Lilly’s Solanezumab Fails, But The Surprise Would Have Been Success

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The Phase III failure of the Alzheimer’s treatment was largely expected, but is nonetheless a disappointment for the disease and for the anti-amyloid field, casting a shadow over other therapies in development, including Lilly’s own pipeline.

Li Lilly & Co’s high-profile anti-amyloid treatment solanezumab failed a third Phase III trial, EXPEDITION3, even though it was conducted in patients with milder Alzheimer’s disease and relied on a biomarker to test patients for amyloid. The trial failure, announced Nov. 23, was largely expected, but nonetheless casts another shadow over the field of research. Lilly’s stock opened 15% lower at $64.34 on the news, as some investors had bought into the stock ahead of the catalyst in the event the data were positive, which would have resulted in substantial upside. Analysts and long-term investors generally considered Lilly’s attempt to run a refined Phase III trial testing solanezumab to be a high-risk bet, given that the drug failed two prior Phase III trials, EXPEDITION and EXPEDITION2, and because of the high number of Alzheimer’s drugs that have failed in late-stage trials.

Lilly said EXPEDITION3 did not meet the primary endpoint, a statistically significant slowing in cognitive decline among people with mild dementia due to Alzheimer’s disease who were treated with solanezumab versus placebo. The primary endpoint was measured by the Alzheimer’s Disease Assessment Scale-Cognitive subscale (ADAS-Cog).

Lilly changed the primary endpoint of the study earlier this year to the single cognitive assessment from the original co-primary endpoint that measured cognition and function. Some investors took the change as a sign that the company was concerned about a weak outcome.

The trial results, including many secondary clinical endpoints, favored solanezumab, but the magnitudes of treatment differences were small, Lilly confirmed.

The company will not pursue a regulatory submission for solanezumab and will work with investigators to conclude the open-label extensions for all three Phase III trials. Lilly will evaluate the data further to determine the impact on development plans for solanezumab and other Alzheimer’s drugs in the pipeline. The firm plans to present more findings from the study on Dec. 8 during the Clinical Trials on Alzheimer’s Disease (CTAD) meeting.

While the news isn’t an enormous surprise, it still is a disappointment. There was hope that by targeting patients earlier in the course of their disease, and by confirming the presence of amyloid pathology via PET screening or cerebrospinal fluid testing, EXPEDITION3 would yield a different result from the two prior trials, which failed in 2012. Despite the risks, Lilly went on to initiate the third trial in 2013 after a pre-specified pooled analysis showed a statistically significant improvement in patients with mild disease.

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from the editor
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Lilly’s turkey came early this year. The news on Nov. 23 that solanezumab had flunked its final trial was a bit like finding out you didn’t get the Maserati you’d requested for Christmas – not a surprise, but sad all the same. Lilly’s share price is now down about 20% since the beginning of this year, and it has lost 11.6% of its value since Nov. 22.

The amyloid hypothesis is the gift that keeps on taking away. People don’t exactly expect it to deliver the goods, but if it did it would be fantastic. Plenty of firms are still plugging away at it, and each time it disappoints they all feel the blow.

Biogen, with aducanumab in Phase III for Alzheimer’s, has slipped 4.8% since Nov. 22, while AC Immune and MorphoSys – partnered with Roche for crenezumab and gantenerumab, respectively – are down 13.4% and 7.3%, respectively. Informa Pharma Intelligence’s Pharmaprojects database lists around 400 candidates in active development for Alzheimer’s, with the amyloid beta precursor protein the leading target. Will there ever be a Maserati among the turkeys?
Purdue Pharma’s business development director and head of medical affairs talk to Scrip about the company’s hunt for new drugs to add to its portfolio outside of the opioid pain therapy space and how it is preparing for generic erosion and increasing pricing pressures in the US.

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Purdue Pharma LP hinted on the sidelines of the BIO-Europe partnering conference earlier this month that a significant acquisition announcement will be made before the end of 2016, which will see the company expand its R&D to a new therapy area outside of opioid pain treatments.

Kathryn Gregory, executive director of licensing and business development at Purdue, told Scrip that the company is looking for the right opportunity and is hopeful to announce a few things towards the end of this year. “We are looking from very early-stage, innovative, non-opioid, non-NSAID (nonsteroidal anti-inflammatory drug) pain products all the way through to anything on the market that is a good fit in terms of our commercial sales force,” Gregory said.

She also noted the company has been looking for “specialty-driven types of opportunities” in the CNS space. Purdue has an interest in movement disorders and epilepsy indications it thinks will sit in the CNS space adjacent to its current pain portfolio. However, Gregory noted that notoriously complicated and risky CNS conditions like Alzheimer’s disease are too much of a stretch for Purdue at this time.

Purdue’s ideal suitor would have a marketed product but a pipeline with room for growth. “We’re looking for more of a cornerstone property,” Gregory said. “It’s not just having a marketed product; we’re also interested in looking at the capability of the pipeline and building out a portfolio. We are looking for a sustainable platform and a sustainable business.”

Purdue has a budget of up to $2.5bn for a potential acquisition, though Gregory noted the company will consider a number of purchases around a new “anchor product” if it cannot find everything it desires for a fresh portfolio line all under one roof.

Purdue’s attempts to diversify away from opioid pain drugs were kick-started last year when the company struck a partnership with Eisai Co. Ltd. for Lemborexant, an insomnia therapy. Phase III clinical trials for Lemborexant, a dual orexin receptor antagonist, launched earlier in 2016. Gregory highlighted that the company will investigate other potential indications for this product under its partnership with Eisai – the drug is already in Phase II trials for excessive sleepiness associated with medical conditions.

In terms of increasing competition for its current pain portfolio in the US, Purdue’s business development head said, “While we see a lot of generic competition in the opioid space, Purdue has an excellent commercial organization that is really able to manage this situation appropriately and is able to maintain a healthy business. Our evergreening is bringing innovation to the marketplace.”

However, Gregory added that the company is ready to quickly move new pain products through development to maintain its lead on the US market. “Obviously we are looking for new products where we feel we can differentiate because we know the pain area so well. We can bring in these programs and develop them quickly because we have the regulatory expertise: we know how to manage the hurdles and the clinical requirements in order to get a product approved,” she said.

**DRUG PRICING CONCERNS**

Looking at the growing drug pricing pressures worldwide, Purdue’s head of medical affairs, strategic research, Tracy Mayne, highlighted that new measures for interpreting the value of medicines, particularly pain therapies, are needed worldwide. “There is a revolution in the US and it is focused on the development of value frameworks.” She noted that there is currently “a huge effort going on by a number of different entities” to talk about disease-specific value frameworks in the US. “We need to define the value of each drug very much within the context of its specific disease,” he said. “Alzheimer’s is a great example, [a value framework] could mean the return of cognition scales or it could be a measure for the burden relief on caregivers – but both of those assessments would be very different than measures for the next arthritis drug.”

In Europe, Mayne highlighted that health technology appraisal bodies, such as NICE which operates in England and Wales, need to update their systems. “Look at a body like NICE and it’s cost per quality adjusted life year measure; that was a great tool 25 years ago but we realize things have changed,” he said. “A drug that reduces pain has a very different value proposition to say a rheumatoid arthritis drug that increases physical function and those value benefits need to be recognized.”

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Combination Strategies A Common Thread In NASH R&D

Intercept continues to lead the non-alcoholic steatohepatitis race, but some analysts think Gilead is making up ground; data presented at AASLD shows those two, along with Allergan/Tobira and Bristol, are jockeying to produce combination regimens for the unmet medical need.

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With hepatitis C on the decline, non-alcoholic steatohepatitis is becoming the focus of liver disease R&D. While Intercept Pharmaceuticals Inc. and Genfit SA have the early lead in drug development, recent deal-making by Allergan PLC and Bristol-Myers Squibb Co., as well as a reshuffled strategy at Gilead Sciences Inc., appear to have the competition in flux.

Intercept continues to lead the race to get the first drug approved for non-alcoholic steatohepatitis (NASH) with Ocaliva – but, not for the first time, Tobira Therapeutics Inc. (acquired by Allergan in September) is arguing that being first to market won’t be as important as figuring out and delivering the best combination of mechanisms to address the complex liver/metabolic disease.

Those and other companies presented data during the American Association for the Study of Liver Diseases (AASLD) conference Nov. 11-15 on their NASH pipelines and talked about combination and biomarker strategies. It all remains up for grabs now as Intercept’s Ocaliva (obeticholic acid) and Genfit’s elafibranor have advanced into Phase III, with Allergan/Tobira’s cenicriviroc right behind them, slated to enter pivotal studies in 2017.

Bristol announced itself as a significant competitor in the space on the eve of the AASLD meeting, paying $100m up front to license worldwide rights to a Phase Ib candidate, ND-L02-s0201, which targets heat shock protein 47 (HSP47) from Nitto Denko Corp. Bristol already had the Phase II candidate PEG-FGF21 for NASH, as well as the recombinant human pentraxin-2 protein candidate PRM-151, currently in Phase II in myelofibrosis and idiopathic pulmonary fibrosis, which gives it the potential to establish an in-house three-drug regimen for the disease.

Michael Burgess, Bristol’s head of cardiovascular, immunoscience, fibrosis and genetically defined disease development, told Scrip the Nov. 10 deal furthers the company’s long-term interest in fibrosis, with a focus on liver and lung disease. The primary focus in liver diseases is on NASH driven by a goal of addressing all-purpose cirrhosis, he said.

“Our real driver is those patients who have more severe disease, [fibrosis scores of] F3-F4,” Burgess said in an interview. Bristol is aiming for a portfolio that targets F3-F4 NASH and all-cause fibrosis, and for drugs that work as monotherapy, but also could be combined for a more effective cocktail, he explained.

Nitto Denko will complete an ongoing five-week Phase Ib study under its agreement with Bristol, but the US-based big pharma already is planning the protocol for a Phase II trial that will launch early next year when Bristol takes over clinical development of the HSP47 molecule.

PRM-151, part of a 2015 option deal to acquire privately held Promedior Inc. and PEF-FGF21, a candidate Bristol has optimized since its licensure from Amobx Inc. fill out what Bristol hopes will be a comprehensive combination strategy in NASH.

“If we look at it from a strategy point of view, we believe that in patients with advanced fibrosis, you need to target both [the] fibrotic component and the underlying insult,” Burgess noted.

Bristol has mouse-model data suggesting that FGF21 could serve a dual purpose, addressing the metabolic syndrome that underlies NASH as well addressing fibrosis directly, he added. The compound is in a 75-patient Phase II study in NASH, which should report out during the first half of 2017. FGF21 has already shown in Phase II in diabetes that it upregulates adiponectin, which Burgess said is closely related to fibrotic activity.

Although not currently being investigated in NASH, PRM-151 attacks a common mechanism of fibrosis, so it could be applied to a combination strategy, he said. Bristol also is working on preclinical candidates that target LPA1, which Burgess said could address fibrosis and the inflammatory effects of NASH.

SAFETY WILL BE A KEY CONSIDERATION

At Intercept, the primary focus is on bringing its bile acid analog Ocaliva through Phase III in NASH, but the company is looking ahead to a combo strategy of its own, CEO Mark Pruzanski said during AASLD.

Pruzanski sees several advantages for Ocaliva – its potential to be the first to market in NASH, previous approval in another liver indication and a substantial safety database – as well as the validation inherent in the fact that several other companies, including Gilead and Novartis AG, are developing FXR agonists for NASH.

“I think imitation is the highest form of flattery,” he said in an interview. “What we’ve seen is that FXR is now considered a validated target and any company looking to stake out a serious claim on the NASH space needs an anchor FXR agonist in its...
armamentarium. We certainly agree with that,” Intercept’s R&D centers on bile acid analogs, and Pruzanski thinks human FXR compounds will prove to offer a better safety and tolerability profile than the synthetic versions others are working on.

“I’ve long maintained that a natural compound analog should be inherently safer in chronic administration than a purely synthetic molecule,” he said. “So far, from a track record standpoint, that hypothesis has been proven correct and there are no less than four other synthetic FXR agonists that either didn’t make it into the clinic or made it to Phase I or early Phase II and have blown up.”

Partly due to its development in PBC, Ocaliva has already been dosed in more than 1,600 clinical study participants, which Pruzanski thinks provides some sense of how the drug will fare as a chronic long-term therapy. He predicts competitors will have to measure up in terms of safety data.

“In PBC alone, we submitted an NDA with 675 patient years of exposure,” he noted. “We have a cohort of PBC patients who’ve been on Ocaliva for more than five years. There’s not been any discernible safety signal with the drug. The side-effect profile of OCA is very well characterized and that is a big advantage. And until and unless a similar safety database is amassed for any other FXR agonist or any other molecule being advanced in NASH, the jury is out.”

In terms of a combination strategy, Intercept presented preclinical data on a second proprietary candidate, INT-767, a dual agonist of FXR and PGR5, at AASLD. It is completing a Phase I study in healthy volunteers, after which Intercept will decide whether to advance it as a candidate for NASH, PBC or both.

Pruzanski said INT-767 is a more potent agonist of FXR than Ocaliva, and has looked better than its predecessor in animal models of both liver and non-liver disease. TGR5 is a dedicated bile acid receptor involved primarily in energy metabolism, the exec said.

Intercept is also looking to add other mechanisms to its NASH pipeline, he said, whether through internal R&D or business development. One area Pruzanski finds promising is GLP-1. The problem is that most GLP-1 analogs that have reached market or are in development – such as established diabetes drugs Byetta/Bydureon (exenatide) and Victoza (liraglutide) – are dosed subcutaneously or intravenously.

“It think that might ultimately work in patients with the most advanced disease, but for patients with earlier-stage disease, who are expected to take the drug for a long period of time, ideally you want to go all-oral,” he said. “But there are oral GLP-1 analogs or receptor agonists that might be interesting.”

Tobra presented one-year biopsy data from patients in its Phase Ib II CENTAUR study of cenicriviroc (CVC), showing that twice as many patients who received the study drug achieved a one-stage improvement in their fibrosis scores compared to those on placebo. Tobra CEO Laurent Fischer pointed out that the 289-patient study enrolled only patients with liver disease at the F2 or F3 stages.

Showing this improvement is important, because fibrosis is linked to clinical outcomes and progression to cirrhosis, he said. The data give CVC solid ground as it moves into Phase III next year. That level of improvement in fibrosis score has not been seen after one year of treatment with a NASH candidate before, he added.

The study is continuing for a second year, with another biopsy after two years of treatment, and Fischer expects to see additional benefit then.

ALLERGAN, GILEAD COMBINATION STRATEGIES UNDERWAY

Fischer said he and his team will lead liver drug development at Allergan, which paid nearly $1.7bn in a buyout of Tobira announced in September. The combined companies already have a NASH combination therapy strategy underway with the DPP-4 inhibitor evogliptin, cross-licensed from South Korea’s Dong-A Pharmaceutical Co. Ltd. in April, he noted. In tandem with acquiring Tobira, Allergan also brought in the preclinical FXR agonist AKN-083 with its $50m purchase of Akarna Therapeutics Inc. in September.

Under the partnership with Dong-A, Tobira obtained rights to develop and market a combination of CVC and evogliptin in North America, Europe and Australia, while the Korean firm gets rights to the combo in its home market, where evogliptin is approved for diabetes as Suganon.

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“Allergan, which has added NASH candidates to its pipeline recently with a series of smaller targeted deals, may be a rising force in the space, but the company is starting over somewhat after abandoning its most advanced candidate for NASH, the LOXL2-targed antibody simtuzumab. For the firm that has dominated the HCV competition, the primary focus now turns to selonsertib (GS-4997), a Phase II inhibitor of apoptosis signal-regulating kinase 1 (ASK1).”

Gilead reported data at AASLD from a study testing selonsertib in NASH patients with fibrosis scores of F2 and F3. Two arms tested the drug in tandem with simtuzumab, but data demonstrated that the antibody did not provide an additive effect, and a cohort testing simtuzumab monotherapy yielded unspectacular results. Selonsertib demonstrated anti-fibrotic activity after 24 weeks of treatment in the first study to assess results not only with liver biopsy, but also with non-invasive tests such as magnetic resonance elastography (MRE). An 18 mg dose of selonsertib produced an improvement of one stage or greater in fibrosis score in 43% of patients (13/30), while a 6 mg dose met that endpoint in 30% of patients (8/27).

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View Preclinical data for INT-767, a dual agonist of FXR and PGR5 here: http://bit.ly/2gntqWq
GSK Strategy Chief: No Major M&A Likely In 2017

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G laxoSmithKline PLC is unlikely to partake in any big M&A plays for the time being as it prepares for a new CEO and continues to bed down and integrate assets acquired by its product swap with Novartis and as its new CEO takes corporate control.

GSK expects further consolidation among rivals in 2017 but its own focus will remain internal, as it keeps integrating assets acquired by its product swap with Novartis and as its new CEO takes corporate control.

“From time to time the stars align. So down the track I would see other opportunities and we’ll take them but I’ll leave it to Emma to outline next year. She’s going through the program now, understanding the opportunities,” Redfern said.

The strategy head does not think the CEO-designate’s lack of an R&D or postgraduate science background will hinder Ms. Walmsley in trying to improve R&D returns; rather it should allow her to assess GSK’s innovative approach with fresh eyes.

“A lot of the big decisions revolve around R&D. One reason why Emma was chosen is partly great leadership skills, partly her great performance focus which reflects her coming from the consumer business where you have to be very customer orientated,” Redfern said.

“The board feels Emma has the best chance of being the best leader of all the businesses including pharma. And it’s interesting, she’s been around the management team for a few years but has the advantage of coming in fresh and can just ask questions of science and she’s spending most of her time on pharma R&D now and is really thinking that through.”

Redfern, a chartered accountant by training who has led GSK’s new business development strategy since 2008, said R&D will remain at the center of GSK operations under the new CEO.

“Ultimately we’re an innovative pharma company. It’s in our DNA. We spend £3bn a year and have 10,000 to 11,000 people in R&D. In the last few years some 25% of our pharma and vaccines business came from products that were launched three years ago or less.”

“We’ll also see more innovation in the consumer business – it’s a different type of innovation obviously but bringing new formulations, new packaging, new customer insights.”

TRUMP-FED M&A FRENZY?

But David Redfern, GSK’s chief strategy officer, did say the surprise US election result of a future Trump Administration would likely lead to a US tax “holiday” which would further fuel sector consolidation.

“Overall I do think there’s likely to be quite a bit of M&A next year. The only thing that’s not clear is just HOW big it gets,” Redfern said. “Do people go after big targets like Bristol-Myers Squibb Co., Amgen Inc., Biogen Inc. – who knows! Everyone’s got issues – and opportunities,” he said rhetorically.

“I do think that it will lead to more capital being spent. And buying innovation in particular. I don’t think there will be M&A to drive diversification. It’s possible, but less likely. What I think you’ll see is more capital being deployed to buy innovation and efforts to buy growth across the industry,” Redfern said.

GSK TO “SIT OUT” BIG M&A DANCE

But that frenzy is not likely to see GSK participation.

“We’re not currently discussing M&A here, largely because we’ve recently done it and we’re busy integrating,” Redfern told Scrip at the meeting’s sidelines.

Another restraining factor is the imminent arrival of Emma Walmsley, head of GlaxoSmithKline PLC’s consumer division, as the successor to Sir Andrew Witty, who has been CEO there since 2008. Ms. Walmsley will be moving there from her current role as CEO of GSK’s Consumer Healthcare division. She has been a member of GSK’s corporate executive team since 2011.

Asked whether Ms. Walmsley, who takes over the GSK reins on Apr. 1, would take a more acquisitive M&A approach, Redfern shrugged and said “It’s far too early to say what Emma is going to do as CEO. We continue to do early research deals and I’m sure that will continue. And on potential divestments of legacy tail assets, from time to time there’s a deal that just makes sense;” he said, without elaborating other than to cite as an example GSK’s sale earlier this year of around half of its 12.4% stake in South Africa’s largest listed pharma company Aspen Pharmacare Holdings Ltd.

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“We’ll also see more innovation in the consumer business – it’s a different type of innovation obviously but bringing new formulations, new packaging, new customer insights.”

DPU R&D APPROACH SET TO STAY

Redfern also sees the company’s R&D approach continuing based on discovery performance units (DPUs) which was an initiative designed by Dr. Moncef Slaoui, GSK’s vaccines chief and former head of R&D, who is retiring from the company in June 2017. The DPUs replaced the group’s previous R&D activities, deconstructing them into 38 focused and accountable DPUs and transforming GSK’s late-stage pipeline, which currently has more than 30 Phase III programs compared with fewer than 10 in 2006.

“The DPU model is working well and I wouldn’t expect radical change to the DPUs. It’s really about how the medicines emerge from the DPUs and there’s a lot of Phase I and Phase II data coming in 2017 and we’ll then ask what’s best to take from that point, which will be the key question,” said Redfern who has also been chair of the HIV partnership, ViV Healthcare Ltd since 2011. ViV was set up in 2009 by combining the HIV management expertise of GSK and Pfizer Inc. The duo was joined three years later by Japanese pharma group Shionogi & Co. Ltd.

“I spend around 50% of my time on that company because it’s grown so big and within that role I spend way more time on the R&D part than the commercial part. A lot of the big decisions revolve around R&D,” he said.

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There is evidence that the accumulation of amyloid plaque deposits in the brain contributes to Alzheimer’s, but the pathway has continued to confound drug makers as a therapeutic target.

WHAT DOES FAILURE MEAN FOR OTHERS?

Two other high-profile drugs are in late-stage development for Alzheimer’s, and investors will wonder what the results of EXPEDITION3 might mean for those investigational drugs: Merck & Co. Inc’s small molecule selective beta secretase (BACE1) inhibitor verubecestat and Biogen Inc’s aducanumab, a monoclonal antibody targeting beta amyloid.

Analysts were mixed about what the results might mean for other drugs in development and the broader amyloid hypothesis. Some like Bernstein Research analyst Tim Anderson advised caution about transferring the results of EXPEDITION3 onto other drugs.

“While Lilly’s, Biogen’s and Merck’s drugs all target the same protein, they all do it differently enough that there should not be much of a read-through from one drug to the other,” he said. “In the case of Lilly, we’ve said for a long time that they may have given too low a dose, which could impact results. Lilly never seemed to have a great answer for why they picked the solanezumab dose they did.”

Credit Suisse analyst Vamil Divan agreed in a same-day note. “Given sola did appear to have a modest impact on cognition and some secondary clinical endpoints, we are not ready to dismiss the amyloid hypothesis at this time, but remain cautious on the likelihood of success for any of these pipeline opportunities in this high-risk area.”

However, Baird Equity Research’s Brian Skorney sounded an alarm, noting, “Today’s failure comes pretty close to a nail in the coffin for the…amyloid hypothesis.”

Leerink analyst Geoffrey Porges said that “this is a serious blow” for Biogen and other companies developing Alzheimer’s therapies. If all of the value of aducanumab were removed from Biogen’s valuation in Leerink’s model, Porges forecast that the company’s stock would be reduced in value by $37, or 10%. Still, he pointed to material differences between aducanumab and solanezumab, such as dose, trial design and the antibody itself.

“We believe investors will not completely discount the value of aducanumab,” Porges said.

Biogen’s stock opened 7.6% lower Nov. 23 at $293.82, though it made up ground during the day. Merck was mainly flat.

FOR LILLY, A CHANCE TO MOVE FORWARD AND TAKE STOCK IN ALZHEIMER’S

For Lilly, the news could represent a chance to clean the slate and move forward, as it heads out of an extended period of significant patent expirations. The company has several new drugs and near-term pipeline products to drive growth, like Trulicity (dulaglutide) for type 2 diabetes and Taltz (ixekizumab) for psoriasis, as well as up and coming like the CDK4/6 inhibitor abemaciclib for breast cancer and the JAK1/JAK2 inhibitor baricitinib for rheumatoid arthritis.

‘Driven by new product launches, we continue to expect to grow average annual revenue by at least 5% between 2015 and 2020.’ – Incoming Lilly CEO David Ricks

Incoming CEO David Ricks sought to assure investors that the company remains on track. “Lilly has strong growth prospects without solanezumab,” he said. “Driven by new product launches, we continue to expect to grow average annual revenue by at least 5% between 2015 and 2020.”

Nonetheless, the EXPEDITION3 failure is a step back for Lilly’s ambitions in Alzheimer’s. The company is investing heavily in the field with the hope of being the leading drug developer in the area. Lilly has a broad portfolio of Alzheimer’s drugs in clinical development that work through an array of mechanisms and the firm has suggested that it might be combination approaches that will eventually yield therapeutic benefits.

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GSK’s Nucala Shows Promise In A Rare Systemic Vasculitis

GlaxoSmithKline PLC plans to submit approval applications next year for the use of Nucala (mepolizumab) in patients with eosinophilic granulomatosis with polyangiitis (EGPA), after the IL-5 antagonist MAb met its endpoints in a pivotal Phase III study that is part of a collaboration between GSK and the US National Institute of Allergy and Infectious Diseases on developing drugs for rare diseases. The Phase III study, dubbed MEA11921, is the first double-blind placebo-controlled trial to be conducted in EGPA, an extremely rare condition, and gaining an approval in this patient population should help Nucala stand out among a clutch of new drugs being developed for eosinophilic conditions. Nucala was approved for marketing in the EU in December 2015 as an add-on treatment for severe refractory eosinophilic asthma in adult patients, and in the US in November 2015 as add-on maintenance treatment of patients with severe asthma aged 12 years and older, with an eosinophilic phenotype. It has also been approved for marketing in Canada, Australia, Japan, Switzerland, Chile, South Korea and Taiwan. Analysts at Informa’s Datamonitor Healthcare expect only a limited uptake for Nucala in 2016, with sales in the US, Japan and the top five EU markets forecast at just over $100m in 2016, rising to $600m in 2020. But competition to Nucala is already increasing: Teva Pharmaceutical Industries Ltd.’s IL-5 antagonist MAb, Cinquaero (reslizumab; Cinquaire in the US) was approved for eosinophilic asthma earlier this year in the US and Europe, and a third MAb, AstraZeneca PLC’s benralizumab, is in Phase III clinical studies.

john.davis@informa.com, 23 Nov 2016
Novo Nordisk ‘Caught Short’ By Lantus Exclusion

Novo Nordisk says it was caught by surprise when US pharmacy benefit managers decided to exclude Sanofi’s basal insulin Lantus and down-grade its own Levemir from formularies in favor of Eli Lilly’s soon-to-be launched biosimilar Basaglar. Novo had been hoping for more time to secure some of Lantus’ US market share with its new diabetes product Tresiba, but now accepts that will not happen.

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The diabetes market has been an area of significant pushback from payers and greater demands for rebates, putting pressure on sales. Novo Nordisk AS has been one of the most significant casualties, and cut its growth forecast for 2017 last month. “People have said, ‘but you knew the biosimilar was coming’,” said Novo Nordisk’s IR manager Melanie Raouzeos at the Jefferies Healthcare conference in London on Nov. 16-17. “We did know it was coming, but we didn’t expect that the PBMs would be so aggressive about accepting it. We thought it would be launched and then take its time to be accepted.”

Novo Nordisk’s basal insulin Levemir (insulin detemir) has always lagged behind Sanofi’s Lantus (insulin glargine) in sales ($2.68bn in 2015 versus Lantus’ $6.98bn), likely because of its comparatively late market entry.

With Lantus going off patent, both companies developed new drugs to shore up their diabetes franchises. Sanofi’s Toujeo (insulin degludec) was approved by FDA in February 2015 and Novo Nordisk’s Tresiba (insulin glargine) in September 2015. However, these have arguably modest benefits over their predecessors.

“Tresiba has had good market access, but we were forced to give higher rebates [than planned]. Biosimilar Lantus left us with no choice,” said Raouzeos. Tresiba has been taking market share from Lantus and “cannibalizing Levemir,” she added.

SEMAGLUTIDE PROMISE

Novo Nordisk has said previously it plans to file its Victoza (liraglutide) follow-on product, semaglutide, in the US by the end of 2016.

Raouzeos noted that semaglutide was recently the second GLP-1 agonist to show positive results in a major cardiovascular outcomes trial (CVOT) in type 2 patients at high risk of CV disease. In the SUSTAIN-6 trial, semaglutide demonstrated a 26% risk reduction compared with placebo.

Victoza demonstrated CV benefit in the LEADER trial earlier this year.

The SGLT2 inhibitor empagliflozin (Jardiance, Boehringer Ingelheim GMBH/Eli Lilly & Co.) was the first to show a reduction in CV death in the EMPA-REG trial.

ANOTHER THREAT

Aside from diabetes, Novo Nordisk’s hemophilia business faces a significant threat.

Competition is expected shortly in the form of Roche’s late-stage promising bispecific antibody for hemophilia A, emicizumab (ACE910), which is being touted as a future blockbuster. Emicizumab, given once-weekly subcutaneously, has demonstrated prophylactic efficacy for people with severe hemophilia A, regardless of the presence of Factor VIII inhibitor antibodies (which develop in around 30% of hemophilia A patients), potentially streamlining treatment of this condition.

Currently, patients who develop inhibitor antibodies are treated with bypass agents such as Novo Nordisk’s NovoSeven and Shire PLC’s Feiba.

If approved, “50% of NovoSeven’s sales are at risk,” said Novo Nordisk’s Raouzeos. Sales in 2015 were around $1.5bn.

However, despite $3bn in cash on its balance sheet and no debt, Novo Nordisk will not be adding “new legs” to its business, said Raouzeos. “In terms of business development, we’re interested in add-ons or adjacent activity, but all M&A will be modest.”

Published online 22 November 2016

Sanofi/Novo Nordisk In Head-To-Head Diabetes Combo Approvals

Sanofi and Novo Nordisk – which are battling to shore up their diabetes franchises in the face of biosimilar competition – have simultaneously garnered US approval for new combination products to treat the disease. However, analysts expect the two companies to adopt different pricing strategies.

The US FDA has simultaneously approved two combinations of a basal insulin and a GLP-1 receptor agonist from Sanofi and Novo Nordisk AS.

Sanofi’s Soliqua (insulin glargine [Lantus] and lixisenatide) and Novo Nordisk’s Xultophy (insulin degludec [Tresiba] and liraglutide [Victoza]), both once-daily treatments, have been approved for adults with type 2 diabetes inadequately controlled by basal insulin or GLP-1 receptor agonists.

Both combos are expected to be launched early in 2017 and will be sold at a discount to the combined price of the component products.

“We expect Sanofi to adopt a significantly different pricing strategy versus Novo and position the combo as a ‘Lantus Plus’, just a small price premium to Lantus,” said Credit Suisse analysts in a note dated Nov. 22. “Xultophy is already available in the UK and in this market Novo has priced it as a premium product, effectively a 20% discount to the sum of its components Victoza and Levemir. This makes sense as Novo does not want to cannibalise its existing monotherapy revenue from both franchises. In contrast, Sanofi’s GLP-1 Adlyxin has negligible sales for GLP-1 mono and the standalone efficacy of it means its potential is limited.”
Juno Stresses Differences Between Its CAR-Ts As JCAR015 Trial Put On Hold Again

Juno stressed structural differences, safety record and potential of its JCAR017 CAR-T therapy during a Nov. 23 call about the disappointing hold on its ROCKET ALL study for JCAR015 – the second clinical hold for the company’s most advanced development program.

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As JCAR015 Trial Put On Hold Again

Chief medical officer Mark Gilbert said during the Nov. 23 call that removing fludarabine from the preconditioning regimen was the right response following the deaths reported this summer, but noted that the company had not expected this would entirely eliminate the risk of neurotoxicity or cerebral edema.

"Unfortunately, it is clear now that fludarabine is not the sole cause (or any cause) of the cerebral edema, although officials in the call were adamant that the removal of the chemotherapy did lessen the toxicity of the treatment,” Biomedtracker analyst Robert Jeng commented in a note.

Juno execs stressed that the company removed fludarabine from the preconditioning regimen as a precautionary step and not as a response to adverse events. They said that JCAR015 was designed to be “entirely separate products” and that the candidates are different in a number of ways that could affect safety profiles. Whereas JCAR015 has a CD28 co-stimulatory domain, JCAR017 and JCAR014 have a 4-1BB domain.

The type of viral vector also differs in that JCAR017 and JCAR014 have a retroviral vector, versus a lentiviral vector for JCAR015.

Bishop said that the company expects FDA will look at JCAR015 and JCAR017 as “entirely separate products” and that the company continues to be “optimistic about its goal of launching JCAR017 in NHL as early as 2018,” Bishop said.

Biomedtracker analyst Jeng, however, concluded that the execs remained “stubbornly optimistic and even defiant” in the face of patient deaths.

"This is quite a major setback for not only JCAR015 but for the Juno pipeline and perhaps the entire CAR-T class. It is simply not clear how much of the severe neurotoxicity is construct-specific or a characteristic of this still relatively new and complex class of therapy,” Jeng commented.

Published online 23 November 2016

Comparison Of CAR-T Programs

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Source: Gena Wang, Jefferies analyst note, July 8, 2016
Nearing Finish Line, HCV Race Focuses On Salvage Therapy

Change was in the air at the American Association for the Study of Liver Diseases meeting held in Boston between Nov. 11-15 and not just because of the recent US election results. The shifting drug development focus in liver diseases from the hepatitis C virus (HCV) to non-alcoholic steatohepatitis (NASH) is palpable, with market-leader Gilead Sciences Inc. recently stating that its latest Phase III, three-drug combination regimen probably signals the end of its R&D work in HCV. Still, Gilead and its two closest pursuers in HCV – Merck & Co. Inc. and AbbVie Inc. – unveiled data for their next-generation direct-acting antiviral (DAA) combination regimens in Boston, and each company is working to produce eye-opening data in one of the few remaining challenges in the space – salvage therapy, that is curing HCV-infected patients who’ve failed a previous round of therapy with a DAA regimen. Elsewhere, Merck is trying to build a case for treating injectable drug users who have HCV as a means to address the greatest risk for new infections and as a possible pathway to eradicating the virus. And AbbVie has completed year one of a five-year effort to collect liver outcomes data for HCV patients cured with its DAA regimens. Gilead plans to file a pan-genotypic triple regimen containing the nucleoside polymerase inhibitor Sovaldi (sofosbuvir), its second-generation NSSA inhibitor velpatasvir and the investigational protease inhibitor voxtalaprevir for approval in the US by the end of 2016. Sovaldi also is a component of Harvoni with the first-generation NSSA inhibitor ledipasvir and it is combined with velpatasvir in Epclusa. Gilead presented data during AASLD from its four Phase III POLARIS studies for the three-drug regimen, also known as sof/vel/vox, showing sustained virologic response (SVR) rates for salvage patients in the 96%-97% range in the POLARIS-1 and 4 trials. Gilead compared the regimen dosed for eight weeks in treatment-naïve patients against Epclusa for 12 weeks in POLARIS-2 and 3. POLARIS-2 was open to all genotypes whereas POLARIS-3 focused on genotype 3-infected individuals with compensated cirrhosis, an area the company cites as one of the greatest remaining unmet needs in HCV. Gilead found, however, that 12 weeks of Epclusa was as efficacious or more so than eight weeks of sof/vel/vox in both of these studies.

Pfizer’s Avelumab Poised For Speedy Review By FDA

Pfizer Inc. and Merck KGAA’s PD-L1 inhibitor avelumab appears on track to be the fourth anti-PD-1/L1 antibody to reach the market and the first for metastatic Merkel cell carcinoma. The companies announced Nov. 29 that a BLA for avelumab was accepted for priority review for the treatment of metastatic MCC, positioning the cancer immunotherapy for FDA approval in the first part of 2017. Avelumab is the cornerstone of Pfizer’s strategy to become a leader in the field of immuno-oncology and getting the drug on the market next year is an important catalyst for the initiative. Pfizer is studying avelumab in dozens of clinical trials in as many as 15 indications, including gastric, ovarian, renal and lung cancer. The company’s long-term focus is on combinations involving avelumab as a backbone, the area in which Pfizer believes it can catch up to immuno-oncology leaders like Merck & Co. Inc., Bristol-Myers Squibb Co. and Roche. Pfizer has said it expects to have a total of 10 IO assets in clinical development by the end of the year. The FDA has approved three other PD-1/L1 inhibitors and multiple new indications for the treatments under the six-month review clock established for priority reviews. Opdivo, Merck’s Keytruda (pembrolizumab), and Roche’s Tecentriq (atezolizumab) are the first PD-1/L1 inhibitors to reach the market.

US Approval Delay For Green Cross

The US FDA has issued a complete response letter (CRL) on Green Cross Corp.’s biologics license application for IV-Globulin SN (IVIG-SN), a human immunoglobulin G for intravenous administration, which although set to delay an approval is not expected by analysts to exact a serious toll on the South Korean company’s North American business plans. The plasma-derived product is administered to protect the body against infection. Green Cross’s BLA, filed in November 2015, was intended to secure approval for the treatment of primary immunodeficiency diseases (PID), a class of inherited genetic disorders that cause an individual to have a deficient or absent immune system. IVIG-SN demonstrated positive results in a Phase III study in patients with PID, meeting its primary endpoint of no acute serious bacterial infections. These results, included in the submission, were well beyond the requirement specified in FDA guidance of no more than one acute serious bacterial infection per patient-year. The FDA has asked Green Cross to submit additional data on manufacturing processes, but hasn’t raised any issues with the product’s efficacy or safety, the company stressed. “We now have a very clear idea about the remaining process to obtain the final approval,” said E. C. Huh, president of Green Cross, in a statement. “We will complete the approval process without setbacks and beef up our US sales and marketing strategy.”
Chiesi Takes Aim At Next-Generation Eosinophilic Asthma Therapy

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Chiesi may be coming late to the development of eosinophilic asthma therapies, but there are certain advantages associated with acquisition target Atopix Therapeutics’ potential products that could strengthen the specialty pharma’s already significant presence in the asthma market.

The privately-held European mid-sized pharmaceutical company Chiesi Farmaceutici SPA is hoping an orally active small molecule being developed by acquisition target Atopix Therapeutics Ltd. for eosinophilic asthma will trump the more advanced injectable monoclonal antibodies in development for the condition, or already marketed by competitors.

Chiesi is to acquire the UK based Atopix for an amount that could exceed €75m ($80m), the Parma, Italy-based company announced Nov. 11. Atopix’s major asset is the oral CRTh2 antagonist, OC459, that is in Phase II proof-of-concept studies in patients with severe asthma and persistent airway eosinophilia despite treatment with high-dose corticosteroids. Atopix also has a back-up compound, ATX2417, that has completed a Phase I study.

The Oxford company has been backed by experienced biotech VC firms including SR One, Wellington Partners, SV Life Sciences and MPM Capital.

Chiesi is taking on OC459 despite the compound’s failure earlier this year in moderate to severe atopic dermatitis; Atopix reported in February 2016 that a Phase II study had found no benefit associated with OC459 in patients with atopic dermatitis, compared with placebo. However, that study did show the compound was generally well tolerated, and provided insight into the mode of action of OC459, Atopix said. CRTH2 antagonists may have no activity in atopic dermatitis but the CRTH2 pathway is active in eosinophilic asthma, Atopix’s executive chair Tim Edwards commented at the time.

The chemoattractant receptor-homologous molecule (CRTH2) receptor is found on TH2 lymphocytes, basophils and eosinophils, and its ligand is thought to be prostaglandin D2 released from mast cells. The pathway is involved in allergic responses that include eosinophilic airway inflammation, with eosinophilic disease being more severe than non-eosinophilic disease, and associated with asthma exacerbations and hospitalization.

The potential of Atopix’s products in eosinophilic asthma is being backed by Chiesi’s vice president and head of R&D, Paolo Chiesi, who believes OC459’s patient-friendly oral dosage form may also be significantly more cost-effective than other therapies in the clinical setting.

Still, Chiesi will find itself up against big pharma companies in the eosinophilic asthma field like Novartis AG and Merck & Co. Inc., that are currently developing CRTH2 antagonists, as well as companies developing injectable monoclonal antibodies for eosinophilic asthma that include AstraZeneca PLC and GlaxoSmithKline PLC. AstraZeneca’s benralizumab is in Phase III clinical studies, and is expected to be dosed every eight weeks, while GlaxoSmithKline’s Nucala (mepolizumab) and Teva Pharmaceutical Industries Ltd’s Cinqaero (reslizumab; Cinqair in the US) are administered every four weeks and already marketed.

Informa Pharma Intelligence’s database Biomedtracker lists the handful of companies that are developing CRTh2-antagonists as follows:

### Selected CRTh2 Antagonists In Development

<table>
<thead>
<tr>
<th>COMPANY</th>
<th>PRODUCT</th>
<th>STAGE OF DEVELOPMENT</th>
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<tr>
<td>Novartis AG</td>
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<td>Phase III</td>
</tr>
<tr>
<td>Pulmagen Therapeutics (Asthma)</td>
<td>ADC3680</td>
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</tr>
<tr>
<td>Merck &amp; Co. Inc.</td>
<td>MK-1029</td>
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<tr>
<td>Panmira Pharmaceuticals LLC</td>
<td>AM211</td>
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</tr>
<tr>
<td>Array BioPharma Inc.</td>
<td>ARRY-502</td>
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<tr>
<td>Boehringer Ingelheim GMBH</td>
<td>AP768</td>
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</table>

Source: Biomedtracker.

Analysts at Datamonitor Healthcare estimate that the asthma market could reach $20.8bn by 2024, a compound annual growth rate of 4.7%, because of the high cost of the biologic therapies that are targeting severe persistent uncontrolled asthma. The market should grow despite the advent of generic versions of commonly used inhalers, they note.

Chiesi has a major interest in respiratory drugs, with its asthma inhaler Foster (beclometasone plus formoterol) accounting for more than 30% of its total revenues. Also in its research pipeline is a triple combination inhaler, which in September 2016 was submitted for approval to the EMA for the treatment of chronic obstructive pulmonary disease. It contains beclometasone, formoterol fumarate and glycopyrronium bromide.

The Italian company has previously taken part in M&A to achieve its aims: it acquired Cary, North Carolina-based Cornerstone Therapeutics Inc. in 2013 for $252m to establish a US base, and to extend its respiratory portfolio. Also in 2013, Chiesi bought Denmark’s Zymenex AS for its Phase III enzyme replacement therapy for alpha-mannosidosis, velmanase alfa, to boost its rare diseases portfolio.

Chiesi’s turnover reached €1.467bn in 2015, 80% of which came from outside Italy and up by 9.4% on turnover in 2014. Sales of the Foster inhaler reached €492m. Net income in 2015 amounted to €228m.

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Industry’s Achievements Lauded At 12th Annual Scrip Awards

The world’s political tectonic plates may be shifting, but this has done little to undermine the achievements of the pharma, biotech and allied industries over the past year, and on Nov. 30 we celebrated the best of these at the 12th annual Scrip Awards in London.

In a lavish ceremony presented by the broadcaster Jeremy Vine, Scrip rewarded excellence across the whole range of business activities.

The Scrip Awards categories range from those that reward the broader achievements of companies, to those for innovation in deal making, advances in R&D and the more personal accomplishments of teams and individuals.

Overall, Genmab was the big winner of the night, receiving two trophies, but the loudest applause went to this year’s Lifetime Achievement Award recipient, Dr. Raymond F. Schinazi.

COMPANIES

The first of the awards that celebrate company successes, PPD’s Pharma Company of the Year Award (sponsored by PPD), went to Shire. The winner of this special award is chosen each year by Scrip’s senior editorial team, based on a variety of key metrics, including its financial performance in 2015, strategic advances, progress in the emerging markets, and advances in the drug pipeline.

Scrip was impressed by Shire’s performance since its planned merger with AbbVie was called off in October 2014. It has produced consistent growth, increased its R&D spend and acquired Baxalta to take a leadership position in rare diseases. This continued progress leaves it poised to enter the top 20 pharma companies worldwide by pharma sales next year.

The always-competitive WuXi AppTec Biotech Company of the Year Award (sponsored by WuXi AppTec) went to Genmab.

Genmab’s business achievements over the period led to a third year of profitability and a significant increase in its valuation. The company received EU and US approval for its first-in-class CD38 antibody Darzalex, plus expanded US approval for Arzerra, and entered into a new collaboration with Novo Nordisk for its DuoBody bispecific antibody technology.

“The deal with Janssen on their now-approved anti-CD38 antibody in multiple myeloma transformed Genmab … into a player,” said the judges.

The Award for Best Company in an Emerging Market (sponsored by ICON) went to Mundipharma Singapore.

Mundipharma’s independent associated companies are privately owned entities covering the world’s pharmaceutical markets. Mundipharma consistently delivers high quality products and in 2016 broke ground on its Betadine manufacturing and R&D facility in Singapore, an important strategic move and one that will enable it to respond quickly to regional health crises.

The judges were impressed by its growth in sales and its deals that have strengthened its position.

The award for Best Contract Research Organization was this year split into two categories to separate the full-service providers from those smaller CROs that provide niche services to their clients.

The winner of the Best Contract Research Organization – Full-service providers was QuintilesIMS, which enjoyed a busy qualifying year, with the creation with Quest Diagnostics of the world’s second-largest clinical trials laboratories, Q2 Solutions, to provide precision medicine enabled by genomics and companion diagnostics. It also announced the merger with IMS Health to create a new type of CRO, one that spans the clinical-commercial continuum.

The judges described the entry as “outstanding”, noting QuintilesIMS’ impressive record of involvement in development of best-selling products.”The new mega-structure offers interesting potential for 2017.”

The Award for Best Contract Research Organization for those companies that provide niche services went to Altasciences Clinical Research. Altasciences offers comprehensive Phase I/II drug development including the full array of required support services. It has improved its range of services to meet sponsors’ expanding needs, leading to the development of specialized offerings, and the judges also noted its strong social media strategy.

DEALS, DEALS, DEALS

The Best Partnership Alliance (sponsored by INC Research) recognizes the importance of pharmaceutical and/or biotech companies working together to develop new medicines. This year the trophy went to AstraZeneca and Human Longevity for their long-term genomic partnership which aims to harness the power of genomic information to propel the discovery and development of novel medicines. The companies hope their partnership will drive new drug target and biomarker identification to select patients who can respond to treatment, and believe it could change the way clinical trials are designed.

“The impact on our industry and patient outcomes if this alliance achieves its goals are immeasurable,” the judges said.

The Licensing Deal of the Year (sponsored by Worldwide Clinical Trials) award celebrates the licensing transactions that are vital both in helping to keep pharma’s pipelines replenished and in generating income for smaller firms.

The winner Galapagos received an up-front payment of $725m consisting of a license fee of $300m and a $425m equity investment from its deal with Gilead to develop the JAK1-selective product filgotinib for the treatment of rheumatoid arthritis and other inflammatory diseases, in a boost to Gilead’s inflammation R&D portfolio.

“Hugely valuable strategically to Galapagos given that the asset had been returned only a few months previously, yet within three months it had found another big partner in Gilead and at much better financial terms,” the judges said. “For Gilead, it’s a decent addition to their portfolio in an important market.”

The award for Financing Deal of the Year (sponsored by EBD Group) went to Immunocore for its series A financing.

Totaling $320m, this was the largest private financing in the life sciences ever in Europe and second largest globally in the sector. The oversubscribed round included some of the most highly regarded institutions in the
healthcare sector and provided the company with financial security to advance its ImmiTAC technology platform and other initiatives.

The judges said, “This financing stood out … due to its sheer scale and the impressive amount raised.”

PEOPLE SKILLS
For those awards that look at individual and team achievement, the award for Management Team of the Year (sponsored by CRF Health) went to Gennmab’s Core Leadership Team.

This team’s most notable achievement in the qualifying year was the swift approval for Darzalex (daratumumab) for multiple myeloma with Janssen, marking Gennmab’s second marketed antibody. This came alongside its broader goal of building the company into a sustainable business and ensuring the creation of a robust pipeline and future product opportunities. “They have taken Gennmab to the next level,” the judges decided.

Meanwhile, Allergan’s president and CEO Brent Saunders won Executive of the Year (sponsored by Lachman Consultants).

Through a year of enormous change for Allergan, Saunders has led the company with a decisive and direct vision. Seeing ahead of changing marketplace and environment conditions, his approach was powered by a deep commitment to customers, patients and driving innovation to overcome unmet healthcare needs.

The judges described him as “an outstanding, inspirational leader with a proven track record prior to becoming CEO at Allergan, and (in the period under review) effectively and efficiently bringing two organisations together.”

R&D MARCHES ON
Developing new drugs is the lifeblood of the industry and the trophies in this area show novelty across the R&D process.

The perennially popular Best Technological Development in Clinical Trials was split into two this year, with categories rewarding advances that are focused on helping sponsors, and those designed to ease the lives of clinical trial participants.

Best Technological Development in Clinical Trials – Sponsor-focused went to Medidata Solutions’ Medidata Payments.

Medidata Payments in the first end-to-end site payment technology, an EDC-driven solution that automatically calculates, triggers and disburses payments to investigators in real-time. It removes the need for time-consuming, error-prone payment processes that can damage relationships with study sites, reducing turnover rates with a process that is as automated as payroll.

The judges said this was a huge challenge across industry and that the technology brought great benefits for streamlining transparency reporting requirements.

The trophy for Best Technological Development in Clinical Trials – patient-focused went to AiCure’s artificial intelligence DOT smartphone app.

AiCure technology is a new approach to artificial intelligence that uses AI to visually confirm medication ingestion on smartphones. The platform was developed to automate directly observed therapy (DOT), the gold standard in monitoring and maximizing adherence, by visually identifying the patient, the drug, and the act of ingestion.

The judges said it was an “impressive technology” noting that lack of compliance was a huge issue for trials and can dramatically impact study results.

QuintilesIMS’ Clinical Advance of the Year Award (sponsored by QuintilesIMS) went to Summit Therapeutics for its Phase II CoDiFy study of ridinilazole in Clostridium difficile infection.

The Phase II CoDiFy study suggests that ridinilazole has the potential to become a front-line treatment in the management of C. difficile infection, an unmet medical need. It exceeded its primary endpoint showing superiority against current standard of carevancomycin and met key secondary endpoints showing its promise in reducing recurrence rates, a key clinical challenge.

The judges said this was an outstanding study for a much-needed new therapy. “The findings represent an important leap forward in prevention of recurrent infections from C. diff. The market for such a treatment is huge.”

HUYA Bioscience International’s Best New Drug Award (sponsored by HUYA Bioscience International) went to Sanofi Pasteur’s Dengvaxia (tetravalent dengue vaccine).

Dengvaxia is the first vaccine against dengue, a disease that affects 390 million people each year. It is indicated to prevent dengue caused by all four of the virus serotypes and is the culmination of over two decades of scientific innovation and collaboration, with 40,000 volunteers participating in the development program. The judges described it as an outstanding product that “clearly addresses a major medical need for a large number of poor people.”

The inaugural Community Partnership of the Year (sponsored by Medidata) award seeks to acknowledge the numerous ways in which pharma and biotech companies give back to the wider community, and the judges awarded it to GlaxoSmithKline’s Newborn Survival Project in India. India has the highest newborn death rate in the world, accounting for 27% fatalities with the first 28 days of birth, mostly from treatable conditions. GSK’s CSR project works with community volunteers to improve the continuum of care for newborns and is estimated to save 6,000 lives each year. The judges described it as excellent: “Keep on doing and expanding it.”

LIFETIME ACHIEVEMENT
The biggest winner of the night was the Lifetime Achievement Award recipient Dr. Raymond F. Schinazi, who is recognized as one of the most influential persons in the life science sector.

A world leader in nucleoside chemistry, Schinazi is best known for his pioneering work on HIV, HBV and HCV drugs, including stavudine, lamivudine, emtricitabine, telbivudine, and most recently sofosbuvir (Sovaldi). More than 94% of HIV-infected individuals in the US on combination therapy take at least one of the drugs he invented.

He is the Frances Winship Walters Professor of Pediatrics and Director of the Laboratory of Biochemical Pharmacology at Emory University and co-Director of the HIV Cure Scientific Working Group for the NIH-sponsored Emory University Center for AIDS Research. Dr. Schinazi has authored over 500 peer-reviewed papers and seven books and holds over 100 issued US patents, which have resulted in 15 New Drug Applications.

After 35 years of service, Dr. Schinazi retired from the Department of Veterans Affairs with his latest position as Senior Research Career Scientist. He is the recipient of numerous awards including the 2015 William S. Middleton Award from the Department of Veterans Affairs which is the highest honor for outstanding achievement in biomedical research.

Dr. Schinazi was appointed to the Global Virus Network (GVN) Executive Committee in 2016.
ASH 2016 Preview: Don’t Miss These 10 Presentations

A CAR-T late breaker from Kite Pharma and sickle cell disease updates from recently acquired Oklahoma biotech, Selxys, lead Scrip’s handpicked top 10 data presentations you shouldn’t miss at this year’s American Society for Hematology annual meeting, held in San Diego, Dec. 2-6.

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The American Society for Hematology’s annual meeting kicks off on Dec. 2; to get you ready for attending this year’s meeting or to help you know what to look out for online, Scrip has selected 10 of the most exciting data readouts expected at the San Diego-based event.

Kite Pharma Inc. has managed to overtake Selxys Pharmaceuticals Corp. as the most anticipated company to present data at ASH 2016, as the former will discuss pivotal data for its CAR-T therapy, KTE-C19, during the late-breaking abstract session on the last day of the meeting. Prior to Kite’s late-breaker announcement on Nov. 22, conference attendees and analysts had been excited to see data for Selxys’ sickle cell disease therapy, as Novartis AG recently decided to act on its 2012 option to acquire the smaller company – a deal worth up to $665m.

1. CAR-T QUESTIONS FOR KITE

Kite will present data from an interim analysis of the pivotal ZUMA-1 trial of its chimeric antigen receptor (CAR) T-cell therapy, KTE-C19, in patients with refractory aggressive non-Hodgkin’s lymphoma (NHL). The company previously released interim topline results from the ZUMA-1 trial in September 2016. This topline analysis from Kite’s Phase II trial revealed that refractory diffuse large B-cell lymphoma (DLBCL) patients treated with KTE-C19 exhibited an overall response rate of 76% and a complete response rate of 47%. While the ORR and CRR fell to 39% and 33% at three months, respectively, these data are still impressive compared to the 23% ORR and 8% CRR exhibited by refractory DLBCL patients in the SCHOLAR-1 study.

SCHOLAR-1 (Retrospective Non-Hodgkin Lymphoma Research) is a retrospective analysis of patients with chemo-refractory DLBCL looking at data from Phase III studies from the Canadian Cancer Trials Group and LYSARC (CORAL Study) and large retrospective databases including from the MD Anderson Cancer Center, Mayo Clinic and University of Iowa Specialized Programs of Research Excellence (SPORE). Despite KTE-C19’s initial strong performance in refractory DLBCL patients, concerns have been raised over patient deaths in the ZUMA-1 study and analysts at ASH will be looking for further insights into adverse events seen in the Phase II study.

Datamonitor Healthcare analysts Dustin Phan told Scrip: “These data demonstrate promising efficacy and suggest that KTE-C19 could achieve accelerated approval if the six-month response rate is as strong as the three-month response rate data already reported.” Nonetheless, Phan noted there continue to be concerns regarding the two patient deaths on trial due to cytokine release syndrome (CRS). While such adverse events are a known side effect of CAR-T therapy, Kite has stated they will continue to analyze the data for predictors of toxicity.

The data presented at ASH will be from an analysis of 93 patients with at least one month of follow-up at cutoff. The larger patient population compared with the last data release will hopefully provide additional insight into the drug’s efficacy and safety in DLBCL. “While these data are impressive thus far, KTE-C19 will need to continue to demonstrate durability of response to gain the confidence of regulatory bodies,” Phan said.

Additionally at ASH, data from another cohort of ZUMA-1 containing transformed follicular lymphoma (TFL) and primary mediastinal B-cell lymphoma (PMBCL) patients will be presented. Results thus far are “similarly promising” in this cohort, Phan said, with an ORR of 91% and a CRR of 73% (both fall to 64% at three months). However, this interim analysis only contains 11 patients.

2. WHAT HAS NOVARTIS ACQUIRED WITH SELEXYS BUY?

Phase II data for Selxys’ SelG1, an anti-P-selectin antibody being evaluated for the reduction of vaso-occlusive crises (VOC) in patients with sickle cell disease, will be presented on Dec. 4 during the ASH annual meeting.

The day before Kite’s late-breaking abstract announcement, Novartis acted on a 2012 option agreement to purchase Oklahoma City-based Selxys for up to $665m in upfront, acquisition and milestone payments. There have been several recent failures of potential sickle cell therapies at late stages of development. In September, a second Phase III study of Mast Therapeutics Inc’s vepoloxamer failed to show that it reduced the duration of VOC compared with placebo, and the company said it was thinking of terminating all clinical development of the product. A week earlier, Emmaus Life Sciences Inc. found the submission of just a single Phase III study in its US NDA for pharmaceutical grade L-glutamine to treat sickle cell disease was being questioned by the FDA. The agency would prefer data from two Phase III studies. As such analysts will be eagerly awaiting Selxys’ data, which is expected to be positive following Novartis’ buyout announcement.

SelG1 is based on the concept that blocking P-selectin—an adhesion molecule that causes cells to stick together—may help avert VOC in sickle cell patients. Current treatment for sickle cell anemia is usually aimed at avoiding crises, relieving symptoms and preventing complications. Bone marrow transplant offers the only potential cure.

3. CAR-T RIVALRY HEATS UP

Competing with Kite’s KTE-C19, Novartis is also due to present first data from its Phase II registration trial for CAR-T therapy CTL019 in pediatric and young adult patients with relapsed/refractory acute lymphoblastic leukemia (ALL). CTL019 was previously granted Breakthrough Therapy designation by the FDA in July 2014 for this treatment setting and also received a PRIME designation from the European Medicines Agency in June 2016.

Data for CTL-019 continue to demonstrate clinical activity in refractory pediatric ALL.
patients but, similarly to KTE-C19, safety and toxicity concerns have been raised for CTL-019 related to CRS. Approximately 82% of patients thus far in this Phase II trial have experienced CRS, with as many as 44% of those patients requiring anti-cytokine therapy. Furthermore, two early deaths occurred prior to initial disease assessment, one due to disease progression and one due to intracranial hemorrhage, while an additional two patients failed to respond. “CTL-019 will likely have to demonstrate impressive efficacy while managing safety and toxicity if Novartis continues to seek a rapid approval,” Phan told Scrip.

4. ABBVIE’S UPDATES ON VENCLEXTA COMBO

Preliminary data will be presented at the meeting from a Phase II trial investigating the safety and efficacy of Roche/AbbVie Inc’s Venclexta (venetoclax) in combination with Rituxan (rituximab) with or without bendamustine for patients with relapsed/refractory follicular lymphoma. Biomedtracker analysts have noted that preclinical and early clinical data suggest the addition of Venclexta to Rituxan with or without bendamustine may improve response over Rituxan or chemotherapy alone. AbbVie will hope to see these positive effects repeated in this larger study.

During ASH, AbbVie and Roche will also be presenting Phase I safety data for Venclexta as a monotherapy for relapsed/refractory multiple myeloma. Venetoclax – which targets the protein B-cell lymphoma 2 (BCL-2) – has been impressing ASH attendees in recent years in chronic lymphatic leukemia (CLL), displaying strong potency even in hard-to-treat patients with 17p deletions. However, in that indication potency has been a double-edged sword as the oral therapy, bendamustine may improve response over Rituxan or chemotherapy alone. AbbVie will hope to see these positive effects repeated in this larger study.

6. WILL CTI’S PERSIST-2 STUDY MEET CO-ENDPOINT?

CTI BioPharma Corp. will present full Phase III data for pacritinib from the PERSIST-2 study, which is testing the drug in patients with myelofibrosis and thrombocytopenia (less than 100,000 platelets per microliter), who are considered to have a shortened median survival time compared with myelofibrosis patients with normal platelet counts.

CTI BioPharma released topline data from the PERSIST-2 study in August this year; preliminary efficacy analysis showed pacritinib therapy was associated with a significant response rate in spleen volume reduction, a co-primary endpoint. However, the drug did not meet the second co-primary endpoint of a greater than 50% reduction in total symptom score (TSS), although it was approaching marginal significance (p = 0.0791).

The fate of pacritinib is also critical for Shire PLC, which has a licensing agreement to jointly commercialize pacritinib in the US with CTI BioPharma and has exclusive commercialization rights for all indications outside the US.
**Baxter Divests Serum Business In Turkey Business Rejig**

Global healthcare company Baxter International Inc. has completed the alignment of its local business in Turkey with the global separation of its biopharmaceutical operations by selling a portfolio of serum products to domestic firm Kocak Farma. Licenses and brands in the serum product portfolio currently belonging to the US firm’s operating arm, a 50/50 joint venture with leading company Eczacibi as Ilac Pazarlama AS known as Eczacibi, Baxter, will be divested to Kocak by the end of the year, along with production and other factory equipment. The JV will cease production in this area, meaning layoffs for around 500 employees and other workers. No figures have been disclosed about the value of the divestment or other arrangements. With a market share of almost 60%, Eczacibi Baxter has been a dominant force in the serum business in Turkey for over 50 years, and Kocak is therefore gaining a strong portfolio. Hakan Kocak, the Turkish firm’s CEO and general manager, underlined that the transfer would help his company to grow and also bring new technology. “Serum is a strategically important product. We will act responsibly and increase production, providing easier access for Turkish patients to these products,” he declared. At the same time - in line with the global spin off of the Baxalta Inc. business in mid-2015 - the biopharmaceutical products of Eczacibi Baxter will be transferred to a new equally owned JV with Eczacibi, Eczacibi Baxalta.

Ahmet Sevindik, 24 Nov 2016

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**Kymab Keeps Cash Coming In With $100m Led By Chinese Investors**

Kymab Ltd. has raised $100 million in a Series C financing led by new investors ORI Healthcare Fund L.P. and including Shenzhen Hepalink Pharmaceutical Co. Ltd. both of China. Existing shareholders Wellcome Trust, Bill & Melinda Gates Foundation, Malin Corporation plc, CF Woodford Equity Income Fund and Woodford Patient Capital plc also participated. CEO David Chiswell told Scrip the company planned to have five programs in clinical testing by 2019 with a pipeline of products in four main areas: immuno-oncology, autoimmunity, hematology and infectious disease. According to Chiswell, the first program – which will enter the clinic next year – is an antibody against the OX40 ligand.

“If you antagonize it then you prevent T cells prolonging an immune response, it’s like tuning it down. In theory you could go for any T cell driven autoimmune disease. We’re initially targeting GvHD because that’s a disease in which you know when the immune response starts: when you do the transplant. We’ll have a poster at ASH with some very exciting data of our antibody in a primate model of GvHD.” The next program to enter the clinic will be in immuno-oncology “but we’re not disclosing the target for that.” Despite a very successful fund-raising history, Kymab’s $100m Series C adds to $120m in Series A and B funds, Chiswell said: “If those five programs are successful we’ll need even more money. We will obviously have to find development partners. But the good thing about being well financed is we can get partners when we have data, when a partnership is worth more to us. The plan is take these programs forward until we get proof of concept data and then seek partners.”

sukaina.virji@informa.com, 24 Nov 2016

**Poland’s Celon Pharma Pursues Innovation**

Having raised just over $60m in an IPO on the Warsaw Stock Exchange in October, the 14-year-old Polish company Celon Pharma SA is aiming to have three of its own investigational innovative products in the clinic in 2017, spearheading a strategic move towards the development of innovative pharmaceutical products. The expansionary strategy is part of a plan drawn up several years ago. “We knew we would need extra capital around about now to invest in research projects and help fund the initiation of clinical trials for our innovative products,” said president and major shareholder, Maciej Wieczorek, in an interview with Scrip. Currently, Celon markets a mix of branded and generic products, including the respiratory agent Salmex (fluticasone plus salmeterol) and the anticancer Aromek (letrozole). The Polish company also entered into collaborations with India’s Lupin Ltd. and Glenmark Pharmaceuticals Ltd. in 2015 involving the marketing of a generic version of GlaxoSmithKline PLC’s Seretide (fluticasone plus salmeterol) in various countries. But some time ago, Celon forecast that the cash flow it generates from the development and sale of generics, and EU research funds for developing innovative products, would still need an injection of capital to support a move into innovative products. A further consideration supporting this path forwards was the increasingly competitive nature of the generics market, Wieczorek noted. In the IPO, Celon raised PLN245m ($63m) from offering 13 million newly issued B series shares to institutional investors and two million B series shares to individual investors, representing 33% of the company and 25% of the voting shares. Wieczorek remained Celon’s majority shareholder and president of the management board after the IPO. The company is the first with a full suite of pharmaceutical activities – R&D, manufacturing and marketing – to be listed on the Warsaw Stock Exchange.

john.davis@informa.com, 24 Nov 2016
Genentech Oncology Director Talks Cancer Vaccine Challenges

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Peter Fong, associate director of oncology business development at Genentech – a division of Roche – talks to Scrip about the company’s latest deal with BioNTech in oncology vaccines and why Genentech is predicting success this time around for more cancer vaccine products, especially when used in combination with newer immunotherapy options.

Genentech Inc’s potential $310m (£278m) deal with messenger RNA company BioNTech AG is not a typical end license deal, Peter Fong, associate director of oncology business development at Genentech, told Scrip at the recent BIO-Europe partnering conference, held in Cologne, Germany.

Genentech’s deal with BioNTech is “a situation where both parties are going to fund development of the product equally and also share in the profits,” he said. Fong also highlighted that the technology “is certainly not your typical monoclonal antibody or small molecule.” Genentech and BioNTech are jointly developing cancer vaccines based on BioNTech’s capabilities in the design, formulation, manufacturing and clinical testing of individualized neo-antigen-based mRNA vaccines, combined with Genentech’s cancer immunotherapy, diagnostic, manufacturing and commercial expertise.

“Every single patient is going to have their tumor sequenced and based on the sequence information we’ll have this vaccine made on an individual basis,” Fong said. However, he highlighted that this personalized vaccine approach has its challenges. “Clearly when you’re making a therapeutic that’s individual for every single patient you’re going to have logistical issues that you have to plan for,” he said.

A patient being treated with one of Genentech, a division of Roche, and privately held BioNTech’s cancer vaccines will have to undergo a tumor resection or biopsy, the tissue will then be sent to a sequencing center where whole sequencing would be performed, based on that genetic information mutations will be identified along with new antigens, these will be ranked and a mRNA vaccine created specific to that tumor. The treatment must then be shipped back to the patient after formulation and injected. “It’s an individualized approach; you are not taking the same antibody and giving it to lots of different patients, you’re taking lots of different patients and making a unique vaccine for each of them,” Fong said. He highlighted manufacturing and commercialization as prime challenges for the two companies to work through. Also, from a regulatory standpoint, Fong noted that this was a new therapeutic approach requiring a different regulatory pathway.

Fong told Scrip that Genentech’s preparation for these challenges began before it even signed the deal with BioNTech. “This kind of preparation really starts in the diligence phase before you sign the deal,” he said. “Once you start going into diligence with a potential partner you’re thinking through a lot of the issues you are going to have to solve with that company. Also for a deal like this you have to have so much alignment and communication internally - all of our respective stakeholders were involved in the process and we have discussed these challenges.” Fong said that one of the reasons Genentech decided to partner with BioNTech in the personalized vaccines space was because of the latter company’s manufacturing know-how.

Roche has a vast immuno-oncology portfolio, including a number of compounds in clinical development and the first PD-L1 inhibitor to reach the market, Tecentriq (atezolizumab), which is approved for use in bladder cancer and non-small cell lung cancer.

However, Genentech still sees promise and opportunity in the cancer vaccine space – historically a tricky development area. Most approaches to cancer vaccines have been unsuccessful due to difficulties identifying the correct cancer targets, or antigens, to vaccinate against; but there has been a new wave of interest for use in conjunction with cancer immunotherapies as cancer vaccines could prime the immune system to seek specific molecular targets.

Fong said Genentech was interested in vaccine development because “despite the great promise of the checkpoint inhibitors you’re still going to have a limited response depending on the patient population and the tumor type. This idea that you can take the brakes off the immune system with checkpoint inhibitors is super exciting,” he said. “However, we want to do more than that. We also want to tell the immune system where to go. When you vaccinate a patient you’re actually telling the T-cells where the tumor is.”

Genentech and BioNTech will start their mRNA vaccine development collaboration by looking at potential combinations of Tecentriq and a vaccine candidate. “Tecentriq has already been developed as a mono-therapy so we’re really just adding the vaccine on top of something that’s already approved in two indications; we’re not starting both of them from scratch,” Fong said.

Fong expects the first patient to be treated with an mRNA vaccine in combination with Tecentriq in 2017.

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Novartis Buys Selexys As Competitors Stumble in Sickle Cell

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Novartis has exercised its option to acquire Selexys in a deal worth up to $665m, following data from the Phase II SUSTAIN trial of SelG1 in sickle cell disease. The move follows several recent failures in the space.

Novartis AG has acquired US biotech Selexys Pharmaceuticals Corp., which has a sickle cell disease treatment in Phase II development, for up to $665m in upfront, acquisition and milestone payments.

The terms of the deal were agreed in 2012 when Novartis obtained an exclusive option to buy the Oklahoma City-based firm.

The company’s SelG1, an anti-P-selectin antibody, is being evaluated for the reduction of vaso-occlusive pain crises in patients with sickle cell disease (SCD) in the Phase II SUSTAIN study. Results from the study are being presented at the American Society of Hematology (ASH) annual meeting on Dec 4.

"Sickle cell disease affects millions of people around the world and there are limited therapies available for treatment of vaso-occlusive pain crises," said Bruno Stringini, CEO of Novartis Oncology. "With this acquisition, Novartis is able to leverage its leadership in hematology research to advance development of a potential new treatment option for patients."

SCD is a hereditary blood disorder characterized by sickle-shaped red blood cells. It is a life-long disease with many forms that can range in clinical severity from asymptomatic to life-threatening. Vaso-occlusive crises (VOC), or pain crises, are the major reason for healthcare encounters in SCD and occur episodically when sickle-shaped red blood cells block blood flow through blood vessels.

SelG1 is based on the concept that blocking P-selectin – an adhesion molecule that causes cells to stick together – may help avert vaso-occlusive crises in sickle cell patients.

Current treatment for sickle cell anemia is usually aimed at avoiding crises, relieving symptoms and preventing complications. Bone marrow transplant offers the only potential cure.

TOUGH AREA

There have been several recent failures of potential sickle cell therapies at a late stage of development. In September, a second Phase III study of Mast Therapeutics Inc’s vepoloxamer failed to show that it reduced the duration of VOC compared with placebo, and the company said it was thinking of terminating all clinical development of the product.

A week earlier, Emmaus Life Sciences Inc. found the submission of just a single Phase III study in its US NDA for pharmaceutical grade L-glutamine to treat sickle cell disease was being questioned by the FDA. The agency would prefer data from two Phase III studies.

A review of Informa Pharma’s R&D pipeline database, Pharmaprints, indicates that Pfizer Inc. and its partner GlycoMimetics Inc. have one of the few potential therapeutics for sickle cell disease at an advanced stage of clinical development – Pfizer started a Phase III study of the synthetic glycomimetic molecule, rivipansel, back in June 2015. The RESET (rivipansel: evaluating safety, efficacy and time to discharge) study is evaluating the treatment of VOC in hospitalized patients aged six years or older. Rivipansel is designed to inhibit all three types of selectin involved in cell adhesion.

Daichi Sankyo Co Ltd’s marketed platelet anti-agregant Effient (prasugrel) has been submitted for the additional indication, use in pediatric sickle cell disease, in some markets.

Karolinska Development portfolio company Modus Therapeutics (which recently changed its name from Dilaforet) is in Phase II with its potential sickle cell product, sevuparin.

Selexys raised a $23 million Series A round led by MPM Capital concurrent with the option agreement in 2012.

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Allergan Up For Alzheimer’s Challenge With Chase Buy

Allergan is paying $125m for Chase Pharmaceuticals and its Alzheimer’s disease candidate CPC-201 that has completed Phase II testing. The modest upfront reflects the Phase III graveyard that Alzheimer’s disease represents. Chase is led by two former Allergan executives.

Allergan PLC has acquired Chase Pharmaceuticals Corp. for an upfront payment of $125m plus potential regulatory and commercial milestones of up to $875m to Chase’s shareholders. These include India’s Cipla Ltd., which held a 16.7% stake in the firm.

Chase’s lead compound, CPC-201, is a patent-protected combination of the most commonly prescribed acetylcholinesterase inhibitor donepezil and the peripherally acting cholinergic blocker solifenacin (which is already approved to treat overactive bladder).

AChEIs have been shown to improve cognition in Alzheimer’s disease patients but dosing is limited by side effects including diarrhea, nausea and vomiting.

In Phase II testing of CPC-201, 29 out of 33 patients (88%) reached 40 mg/day of donepezil (maximum dose allowed), without experiencing dose-limiting adverse events. Allergan believes that Chase’s next-generation formulation offers the possibility of better dosing with the potential for improved cognition and function in Alzheimer’s disease patients.

Chase recently completed an end of Phase II meeting with the US FDA and based on feedback from the agency, Allergan intends to advance CPC-201 into a single Phase III registration study in 2017.
Amid Brexit Chaos, UK PM Promises More R&D Funding, Lower Taxes, And Other Pro-Innovation Measures

The UK prime minister has promised more government R&D funding and other incentives in an attempt to reassure businesses worried by the uncertainty created by the Brexit vote. The move comes shortly before the Chancellor’s autumn statement and the next meeting of the UK EU Life Sciences Steering Group.

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In a move intended to reassure science-based companies amid the chaos caused by the UK Brexit vote, the UK prime minister Theresa May has announced that the government is to invest an extra £2bn into R&D by 2020 and to establish an Industrial Strategy Challenge Fund for priority technologies as part of what she called a “modern, ambitious industry strategy.”

Addressing the annual conference of the Confederation of British Industry, May said she would also commit to the UK having the lowest corporation tax among the G20 group of countries. The tax is already scheduled to fall to 17% by 2020 and suggestions are that it could be reduced still further, possibly to 15% or lower.

Also on the cards is a review of the R&D tax credit, which has already been shown to stimulate additional investment in the UK. The Treasury is to look at how to make this support “even more effective” to ensure that the UK continues to actively encourage innovation, May told the conference.

She added that a Patient Capital Review would be launched to help companies secure the longer-term investment they need to transform ideas into business, and that the small business innovation research initiative would also be reviewed.

Her speech came in advance of the autumn statement to be delivered by Chancellor Philip Hammond on Nov. 23, when he is expected to announce measures for tackling issues such as the high level of UK government debt, the possibility of slowing economic growth, and a likely rise in inflation following the plunge in the value of the pound.

The Association of the British Pharmaceutical Industry and the BioIndustry Association both said they welcomed the extra R&D funding promised by the prime minister as well as the government’s pledge to support and invest in science and technology innovation.

Mike Thompson, the ABPI’s chief executive, said: “As we look ahead to the autumn statement on Wednesday, reports today of an extra £2bn of funding for a year for the sector will help to ensure this becomes a reality. This is hugely welcome and will be well received by everybody involved in UK life sciences.”

BioIndustry Association CEO Steve Bates said it was “fantastic to see this government showing an understanding of what is important to life science businesses.” While the continued commitment to R&D was welcome, he said, “for us the focus on improving the R&D tax credit regime, the focus on patient capital, and the review of the small business research initiative are crucial and very welcome. The UK is becoming the location from which the global leading life science businesses of the future will grow.”

HOW WILL IT BE USED?

Quite how the R&D funding promised by the prime minister will benefit the biopharmaceutical industry is unclear, though, as she gave no details in her speech as to how the funding would be spread across the various R&D sectors. Martin Turner, policy and projects manager at the UK Biolndustry Association, said “we look forward to hearing in greater detail in the autumn statement and beyond how this funding will impact on the sector.”

For Ed Corbett, engagement manager at pharma strategy consultants Novasecta, the announcement represented “a small step towards calming UK pharma/biotech nerves” following the Brexit vote.

“If I were a pharmaceutical or biotech CEO in the UK I would cautiously welcome this,” he said, although he added that “how the funding will be allocated and what will be used as a model is very unclear.” He suggested to Scrip that it might mimic the EU’s Horizon 2020 research funding program, to which the UK could lose access if it leaves the single market. But he pointed out that Horizon 2020 “is worth €80bn versus £2bn.”

Similarly, he said that the UK figure was “significantly smaller than the £26bn the US government invests in the National Institutes of Health every year, and therefore may not make the UK as competitive as hoped. This, combined with outstanding uncertainty on free movement of people, upon which pharma/biotech depends, will mean that the UK’s position as a global leader in life science research is by no means guaranteed.”

The government position, he said, “reflects the general uncertainty of Brexit. It is nice mood music but we need to know how and when it will be allocated.”

AUTUMN STATEMENT AND BREXIT

The Chancellor’s autumn statement will coincide with the next meeting of the UK EU Life Sciences Steering Group, which is trying to assess the impact of Brexit on the life science sector. The meeting is expected to look at ways of mitigating the effects of a UK departure in key areas like commercial and trade, regulatory convergence, and movement of people.

Corbett, whose firm has interviewed key heads of pharma and biotech firms about the impact of the UK leaving the EU, said that senior leaders in EU-headquartered companies “have said that because of the general uncertainty they are holding off on short-term investment decisions.” A key issue raised, he said, was the movement of people. “One member of our panel of CEOs said that companies and our people are very rattled.”

The uncertainty has been compounded after the international trade secretary, Liam Fox, told Labour MP Daniel Zeichner that he did not agree that the UK needed to remain part of a Europe-wide regulatory system.

This chimes with fears expressed by many in business that the UK is heading for a so-called “hard” Brexit, with full withdrawal from the single market and the EU customs union.

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NICE Backs Imbruvica In CLL On Price Cut Despite Outcome Uncertainties

The UK’s National Institute for Health and Care Excellence has reversed its earlier stance on Johnson & Johnson /AbbVie Inc.’s blockbuster chronic lymphocytic leukemia drug Imbruvica (Ibrutinib) and now provisionally backs its use to treat some patients with chronic lymphocytic leukemia (CLL) routinely on the publicly funded National Health Service after receiving more input on the drug and a promised price cut. In June, NICE issued draft guidance rejecting the drug for treating pre-treated patients with CLL, and asked the drug’s makers to put forward a case for including it on England’s new Cancer Drug Fund for those with genetic changes. But J&J’s corporate entity in Europe Janssen Inc. declined to do so, saying there were already observational data available for this group, and that collecting further data through the CDF would not address the uncertainty in this population. Instead the drug’s makers offered an undisclosed price discount, which NICE concluded made the therapy cost effective. The orally administered therapy had only previously been available through the Cancer Drugs Fund despite patients with this type of leukemia being difficult to treat and having limited treatment options. Some existing treatments for the disease can also cause severe side effects. But the promised cost cut to the NHS means Imbruvica is now recommended in revised draft guidance as a routine option for people with CLL who have had treatment before, or who have genetic changes known as 17p deletion or TP53 mutation. Up to one in 10 adults with chronic lymphocytic leukemia have a form of cancer with such genetic changes, which makes their disease progress quicker and more difficult to treat. “Patients with relapsed/refractory CLL who are not suitable for chemo-immunotherapies, such as regimens which include the standard-of-care Roche /Biogen Inc.’s Rituxan (rituximab), have poor prognoses and very little treatment options,” said Datamonitor Health-care analyst Dominique Fontanilla. sten.stovall@informa.com, 25 Nov 2016

Expanded US Approval Set To Take Janssen’s Darzalex Higher

The US FDA has approved Janssen Biotech Inc.’s Darzalex (daratumumab, licensed from Genmab AS) in combination with lenalidomide (Celgene Corp.’s Revlimid) and dexamethasone, or bortezomib (Velcade) and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy. This go-ahead for second-line use brings the anti-CD38 monoclonal forward in the treatment arc for this disease. Darzalex was first approved in the US, rather earlier than expected, almost exactly a year ago to treat patients with multiple myeloma who have received at least three prior lines of therapy, including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD), or who are double-refractory to a PI and IMiD. That US approval was followed by one in the EU in April under an accelerated procedure for relapsed or refractory disease. The new supplemental approval – which was based on the open-label Phase III CASTOR and POLLUX studies – comes three months after a supplemental sBLA was submitted to the FDA in August 2016. Darzalex received FDA Breakthrough Therapy Designation for this indication in July 2016. It puts Darzalex on a more equal footing to its rival monoclonal Empliciti (elotuzumab) from AbbVie Inc., which was approved in the US shortly after Darzalex received its first approval there, but for earlier-line use in combination with Revlimid and dexamethasome in patients who have received one to three therapies. Empliciti is a SLAMF7 (signalling lymphocyte activation molecule family member 7) protein inhibitor. alex.shimmings@informa.com, 22 Nov 2016

Sage Therapeutics On PRIME, Partnerships and Pricing For Its PPD First

SAGE Therapeutics Inc.’s Sage-547 is on track to become the first ever pharmaceutical indicated for postpartum depression. It has won PRIME designation from the European Medicines Agency and Breakthrough Therapy Designation for the treatment of PPD from the US FDA. Jeff Jonas, the company’s CEO, speaks to Scrip about what when it expects to launch, what it wants from a partner and what it might charge. Sage has announced it has won PRIME designation from the European Medicines Agency. The PRIME program is aimed at accelerating the regulatory process for promising investigational medicines that could offer patients benefits in disease areas where there are no treatments, or which might offer a major therapeutic advantage over existing treatments. The news came after Sage-547 won Breakthrough Therapy Designation for the treatment of PPD in September. The designations were based on results from a Phase II placebo-controlled 202A study of Sage-547 in severe PPD. Datamonitor healthcare analyst Maha Elsayed says that the PRIME and FDA Breakthrough designations underscore the urgent need for treatment options for these patients. She points out that there are no drugs specifically designed for women with PPD and that the main forms of treatment are psychotherapy or classic antidepressants. francesca.bruce@informa.com, 25 Nov 2016
The TIGER That Came To Lilly

The reasons behind Lilly’s latest clinical failure had much less to do with the indication and more to do with repeating the past mistakes of Inspire and Sunesis. Unfortunately, that same die has already been cast for the trials of Biogen and Ophthotech that are due to report imminently.

Andy Smith

In 2008 I remember arguing with my colleagues at the time about the results of a ‘positive’ clinical trial that I felt had effectively failed and whose results were unlikely to be reproducible. Even eight years later tiny effect sizes and high p-values seem not to be a barrier to the progression of drugs in small or needy patient populations. Thankfully these types of results are frequently the harbinger of ultimate clinical, regulatory or commercial failure and with one down and two to go before the year-end there is probably much more risk than reward for the sector.

THE TIGER

In 2008 when Inspire Pharmaceuticals Inc. announced the ‘positive’ results of its TIGER-1 Phase III clinical trial of denufosol in 332 cystic fibrosis patients its stock price soared, opening up 75% as investors raised their hopes for the second Phase III TIGER-2 study and ultimate approval of a blockbuster drug. To my cynical eye a p-value of 0.047 in one primary endpoint and the failure in the other key endpoint of exacerbations – which the FDA more recently favors – were important warning signs. When Inspire then announced changes to the protocol of the TIGER-2 study, the failure of denufosol was cemented for me. In TIGER-2 the treatment period was doubled from 24 to 48 weeks, the target enrolment was increased from 350 to 450 patients and the enrolment criteria were modified to include less severe patients. The chopping and changing of clinical trial protocols has been a key fault line that has run through the subsequent and failed clinical studies of Sunesis Pharmaceuticals Inc. and last week, Eli Lilly & Co.

Just as TIGER-2 failed, Lilly reported the widely anticipated third Phase III EXPEDITON3 results of solanezumab in Alzheimer’s disease (AD) last week, unveiling a comprehensive failure that sent the company’s stock price down about 11% on the day of the announcement. Like TIGER-2, the EXPEDITON3 protocol had been changed from the previous two failed Phase III studies in order to magnify a small, retrospectively defined treatment effect that, in the end, turned out not to exist.

Solanezumab’s failure has less to do with the AD indication and much more to do with the baloney sold to Lilly’s management by the senior vice presidents of R&D so that they could stay in their jobs and collect bonuses after the failures of first two EXPEDITON Phase III studies in 2012. The fall-out from the failure of EXPEDITON3 therefore has ramifications not just for any other disease-modifying drug intervention aimed against amyloid-beta in AD, but any other company where failure is rewarded with an opportunity to repeat past mistakes.

BIOGEN

Investment bank analysts had mixed responses to solanezumab’s failure, with perhaps those from UBS – reducing their share price, removing $1.1bn in sales and maintaining their neutral rating – being the fairest. At the other end of the spectrum, those from Leerink Partners and Morgan Stanley promoted a rose-tinted view of the latest failure of the amyloid hypothesis in AD as it related to a very similar antibody (aducanumab) and early AD patient population in Phase III development at Biogen Inc. Despite this quarterbacking Biogen’s share price did fall over 6% in sympathy on the day of Lilly’s announcement, but even that fall did not convey the fact that with aducanumab Biogen is committing an almost carbon-copy of the solanezumab faux pas.

Biogen initially presented interim Phase Ib data for aducanumab (formerly BLI037) back in 2014 that showed some interesting effects in small groups of early AD patients but without a convincing dose-response and with worrying safety signals. Before the full Phase I dataset was released Biogen announced its move into Phase III without conducting any Phase II studies and the CMO unloaded $10m worth of Biogen stock. When a fuller data set on aducanumab Phase I studies was presented in 2015 the linear relationship between the product’s safety and efficacy had declined so much that the announcement contributed to a 25% fall in Biogen’s stock.

The fact that they share the same target and early AD patient population as EXPEDITON3 make me think that the aducanumab Phase III studies are destined to fail when they report later this year. Of course, there is always the possibility for a Lilly-inspired data mine in order to find a small retrospectively defined subset and a hitherto unknown and unvalidated endpoint on which a ‘positive’ adjective could be applied in the trial announcement.

OPHTHOTECH

With Ophthotech Corp’s Phase III trial results for its anti-PDGF apatamer Fovista (pegpleranib) also expected before the end of the year, and coming a few months after the Phase III failure of Regeneron Pharmaceuticals Inc’s rinucumab – an antibody against the same target in the same patient population as Fovista – Fovista also has all the potential for failure but a ‘positive’ announcement.

I have predicted the clinical trial failures of Circassia Pharmaceuticals PLC and Lilly so far this year and the reasons for those failures can be extended to other companies replicating their mistakes and set to report hotly anticipated Phase III data before the year-end. With the share price of Lilly joining those of AstraZeneca PLC and Novartis AG at their 52-week lows this week, it may be time to sell in November (instead of May) and go away.

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Andy Smith gives an investor’s view on life science companies. He has been lead fund manager for four life science–specific funds, including 3i Bioscience, International Biotechnology and the AXA Framlington Biotech Fund, and was awarded the techMark Technology Fund Manager of the year for 2007.
Selected clinical trial developments for the week 18–24 November 2016

<table>
<thead>
<tr>
<th>LEAD COMPANY/PARTNER</th>
<th>COMPOUND</th>
<th>INDICATION</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase III Suspended</strong></td>
<td></td>
<td></td>
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<tr>
<td>Eli Lilly &amp; Co.</td>
<td>solanezumab (beta amyloid targeted MAb)</td>
<td>mild Alzheimer’s disease</td>
<td>EXPEDITION3; primary endpoint not met.</td>
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<tr>
<td>Acorda Therapeutics Inc.</td>
<td>Ampyra (dalfampridine)</td>
<td>ischemic stroke (post stroke walking difficulties)</td>
<td>MILESTONE; efficacy not sufficient in this additional indication.</td>
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<tr>
<td>Spectrum Pharmaceuticals Inc.</td>
<td>Qapzola (apaziquone) intervesical instillation</td>
<td>bladder cancer</td>
<td>Enrolment halted, a new smaller study to start.</td>
</tr>
<tr>
<td><strong>Phase III Results Published</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Collegium Pharmaceutical Inc.</td>
<td>Xtampa ER (oxycodone) tamper resistant</td>
<td>chronic pain</td>
<td>Online Nov. 10 in the journal, Drugs.</td>
</tr>
<tr>
<td><strong>Phase III Completed</strong></td>
<td></td>
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<tr>
<td>Johnson &amp; Johnson/Bayer AG</td>
<td>Xarelto (rivaroxaban)</td>
<td>prevention of recurrent venous thromboembolism</td>
<td>EINSTEIN CHOICE; Evaluating a reduced dose.</td>
</tr>
<tr>
<td><strong>Phase III Interim/Top-line Results</strong></td>
<td></td>
<td></td>
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<tr>
<td>GlaxoSmithKline PLC</td>
<td>Nucala (mepolizumab)</td>
<td>eosinophilic granulomatosis with polyangiitis</td>
<td>Met primary and secondary endpoints, filings for the new indication next year.</td>
</tr>
<tr>
<td>Omeros Corp.</td>
<td>Omidria (phenylephrine and ketorolac) inj</td>
<td>ocular inflammation</td>
<td>Well tolerated in children, in an FDA-required post-marketing study.</td>
</tr>
<tr>
<td>AcelRx Pharmaceuticals Inc.</td>
<td>ARX-04 (sublingual sufentanil)</td>
<td>moderate to severe pain</td>
<td>Effective and well tolerated.</td>
</tr>
<tr>
<td><strong>Phase III Initiated</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Gilead Sciences Inc./Galapagos NV</td>
<td>filgotinib</td>
<td>Crohn’s disease</td>
<td>DIVERSITY; triggers $50m milestone for Galapagos.</td>
</tr>
<tr>
<td>Astellas Pharma Inc.</td>
<td>gilteritinib</td>
<td>acute myelogenous leukemia</td>
<td>As maintenance therapy.</td>
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<tr>
<td>Bristol-Myers Squibb Co.</td>
<td>Opdivo (nivolumab)</td>
<td>mesothelioma</td>
<td>CheckMate743; with ipilimumab as first line therapy.</td>
</tr>
<tr>
<td>Innoven Biologics Inc.</td>
<td>IBI305 (biosimilar bevacizumab)</td>
<td>non-squamous non-small cell lung cancer (NSCLC)</td>
<td>In China.</td>
</tr>
<tr>
<td>Symbio Pharmaceuticals Ltd./The Medicines Co.</td>
<td>SyB-P-1501 (lonsys; transdermal fentanyl)</td>
<td>pain</td>
<td>In Japan.</td>
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<tr>
<td><strong>Phase III Announced</strong></td>
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<tr>
<td>AstraZeneca PLC</td>
<td>durvalumab</td>
<td>head and neck squamous cell carcinoma</td>
<td>EAGLE, KESTREL; partial clinical hold lifted by FDA, enrolment resumes.</td>
</tr>
</tbody>
</table>

Source: Biomedtracker
APPOINTMENTS

Gamida Cell, a company focused on cancer and orphan genetic diseases, has appointed Julian Adams chair of its board of directors. Adams brings over 30 years’ experience to the company and is president of research and development at Infinity Pharmaceuticals. Before Infinity, Adams was the senior vice president of drug discovery and development at Millennium Pharmaceuticals.

Paul Hayes, group finance director of The Virtue Group Plc., has been appointed Consort Medical Plc’s group chief financial officer (CFO). Hayes will succeed Richard Cotton and join the company as CFO and an executive director on the board in May, 2017. Previously, Hayes was group financial controller at Signet Jewellers Ltd. (formerly Signet Group Plc) and before this, he held a senior director role at RHM Plc.

Addex Therapeutics, a company focused on neurological disorders, has appointed Roger G. Mills to the newly created position of chief medical officer. Mills has gained over 25 years of biopharma experience at various companies including Acadia Pharmaceuticals, Pfizer, Gilead Sciences, Abbott Laboratories and Wellcome. Most recently, Mills was executive vice president, development and chief medical officer at Acadia. He currently serves as a visiting professor at the Centre for Age Related Diseases, Institute of Psychiatry, Psychology and Neuroscience, King’s College London.

Myovant Sciences Ltd., a company focused on women’s health disease and other endocrine-related disorders, has appointed Terrie Curran to its board of directors as an independent director. Curran is president of worldwide markets for the inflammation and immunology portfolio at Celgene Corporation. Previously, she was senior vice president and general manager of women’s health and endocrinology at Merck & Co. Inc.

Paragon Bioservices, a manufacturer of biopharmaceuticals, vaccines and viral vectors, has appointed John Conner senior vice president of GMP manufacturing. Conner is a biotech operation executive, who most recently was senior vice president of CytoVance Biologics. Before this, he was associate director, technical support of CancerVax Corporation and he also held management positions at the John Wayne Cancer Institute and Gene Therapy Laboratories.

Industry veteran David Rodman has joined the biopharma company miRagen Therapeutics Inc. as executive vice president of research and development. With more than 25 years of experience, Rodman is an elected member of the American Society for Clinical Investigation and was named a fellow and established investigator of the American Heart Association. Before miRagen, Rodman was vice president of clinical development at Vertex Pharmaceuticals Inc. and before this, he was executive director, respiratory translational medicine at the Novartis Institutes for biomedical research.

Richard Malamut has joined CNS focused, Avanir Pharmaceuticals Inc., as senior vice president, research and development, and chief medical officer. Before Avanir, Malamut was the senior vice president of global clinical development at Teva Pharmaceutical Industries Ltd. Previously, he held roles working in pain, psychiatry and neurodegenerative diseases at Bristol-Myers Squibb and AstraZeneca, as well as consulting for Avanir, Schwarz Bioscience and Shire Pharmaceuticals.
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