you get a 20% margin, so $400 million. Then let’s say you’re five years or seven years away from getting a product [launched], and let’s say you have to discount that back, because of the risk, by 20% to 25% or something like that, you start to do that math and the present value of some of these companies is tight. If you just give everybody the benefit of the doubt, it’s a $2bn drug, or it’s a 20% margin, then just discount it back to today, what you find is that some valuations are hard to swallow or explain.

Horne: I still think even with all of the consolidation at the top, if you net out all of the mega-merger stuff that’s going to happen this year, because number 10 through 50 is bigger, and because prices are going to go down, the people who are looking to buy their third asset and fourth asset who can actually stomach [a high valuation]. You know, $500m is not something to turn your nose up at, it is a big outcome, mostly, depending on what it cost to get there. I think there will be a lot of M&A this year.

Purcell: You think there is going to be a lot of mid-sized M&A this year?

Horne: I think there will be a lot of people who can step up, because they are large enough now and because valuations have come down. I think people will step up. [Fully integrated biotech companies (FIBCOs)] are back on track now.

Litton: I think what might be interesting, and I will play the devil’s advocate on this, is that I think debt capital for big pharma is still very, very cheap, and so as you get more pressure, I think big pharma has also been very conservative. Not to say there isn’t going to be deals, there will be deals done, and I think they look at it and they say, “Oh, gosh. That is 30% less than when I was looking at it six months ago,” so there is some appetite to that.

But I have also found the interaction, and this has happened over the last two years, much more, I really want no risk associated with this. I will pay for that, because when I’m borrowing the money, whether I am paying 20 basis points or 25 basis points, I want that asset so that it’s completely de-risked.

Purcell: So your devil’s advocate thing is that pharma is only going to buy more de-risked assets, whereas in the last six months they have gone earlier.

Litton: Yes, any group that has done a lot of deals, they are going to become a little bit more conservative.
At the end of last week, snowfalls and blizzards engulfing the East Coast brought not just an early end to the working week and the first positive weekly stock market close of the year, but a weather system that postponed my trip to New York City and Philadelphia. It will probably take more than the optimism engendered by an early start to last weekend to reverse the dismal year-to-date performance of life science stocks. That would take a positive earnings season.

Such a reversal of fortunes is possible, if rare. The third-quarter 2008 financial performance of companies including Amgen Inc., Celgene Corp. and Gilead Sciences Inc. re-rated the profile of profitable biotechnology companies and helped start a seven-year bull run for biotech companies (albeit with a stuttering start thanks to the last financial crisis) which only ended last summer. It may, however, be too soon for an earnings season to rehabilitate the stock prices of depressed biotech stocks that have only recently corrected. The 2008 re-rating of the sector, by contrast, came after biotech had spent years in the doldrums.

The investment bank analyst community that has spent the past six months proclaiming the value of the biotech sector after each dramatic market drop only to see its “Buy” recommendations fall further in subsequent market corrections has been surprisingly guarded about the help that earnings season can offer to an out-of-favor sector. The analysts from JP Morgan warned about the effects of currency weakness (or US dollar strength) on the earnings about to be reported by Abbott Inc., for example. About half of Abbott’s sales come from emerging markets. So, for me, the attractions of the relaxation of China’s one child policy to a company that sells a lot of infant formula is likely to be tempered in the short term by an 8% dent to sales from foreign currency translations.

For the healthcare conglomerate Johnson & Johnson (J&J), the analysts from JP Morgan suggested a possible $100m impact on its fourth-quarter sales from foreign exchange headwinds but also predicted another low quality beat of analysts’ consensus earnings estimates derived from one-off cost cuts and the proceeds of the divestment of its Cordis stent division. Perhaps the scene for J&J’s fourth-quarter financial results has already been set by its recent announcement of 3,000 job cuts and a restructuring at its struggling medical device and diagnostics division.

Despite being on the right side of a strong US dollar, a similar signal of the fourth-quarter financial performance of Sanofi may have also been implied by reports last week of sizable job cuts at the French company. Whilst there are excellent financial reasons to cull Sanofi’s insulin franchise after last year’s US commercial debacle and the ill-fated foray into inhaled insulin, the difficulty of removing any of the expensive staff responsible based in France is likely to have a disproportionate effect on its workforce and competence outside that country.

Investment bank analysts have been surprisingly guarded about the help that earnings season can offer to an out-of-favor sector.

After the depressing stock market start to 2016 and the disaffection with the sector since the summer of 2015 there could be a tendency for companies reporting their financial results for the next few quarters to “kitchen-sink” all the bad news whilst expectations remain low. If it is not earnings that will rescue the sentiment of the life sciences sector, then perhaps the recent trend in asset sales will help soften the fall. Earlier this week The Medicines Company Inc. reportedly followed up on the recent sale of its hemostasis products to Mallinckrodt by appointing bankers with a view to selling the rest of the company.

This is quite a turnaround for The Medicines Company as about this time a year ago it was staring down the twin barrels of the early appearance of generic competition against its main revenue-generating anticoagulant product Angiomax (bivalirudin) and a number of contingent payments arising from the acquisitions of some of its other products – which it could not afford. Fortunately for The Medicines Company at the time, biotech was still riding high in January 2015 and its investment bankers were happy to earn the fees on a $250m convertible debt offering. Despite the debt offering which plugged the contingent fee cash flow problem, The Medicines Company then reported a few quarters of falling (principally Angiomax) sales, having previously stuffed the hospital wholesaler channel resulting in a fall in demand of Salix Pharmaceuticals Inc.-like proportions. The rest of 2015 was a further catalog of disasters for The Medicines Company as the financial impact of generic Angiomax required it to announce that it was exploring strategic options in November 2015 and subsequently resulted in the divestment of three approved hemostasis products to Mallinckrodt for $457m plus $235m in milestones. A number of analysts were quick to put aspirational prices tags on the residual company, but the analysts from Citigroup were more cautious, suggesting “an outright sale unlikely.”

The loss of Angiomax exclusivity and the sale of its hemostasis products have relegated The Medicines Company back to loss-making status with limited visibility on the repayment of its now enlarged debt principal and semi-annual interest payments. This type of investment proposition of cash burn and significant debt in an environment where investors are shunning primary and secondary biotech stock offerings has elevated The Medicines Company to the least likely acquisition candidate since Clovis Oncology Inc. tried and failed to get bought. With the forthcoming earnings season and a possible acquisition of The Medicines Company unlikely to pull the life science sector out of its current doldrums, share prices, like the weekend snow on the East Coast, seem set to fall heavily.

The Magna Biopharma Income fund holdings include Amgen, Gilead and Abbott.

Andy Smith

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

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**Pipeline Watch**

*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.*

<table>
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<tr>
<th>Late-stage clinical developments for the week 15-21 January 2016</th>
<th>Lead Company</th>
<th>Partner Company</th>
<th>Drug</th>
<th>Indication</th>
<th>Market</th>
<th>Comments</th>
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<tr>
<td><strong>REGULATORY APPROVAL</strong></td>
<td>Novartis AG</td>
<td>Genmab</td>
<td>Arzerra (ofatumumab)</td>
<td>chronic lymphocytic leukemia</td>
<td>US</td>
<td>For extended treatment of patients who are in complete or partial response after at least two lines of therapy for recurrent or progressive chronic lymphocytic leukemia.</td>
</tr>
<tr>
<td><strong>ORPHAN DRUG DESIGNATION</strong></td>
<td>Nivalis Therapeutics Inc.</td>
<td>N91115</td>
<td>cystic fibrosis</td>
<td>US</td>
<td>Nivalis announced that the FDA has granted Orphan Drug Designation to its lead investigational drug, N91115, for the treatment of the cystic fibrosis</td>
<td></td>
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<tr>
<td><strong>FAST-TRACK STATUS</strong></td>
<td>Zogenix Inc.</td>
<td>ZX008 (Brabafen)</td>
<td>Dravet syndrome</td>
<td>US</td>
<td>Zogenix announced receipt of Fast Track designation from the FDA for ZX008 as a treatment of seizures associated with Dravet syndrome, a rare and catastrophic form of childhood epilepsy. The company recently initiated its first Phase III clinical trial in the US, and the second trial, primarily to be conducted in Europe, is expected to begin this quarter.</td>
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<tr>
<td><strong>BREAKTHROUGH THERAPY DESIGNATION</strong></td>
<td>AbbVie Inc.</td>
<td>Roche</td>
<td>venetoclax</td>
<td>chronic lymphocytic leukemia</td>
<td>US</td>
<td>AbbVie announced that the FDA has granted Breakthrough Therapy Designation for venetoclax in combination with rituximab for the treatment of patients with relapsed/refractory chronic lymphocytic leukemia. The designation was based on results from the M13-365 study. In April 2015, the FDA granted Breakthrough Therapy Designation to single agent venetoclax for the treatment of CLL in previously treated (relapsed/refractory) patients with the 17p deletion genetic mutation.</td>
</tr>
<tr>
<td><strong>REGULATORY FILING</strong></td>
<td>Eli Lilly &amp; Company</td>
<td>Incyte</td>
<td>baricitinib</td>
<td>rheumatoid arthritis</td>
<td>US</td>
<td>Lilly has submitted a US NDA for the approval of oral once-daily baricitinib for the treatment of moderately-to-severely active rheumatoid arthritis. As a result, Incyte will receive a milestone payment of $35m from Lilly. If baricitinib is granted US approval, Incyte will receive a milestone payment of $100m from Lilly.</td>
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<tr>
<td><strong>PHASE III TRIAL INITIATION</strong></td>
<td>Aclaris Therapeutics Inc.</td>
<td>A-101</td>
<td>benign pigmented lesions</td>
<td>–</td>
<td>Aclaris announced the initiation of two Phase III clinical trials to evaluate A-101 Topical Solution for the treatment of seborheic keratosis. Approximately 800 subjects will be randomized in these multi-center, double-blinded, vehicle-controlled, clinical trials, which are being conducted at 34 US investigational centers.</td>
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<tr>
<td><strong>PRODUCT LAUNCH</strong></td>
<td>Valeant Pharmaceuticals International Inc.</td>
<td>EGP-437 (iontophoretically-delivered dexamethasone phosphate ophthalmic solution)</td>
<td>uveitis</td>
<td>–</td>
<td>EyeGate Pharmaceuticals announced that the first patient was enrolled in its confirmatory US Phase III clinical trial of its EGP-437 combination product in patients with non-infectious anterior uveitis. The trial intends to enroll up to 250 subjects and is designed to evaluate the safety and efficacy of iontophoretically-delivered EGP-437, a novel formulation of dexamethasone phosphate ophthalmic solution, through the Company’s EyeGate II Delivery System, in patients with unilateral or bilateral non-infectious anterior segment uveitis.</td>
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January 29th 2016 | 23
Merck has appointed Gary Zieziula president and managing director of the company’s biopharma business in US and Canada and Marc Horn will lead the biopharma business in China as managing director. Zieziula joined Merck in 2014 as chief commercial officer in the US and has previously held senior level positions at Bristol Myers-Squibb, Roche and Amag Pharmaceuticals. Currently Horn is the regional chief financial officer (CFO) of Merck responsible for Eastern Asia for Healthcare, Life Science and Performance Materials. He has over 16 years’ experience in finance in the pharma and chemicals industry and has held positions at Bayer and Lanxess.

The Dementia Discovery Fund (DDF), a global investment fund managed by SV Life Sciences, has appointed Tetsuyuki Maruyama chief scientific officer – effective April, 2016. Maruyama joins DDF from Takeda Pharmaceutical Co. Ltd. where he was senior vice president, general manager, pharmaceutical research division for the past five years. Prior to this he was director of GlaxoSmithKline plc’s neuroscience research centre in Singapore and led Alzheimer’s disease target discovery efforts at Merck Sharpe & Dohme Ltd.

Actinium Pharmaceuticals, Inc. has appointed Kevin Zikaras senior clinical scientist and Rowena Choudrie senior director, pharmaceutical product development. Zikaras joins Actinium from Bristol-Myers Squibb where he was clinical protocol manager in the immuno-oncology group. Choudrie has over 20 years’ experience in the pharma industry and most recently was senior director, pharma development, global technical operations at NPS Pharmaceuticals. Previously, she worked at Palatin Technologies, Inc. as director, formulation development and manufacturing.

Recipharm has appointed Anke Mollowitz key account director. Mollowitz has more than 13 years’ experience in sales and in 2005 she joined Haupt Pharma Wülfing GmbH. At Haupt Pharma Mollowitz worked as sales representatives and project manager and later, she was head of customer service.

Phico Therapeutics, a company developing antibiotics, has appointed Nicki Thompson chief business officer (CBO). With more than 20 years’ experience, Thompson joins Phico from F. Hoffmann-La Roche Ltd. where she was vice president and global head of external drug discovery. Previously, she was senior director, business development for GlaxoSmithKline’s Centre of Excellence for External Drug Discovery.

Minoryx Therapeutics, a company focused on orphan diseases, has appointed Dr. Khalid Islam chair of the company’s board of directors. Islam was previously chair and CEO of Gentium S.p.a and president and CEO of Arpida AG. Prior to this, he worked in academia at Imperial College (University of London) and at Milan University, where he was a contract professor.

Aytu BioScience, Inc., a healthcare company focused on treatments for urological and related conditions, has appointed the company’s CEO Josh Disbrow and its chief operating officer (COO) Jarrett Disbrow to the board of directors. Josh Disbrow and Jarrett Disbrow were the founding management team at Arbor Pharmaceuticals and served as vice president of commercial operations and president/CEO until the company’s acquisition in 2010. Prior to the formation of Aytu BioScience, Josh Disbrow was COO of Ampio Pharmaceuticals and CEO of Ampio subsidiary Luxoxis. Recently Jarrett Disbrow was CEO of Vyrix Pharmaceuticals.

PureTech Health Plc. has launched its scientific advisory board (SAB) and appointed Harry L. Leider, chief medical officer of Walgreens Co., senior advisor to the company. The SAB is chaired by H. Robert Horvitz, Nobel Laureate and David H. Koch. Members of the SAB include Dennis A. Ausiello, chief emeritus of medicine at Massachusetts General Hospital; James J. Collins, Termeer professor of medical engineering & science and professor of biological engineering at MIT; Sanjiv Sam Gambhir, Ludwig professor and chair, department of radiology; Raju Kucherlapati a PureTech board member and PureTech co-founder and board member, Robert Langer.

TapImmune, Inc., an Immunology-oncology company, has appointed Frederick G. Wasserman to its board as an independent director. Wasserman has previously been president, chief operating officer and chief financial officer of entrepreneurial, middle-market companies.