Sanofi’s New Diabetes & CV Head Guenter Has Difficult Job Ahead

STEN STOVALL sten.stovall@informa.com

Sanofi SA’s CEO Olivier Brandicourt has shaken up his top management team for the second time since taking over the reins last year, changing the head of its key diabetes franchise in an urgent effort to turn things round. He clearly hopes Peter Guenter’s wide-ranging commercial insights can help achieve that.

Sanofi’s chief executive, a French national, has been in the job just over one year and is under pressure to show progress in countering the effects of rising competition and US drug pricing strain on the diabetes portion of the business, where sales fell 4.5% to €1.73bn ($1.99bn) in the first quarter of this year – a slide that the company predicted in 2015 before reporting a 6.8% drop in diabetes sales for 2015. Sanofi expects sales for the franchise to sink 4% to 8% annually through 2018.

MUSICAL CHAIRS LEAVE WITZ STANDING

So it’s perhaps not surprising that Brandicourt’s latest organizational revamp, announced May 23 and which builds on a restructuring unveiled last November, sees Pascale Witz jettisoned and Sanofi veteran Peter Guenter put in her place to oversee diabetes and cardiovascular activities within France’s biggest drug maker.

No explanation was given by the company other than to say the changes supported its 2020 Strategic Roadmap, unveiled in November 2015 to a lukewarm reception from investors and analysts. A Belgian national, Guenter started his career in sales at Smith-Kline Belgium in 1986. He then joined the Synthelabo in 1995 and held various positions in France, Europe and global marketing. After the integration of Synthelabo in Sanofi he was appointed in 2000 as general manager Belgium. In 2002 he became vice president for commercial operations for Eastern Europe, eventually becoming senior vice president for European commercial operations in July 2011. In July 2013, he was appointed executive vice president for global commercial operations.

From June 1, 2016 he replaces Pascale Witz, who had been head of the diabetes and cardiovascular business since January 1, 2016 and is leaving the company.

BIG CHALLENGES AWAIT GUENTER

Analysts say the challenges facing Guenter are considerable.

“It appears that Olivier Brandicourt believes the operational and commercial background that Guenter brings to the position will be more valuable in delivering as much growth as possible for several products in Sanofi’s diabetes portfolio and pipeline,” commented Datamonitor Healthcare analyst Justin Burns.

“Reversing the market dynamics that are causing the near-term decline in diabetes sales isn’t likely. However, Guenter is well-equipped from a competitive standpoint to at least stem the decline in sales while also managing the launch of several products, specifically Toujeo, Lixilan, and SAR342434, that should return growth to the portfolio from 2018. Leveraging those opportunities from a commercialization standpoint will be critical for Sanofi’s growth over the long term,” Burns added.

Also falling under Guenter’s area of management will be the LDL-lowering PCSK9 inhibitor, Praluent (alirocumab).

“The uptake for this drug should continue to be slow until final results from the cardiovascular outcomes study are released early next year. However, the pushback already coming from payers, as well as competition with Amgen Inc’s Repatha, will require a deft commercialization strategy in order to fully realize the potential for this product,” Burns said.
That pharma has a poor reputation is so much taken for granted that it comes as some surprise to hear that, among the general UK public at least, it is actually the third most reputable industry in the country. So says a new report from the Reputation Institute, 2016 UK Pharma RepTrak.

But before UK pharma starts to preen itself too much, it should be noted that neither of the two biggest and best-known British firms, GlaxoSmithKline and AstraZeneca, covered themselves with glory. Indeed, GSK languishes at the bottom with Pfizer. It is AbbVie, Sanofi and Novo Nordisk that top the ranking.

It seems the UK likes pharma more than nearly all other markets, including key European ones, but its fondness for the industry is driven more by perceptions of the companies themselves rather than for any individual drug they produce. For the RepTrak researchers, the lesson is clear: who you are as a company matters. “The pharmaceutical companies should focus on engaging and telling their corporate story to put a human face on the companies behind the drugs,” they say.

Finding Stars And Staying Independent, Biotech Veteran David Chiswell’s Five Year Plan
http://bit.ly/1U961Wr

David Chiswell has worked tirelessly to build up the British biotech industry for over 30 years. Now, as CEO of Kymab, he is looking to the future of the industry and how to find its rising stars.

Accellta CEO Says Israeli Stem Cell Specialist Seeks Global Partners
http://bit.ly/1IsloAYA

Itzchak Angel tells Sten Stovall about the Israeli group’s stem cell culturing processes and future expansion plans, including a planned $15m capital-raising exercise and ongoing search for future corporate partners.
Panel Embraces Sanofi Diabetes Combo, Shuns ‘Pen’ Devices

DONNA YOUNG donna.young@informa.com

A n FDA panel of advisors on May 25 voted 12-2 to back approval of Sanofi SA’s experimental fixed-ratio combination (FRC) type 2 diabetes medicine, which marries the company’s experimental glucagon-like peptide-1 (GLP-1) receptor agonist lixisenatide with its already marketed drug Lantus (basal insulin glargine).

Sanofi is seeking to market the combo drug, which has gone under the nickname “LixiLan,” as iGlarLixi.

But most members of the FDA’s Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) expressed concern over the two titratable pen devices Sanofi has proposed for commercial use to deliver the FRC product, which the panelists said were too complicated for patients and their healthcare providers.

While insulins are measured in units, GLP-1s are measured in milligrams or micrograms.

Sanofi wants to label the combo product’s dose in units and reflect only the dosing on the insulin component alone in the labeling. It’s also established a complicated dosing regimen.

For instance, a yellow color pen would be used for insulin-naive patients to initiate treatment at a recommended daily insulin glargine (100U/mL) dose of 10 units, with a corresponding dose of 5mcg of lixisenatide.

But in patients switching from basal insulin to iGlarLixi, Sanofi wants to provide two different starting doses, which would be dependent on previous insulin need: the yellow pen with 20 U/10mcg or the green pen with 30U/10mcg.

The dose of iGlarLixi would be adjusted based on the need for basal insulin – primarily on the basis of fasting self-monitored plasma glucose levels.

After initiation of iGlarLixi and during titration, the yellow pen would be used for total daily insulin glargine doses of 10U to 40U, and the green pen for total daily doses of 41U to 60U, thereby not exceeding the maximum lixisenatide starting dose of 10mcg.

Patients using the yellow pen that require more than 40U could be switched to the green pen, Sanofi said.

The firm argued the flexibility of iGlarLixi dosing allows patients to titrate based on their individual responses to treatment.

But EMDAC panelist Ellen Seely, a professor of medicine at Harvard University, insisted the pen was “asking for trouble” and “really needs to be redesigned.”

“I feel really strongly you cannot use the proposed pen,” Seely declared, although she voted in favor of approving iGlarLixi for the US market.

Panelist Kenneth Burman, director of endocrinology at MedStar Washington Hospital Center, said he based his “no” vote “solely on the pen design,” adding that “everything else was fine” with iGlarLixi.

He pointed out that in Sanofi’s human factor study, one out of 15 pharmacists and one out of 45 nurses and patients had difficulties with the pens.

But other than the pen devices, “the advantages are worth the disadvantages” of the combo drug, Burman said.

Panelist Daniel Budnitz, director of the Medication Safety Program at the US Centers for Disease Control and Prevention, said that while he voted in favor of Sanofi’s combination drug, that vote could have just as easily been against iGlarLixi – telling the FDA he was concerned about the potential doctors would put some patients on two drugs “when one would have been effective.”

He also raised concerns about the pens and the proposed way in which Sanofi wants to label them.

Budnitz urged the FDA to ensure there is a standardized vocabulary for labeling injectable combination diabetes medicines – arguing that task should not be left to the prescribing community to develop.

EMDAC chair Robert Smith, a professor of endocrinology at Brown University in Providence, RI, said that while he was “swayed” to vote in favor of approval for iGlarLixi, that support came “contingent” on the FDA ensuring there was some type of guidance in place to address “special circumstances,” like when patients are hospitalized with interrupted nutrition.

Smith also suggested the FDA require post-approval assessing of serious allergic reactions.

“I don't think that's adequately resolved,” he said.

Smith also called for a post-approval study to examine how patients would transition from a GLP-1 to the iGlarLixi device – pointing out Sanofi lacked data on that.

Sagient Research’s BioMedTracker, an affiliate of Scrip, noted there is time to work on the device issues, given the FDA is not expected to make a decision on iGlarLixi until Aug. 23, “though if major work needs to be done on the pens and testing for understanding of the device, it is conceivable there could be a delay.”

Given the positive vote for iGlarLixi, the BioMedTracker analysts increased the likelihood of approval of the drug by 7% – from 91% to 98%.

COMPETITION

Sanofi has been counting on iGlarLixi and the firm’s single-agent lixisenatide, which the EMDAC also reviewed but didn’t hold a vote on, to boost its diabetes product sales, given revenues from Lantus have been on a continued decline due to competition from biosimilars and the recent US approval of Eli Lilly & Co’s and Boehringer Ingelheim GmbH’s Basaglar (insulin glargine injection).

Sanofi also may soon face new competition from Novo Nordisk AS’ fixed-dose combination diabetes medicine, which unites the active ingredients of Danish firm’s GLP-1 receptor agonist Victoza (liraglutide) and Tresiba (insulin degludec), a basal insulin, into one single subcutaneous shot.

At a meeting a day earlier the EMDAC unanimously voted to approve Novo’s combination medicine, which the company wants to market as Xultophy – the same name it uses in Europe.

Novo’s combo medicine currently goes under the name IDegLira for the time being.
Aft er spending the day scrutinizing Novo Nordisk AS’ fixed-dose combination diabetes medicine, which unites the active ingredients of the Danish firm’s Victoza (liraglutide) and Tresiba (insulin degludec) into one single subcutaneous shot, the FDA’s Endocrinologic and Metabolic Drugs Advisory Committee unanimously threw its support behind the product, declaring the US agency should approve the drug.

Victoza, a glucagon-like peptide 1 (GLP-1) receptor agonist, and Tresiba (insulin degludec), a basal insulin, already are sold on the US market as single agents – gaining nods from the FDA in 2010 and 2015, respectively.

But Novo is looking to boost its diabetes sales with the new type 2 diabetes combination – going up against several other competitors in the marketplace, potentially even Sanofi SA, whose own diabetes combo went before the same FDA committee on May 25 (see p3).

Novo is proposing to sell its combo product, which has gone by the name IDegLira, under the brand name Xultophy, the moniker it uses in Europe, where it was first approved in September 2014.

The FDA, which is expected to make a decision later this year on whether to approve the drug – an action date Novo is keeping secret for now – has yet to sign off on the use of Xultophy in the US, so the company is sticking with using IDegLira for the time being in identifying its combo product.

Analysts at Sagient Research’s BioMedTracker, an affiliate of Scrip, raised their LOA prediction by 3% for Novo’s combo – putting it at 98%, which is 9% above average – with the caveat that there is some possibility of a delay in approval due to issues over labeling and the pen device.

Analysts Andrew Frost and Natasha Bo-liter from Citeline, also an affiliate of Scrip, said there are at least 18 antidiabetic combination products currently approved for the US market, the majority of which include metformin.

They noted that other companies with diabetes combination products in late-stage development include Pfizer Inc. and Merck & Co. Inc., which are collaborating on ertugliflozin plus metformin and ertugliflozin plus Januvia (sitagliptin) under a 2013 partnership.

Other partnerships on diabetes combination drugs include Boehringer Ingelheim GmbH’s and Eli Lilly & Co.’s development of an extended-release formulation of empagliflozin plus metformin; Johnson & Johnson subsidiary Janssen’s pursuit of a once-daily fixed-dose combination formulation of canagliflozin and extended-release metformin, which is using Depomed Inc.’s Acuform technology; and AstraZeneca PLC’s and Bristol-Myers Squibb Co.’s collaboration on a fixed-dose combination of saxagliptin and dapagliflozin. So Novo is facing stiff competition.

But EMDAC panelist Marie Gelato, a professor of medicine and director of the master’s program in clinical research at Stony Medicine Stony Brook University in New York, insisted ‘diabetes is a tough disease and I think we need all of the things we can muster to get it under control and keep patients from developing complications’.

Gelato said she was “impressed” by the fact that study participants who were on insulin were able to get their A1Cs to target with Novo’s drug, “even though it was something I wouldn’t have thought”.

The FDA, however, had been somewhat critical in its review Novo’s new drug application – questioning the design of the company’s trial comparing IDegLira with Tresiba and declaring it may have been biased in favor of the combo. But most on EMDAC held the opinion that IDegLira’s safety profile was similar to the individual components – agreeing the combo provided superior glycemic control and mitigated the main adverse effects of basal insulin treatment: hypoglycemia and weight gain.

Panelist Peter Wilson, a professor of medicine and public health at Emory University in Atlanta, however, said he’d like to see “12-month-plus weight data” before he would be fully satisfied.

Some on the committee were hesitant to back IDegLira’s use in patients naïve to basal insulin or a GLP-1 agonist receptor medicine, while others felt there were circumstances in which the drug’s administration would be appropriate in those patients.

Novo officials emphasized IDegLira is intended to be used for “treatment intensification.”

“IDegLira may be most appropriate for those who need ambitious therapy,” said Stephen Gough, senior principal clinical scientist at Novo Nordisk. Novo said IDegLira is intended to be administered using a pre-filled pen device containing a fixed ratio of 100 units of insulin degludec and 3.6mg per mL of liraglutide.

The dose of IDegLira is titrated based on fasting plasma glucose, using a simple titration algorithm similar to current practice for basal insulin therapy.

The pre-filled pen allows for dose adjustments in increments of 1 unit of insulin degludec and 0.036mg liraglutide.

Novo said the fixed insulin degludec/liraglutide ratio ensures that as the dose of the combo is increased or decreased, the ratio between the two components does not change.

The dose range is from 1 to 50, with the maximum dose allowed by the device corresponding to 50 units of insulin degludec and 1.8mg of liraglutide.

But some on the committee were concerned about the 50-unit cap for insulin degludec, noting some patients may require more.

Others raised concerns that IDegLira allows for doses of the Victoza component that are lower than what’s approved in the US for glycemic lowering.
**IMMUNO-ONCOLOGY**

**Key Targets And Deal Facts**

Immuno-oncology is one of the most active areas of drug development with companies small and large racing to bring new therapies into the clinic that address the hottest targets in cancer treatment – enthusiasm reflected by the number of firms entering into IO deals.

**10 key immuno-oncology drug targets**

(PD-1/PD-L1, CTLA4, GM-CSF/GM-CSFR, LAG3, TIM3, TLR, IDO, CD40, CD47 and OX40)

**99** drugs and biologics in development

**The largest immuno-oncology category is therapeutic candidates that target PD-1 or PD-L1 with 37 compounds in development.**

**82%** of immuno-oncology drugs are partnered

**But only 48% of all cancer drugs involve a development collaboration.**

---

**The top five indications for immuno-oncology deals between 2011 and 2015**

- **Lung Cancer**: 40
- **Melanoma**: 35
- **Non-Hodgkin Lymphoma**: 30
- **Solid Tumors**: 25
- **Leukemia**: 25

**Total** immuno-oncology deals between 2011 and 2015: 229

**Immuno-oncology transactions provided the acquired companies and licensors with a total of**

- $6bn in upfront fees
- And up to $33bn in milestone fees plus royalties

Marisol Touraine, the health minister, also said that a raft of national measures to strengthen the assessment of Phase I study applications in France would be put in place, and that the 90 clinical dossiers of the healthy volunteers who took part in the study will be subject to an independent expert evaluation.

These dossiers will also be sent to European expert groups looking into the matter, she said, adding that harmonized methods of evaluating and managing serious accidents such as these need to be introduced at EU level.

The announcements were made alongside the publication of the final report on the trial – in which one volunteer died and several others were hospitalized with neurological damage – by the government’s general social affairs inspectorate (IGAS).

In the report, which was presented by Touraine at a press conference on May 23 – but, according to Biotrial, leaked to the media the day before – IGAS confirmed that, in line with its interim report in February 2016, the conditions under which the trial was authorized by the regulatory body ANSM and the local ethics committee (CPP) did not contravene regulations.

It did say, however, that there were questions to be answered regarding the evaluation by ANSM and the CPP of the level of risk of the product (BIA 10-2474), the latitude given to those responsible for running the study, and the division of responsibilities between Biotrial and Bial, the Portuguese company that developed the product.

According to Touraine, IGAS found that the two companies were to blame for the accident with regard to the choice of dosage of BIA 10-2474 to be administered to the volunteers, and the delay in reporting the incidents to the health authorities. It said Bial was also to blame with regard to its “scientific and ethical responsibility” to pursue inquiries into understanding the accident.

As for Biotrial, it did not properly seek information on the health of the first volunteer to be hospitalized (the one who later died) in good time and did not then suspend administration to the other five. Moreover, the inspectors found, Biotrial “did not formally inform the other volunteers” of the hospitalization of the first volunteer the day before, and this “did not allow them to give their informed consent to the continuation of the trial.”

Moreover, Touraine said, following the suspension of the trial on Jan. 11, 2016, Biotrial did not “put in place a strengthened and systematic monitoring of the five other volunteers, notably at the neurological level,” and there were “difficulties in information exchange between Biotrial and the Rennes University Hospital Centre.”

But Biotrial has taken issue with all the key points raised in the final report. In a strongly worded statement, it said it was “shocked” to hear the health minister’s statement on May 23, saying that it only received a copy of the IGAS report at 10.30 that morning, at the same time as the press conference was being held (to which it says it was not invited). It also claimed the report had been leaked to the media the day before. In response to the findings of the report, it said it had already put an action plan in place “some months ago” after discussions with ANSM. It also said that the report, “in order to stay consistent with the report that was hastily published in February,” did not include any input from Biotrial.

It said it “deplored” the methods, “contrary to legal procedures,” that were used to produce the report, and contested all the failings alleged therein. It also said the report had three “major shortcomings” of its own: it did not respect the adversarial process, it did not respect the rights of the Biotrial staff interviewed (for example, it claimed the inspectors did not keep minutes of the interviews), and it did not mention any possible conflicts of interest. In this last case, Biotrial claimed that prior professional collaborations between some of the IGAS inspectors and the general directors of the Rennes University Hospital and ANSM should have been made public.

It said it reserved the right to “petition the court for a nullification of the report” and that IGAS should “commit to reforming its procedures… in order to align with European Standards.”

It added: “Biotrial deplores this situation, especially since it has always strictly respected the test protocol validated by the ANSM, and that it has been shown that it is the Portuguese Laboratory Bial’s compound, by its unexpected and unpredictable toxicity, which is at fault for the accident.”

Explaining her own four-point plan in more detail, Touraine said that firstly, the action plan to be put in place by Biotrial “without delay” should include risk-minimization measures, better monitoring of those taking part in trials, and strengthening of training of its staff, “particularly where pharmacovigilance is concerned.” If Biotrial does not produce an action plan within one month, its authorization as a research centre for Phase I trials will be suspended,” Touraine declared.
Synergy Flaunts Constipation Data From Linzess Challenger

SUKAINA VIRJI sukaina.virji@informa.com

Synergy Pharmaceuticals, which is waiting on a decision from the US FDA on its constipation drug plecanatide, provided additional data from two pivotal Phase III trials at Digestive Disease Week (DDW) in San Diego recently. The product will go up against Linzess, which is marketed by Allergan and Ironwood Pharmaceuticals, and is expected to compete on its better side effect profile.

Synergy Pharmaceuticals Inc. filed for FDA approval in January this year for the once-daily tablet plecanatide, a uroguanylin analog, as a treatment for chronic idiopathic constipation (CIC). The FDA has accepted for FDA review with a PDUFA target action date of January 29, 2017.

The plecanatide NDA was supported by two double-blind placebo-controlled Phase III trials (Study-00 and Study-03) and one open-label long term safety study. A total of more than 2,700 patients with CIC received a once-daily dose of either plecanatide or placebo across the two placebo-controlled trials.

The primary endpoint for both pivotal trials was the durable overall complete spontaneous bowel movement (CSBM) responder endpoint, as defined by the FDA. As previously disclosed, both plecanatide 3 mg and 6 mg doses met the primary endpoint and demonstrated significance in the proportion of patients in the intention-to-treat population who were durable overall CSBM responders compared to placebo during the 12-week treatment period (21.0% in 3 mg and 19.5% in 6 mg dose groups compared to 10.2% in the placebo group; p<0.001 for both doses in Study-00 and 20.1% in 3 mg and 20.0% in 6 mg dose groups compared to 12.8% in the placebo group; p=0.004 for both doses in Study-03). The most common adverse event was diarrhea (5.9% in 3 mg and 5.7% in 6 mg dose groups compared to 1.3% in the placebo group for Study-00 and 3.2% in 3 mg and 4.5% in 6 mg dose groups compared to 1.3% in the placebo group in Study-03).

It is this diarrhea rate that is expected to make a difference to physicians when deciding on whether to prescribe plecanatide or Linzess (linaclotide).

The incidence of diarrhea with plecanatide is a big improvement versus the 16% diarrhea rate for patients treated with Linzess.

When the topline results were reported last year with plecanatide, analysts commented that the data were the “best” that could have been hoped for. “Both doses, 3.0mg and 6.0mg, met the primary endpoint with flying colors,” said Canaccord Genuity analyst Corey Davis at the time.

Ironwood stands to earn a low single-digit royalty from plecanatide sales. Synergy and Ironwood settled a patent dispute in 2012, which gave Synergy rights to Ironwood’s method of use patents.

Linzess is the only other guanylate cyclase agonist on the market or in late-stage development, according to Citeline’s Pharmaprojects. It was approved by the FDA in 2012 for CIC and irritable bowel syndrome with constipation (IBS-C). Linzess sales were $455m for the full year 2015, up by 53% compared to 2014.

Ironwood Pharmaceuticals Inc. and Allergan PLC are shortly expected to file a supplemental new drug application (sNDA) for a lower (72 mcg) dose of Linzess. If approved, the companies say they expect the 72 mcg dose “to accelerate physician prescribing of Linzess within the large, heterogeneous adult CIC patient population.”

AstraZeneca’s ZS-9 Timeline Hit By FDA Complete Response Letter

STEN STOVALL sten.stovall@informa.com

The regulatory timeline for AstraZeneca PLC’s promising potassium-binding compound ZS-9 has been derailed for the time being by a complete response letter from the FDA due to manufacturing deficiencies found by investigators during a pre-approval inspection at a plant making the medicine in Coppell, Texas.

Still, the British drug maker – which acquired the asset when it bought US-based ZS Pharma Inc. last year for $2.7bn – believes the issues are straightforward and will not require new clinical data to be generated for the therapy. The FDA also acknowledged receipt of recently submitted data on ZS-9 which it has yet to review, AstraZeneca said in a statement issued May 27.

“AstraZeneca remains committed to the development of sodium zirconium cyclosilicate as a treatment option for patients with hyperkalemia. Interactions are ongoing with other health authorities in the European Union and Australia, where sodium zirconium cyclosilicate is currently under separate regulatory review,” it said, but gave no details of the CRL’s contents. Sodium zirconium cyclosilicate is not currently approved for any indication in any market.

Analysts at Berenberg said the CRL is a class-II letter that will allow for a six-month review once AstraZeneca has replied. “Assuming the company can refile in a matter of months, an approval in the first quarter of 2017 could be possible,” the analysts said in a reaction note.

When announcing its planned purchase of ZS Pharma in November 2015 AstraZeneca’s CEO Pascal Soriot said the pure pharma anticipated an FDA decision on ZS-9 by May 26 this year.

He said the acquisition “gives us access to a near launch-ready, potential best-in-class asset in ZS-9, which, if approved in the US in the first half of 2016, will start bringing in revenue to contribute to our top line by early in the second half of next year.” That timeline is now not possible.
Ten Programs To Watch Out For At ASCO

ALEX SHIMMINGS alex.shimmings@informa.com

The ASCO abstracts are out – and with them a scramble to see exactly what will be hitting the headlines in early June. Here, with the help of Sagient’s BioMedTracker, Scrip takes a look at some of the more interesting studies due to be presented in Chicago next week.

1. J&J’s DARZALEX FOR MULTIPLE MYELOMA

Johnson & Johnson has the distinction of a late-breaking presentation on June 5 for the first quantitative data from its CASTOR study of Darzalex (daratumumab) in patients with relapsed/refractory multiple myeloma.

Darzalex received accelerated approval in November 2015 well ahead of schedule as a fourth-line treatment for multiple myeloma, but positive results from CASTOR could advance the first anti-CD38 antibody therapy into a second-line setting (in combination with bortezomib and dexamethasone). An interim analysis in March 2016 already disclosed that the study had met its primary PFS endpoint, but no further details have been released as yet.

Meanwhile, the company has just released top-line data from its “twin” study POLLUX, which is also evaluating Darzalex in the relapsed/refractory setting but in combination with lenalidomide/dexamethasone.

These positive results from two pivotal trials will be vital for full approval of Darzalex, its advancement earlier into the treatment paradigm and for uptake of the product, which is a key growth driver for J&J.

2. BRISTOL–MYERS SQUIBB’S OPDIVO

Bristol-Myers Squibb Co. is set to present a raft of data to bolster the clinical case for its leading anti-PD-1 immuno-oncology drug Opdivo (nivolumab) in brain cancer, colorectal cancer, gastric cancer, melanoma, urothelial cancer and non-small cell lung cancer (NSCLC).

In NSCLC, BMS will present updated two-year overall survival (OS) data from the Checkmate-057 and -017 studies in non-squamous and squamous disease respectively that show that its superiority over docetaxel is maintained at this landmark time point.

Meanwhile, data are due from the Checkmate-012 study of first-line use of Opdivo with Yervoy (ipilimumab) in advanced NSCLC – a setting where it will need to jostle with a number of other combination approaches.

BMT analysts noted that responses were seen regardless of PD-L1 status, with higher responses observed in PD-L1+ patients. “However, we await further safety and efficacy data to be presented on subpopulations of the study to determine the clinical utility of this combination in NSCLC. Although the magnitude of benefit in comparison to monotherapy with Opdivo may not justify use of the combination in PD-L1+ patients, the combination may form a more attractive option for PD-L1- patients who have poorer responses to PD-1 inhibitor monotherapy. If first-line PD-L1- patients form the primary target population for the Opdivo + Yervoy combination in NSCLC, the regimen would compete with immunotherapy + platinum-based chemotherapy combinations, which have shown substantial response rates in this subset of patients.”

Analysts at Credit Suisse agreed that the data are intriguing but they too said they would await the full presentation of these data to better understand the likelihood of success for the Opdivo+Yervoy combo in the ongoing pivotal CheckMate-227 study in first-line NSCLC.

Opdivo data in other tumor types include those from the CheckMate-032 study in metastatic urothelial cancer. These look good but here the product is lagging Roche’s anti-PD-L1 product Tecentriq (atezolizumab), which has just been approved four months ahead of schedule.

3. MERCK & CO’S KEYTRUDA

Not to be outdone, Merck & Co. Inc. has a range of presentations for its PD-1 checkpoint inhibitor Keytruda (pembrolizumab). In addition to updated survival data from the melanoma studies KEYNOTE-006 and -001, first time data will be presented for the product in head and neck cancer from KEYNOTE-055, as well as combination data in NSCLC.

The -055 data are the first Phase II results for Keytruda in recurrent/metastatic head and neck squamous cell carcinoma and corroborate the encouraging response rates observed in the Phase Ib KEYNOTE-012 trial. “While we expect that Keytruda will potentially gain its first approval in the second-line platinum-refractory recurrent/metastatic HNSCC setting based on upcoming KEYNOTE-040, these promising, early results will likely play a supportive role in the PD-1 inhibitor’s potential approval. In this study, Keytruda is well tolerated and results in an ORR of 18% in patients who failed both platinum-based chemotherapy and Erbitux,” said the BMT analysts.

In combination use, data will come from the KEYNOTE-021 study in NSCLC, demonstrating Keytruda’s efficacy in combination with standard platinum-based chemotherapies in first-line NSCLC. ORR in the overall population of 74 patients reached 57%, and substantial responses were observed regardless of PD-L1 status. “Similar outcomes were previously reported in trials testing [Roche’s] Tecentriq and Opdivo alongside chemotherapy. In combination with carboplatin and paclitaxel for first-line patients, Keytruda, Tecentriq, and Opdivo demonstrated ORRs of 52%, 50%, and 47%, respectively. Together, these outcomes solidify the future position of immunotherapy-chemotherapy combinations in the treatment of NSCLC.”

Finally, further data in relapsed classical Hodgkin’s lymphoma from the Phase II KEYNOTE-087 trial look promising. About 20-30% of HL patients are not eligible for allogeneic stem cell transplant (ASCT) or relapse following current therapies. “According to study results, patients who are not candidates for ASCT and failed previous Adcetris therapy may benefit more from Keytruda treatment,” BMT says.

4. & 5. ABBVIE’S VENCLEXTA AND ROVA-T

AbbVie Inc’s selective Bcl-2 inhibitor Venclexta (venetoclax), which was approved last month in the US for chronic lymphocytic leukemia (CLL), is looking to be a contender in acute myelogenous leukemia (AML) based on data from two early studies being presented at ASCO. There is a significant unmet need for tolerable effective therapies that are suitable for frail and elderly AML patients who are ineligible to receive standard high-intensity induction chemotherapy at first-line. Currently, these patients are enrolled into clinical trials,
given low-intensity chemotherapy or treated with best supportive care. Venetoclax is being investigated in two clinical trials as part of a combination regimen alongside chemotherapy in this difficult-to-treat patient population. Both of these trials will have updated results at ASCO 2016.

In a Phase Ib study, the venetoclax/low dose cytarabine combination had an acceptable safety profile and demonstrated clinical activity, with an ORR of 44%. In another Phase Ib with decitabine or azacitidine the 400 mg and 800 mg Venetoclax doses yielded an ORR of 76%. The ORR was also encouraging in patients with adverse cytogenetics and IDH1/2 mutations (88% and 82% in these patient populations, respectively) who traditionally have a worse outcome to current therapy. “These are encouraging data in total for Venetoclax in a patient population which has historically proved so difficult to treat. Elderly patients represent a large proportion of the AML patient population, many of which are too frail to receive standard intensive induction chemotherapy, so this is a market which could be potentially very lucrative,” the BMT report states.

Meanwhile, another AbbVie product that will come under much scrutiny in Chicago is the antibody-drug conjugate rovalpituzumab tesirine (or Rova-T) for small cell lung cancer (SCLC), which will come into AbbVie's fold with the recently announced $5.8bn acquisition of Stemcentrx.

No details of its ASCO presentation are yet available for the stem cell protein Dll3 (delta-like protein 3)-targeted drug. It is being studied in third-line SCLC, for which there is no approved therapy, and overall survival data are eagerly expected at the meeting.

6. CELATOR’S VYXEOS FOR AML

Another likely new candidate in AML is Celator Pharmaceuticals Inc’s Vyxeos (CPX-351), a 5:1 liposomal formulation of cytarabine and daunorubicin. Final results of a Phase III trial of CPX-351 versus 7+3 in older patients with newly diagnosed high-risk (secondary) AML will be presented at ASCO; top-line data were released in March.

**Celator is expected to submit an NDA to the FDA in the third quarter following the release of the final results from this Phase III trial. These results further build upon top-line data released in March and demonstrate that Vyxeos significantly improves OS, ORR, and CR in comparison to standard of care, 7+3 cytarabine and daunorubicin, in this difficult-to-treat patient population.**

The data put Vyxeos in a strong position to become standard of care for this patient population, and Celator will look to expand Vyxeos’ label if it reaches the AML market.

7. JUNO’S JCAR015 FOR ALL

Turning to acute lymphocytic leukemia, and to the much-hyped CAR-T immune-oncology therapies, Juno Therapeutics Inc. is due to present data for its JCAR015.

Chimeric antigen receptor T-cell therapies have generated much excitement for hematologic malignancies and their first approvals are fast approaching in the lead indication, ALL. Both JCAR015 and Novartis AG’s CTL019 could receive approvals by the end of 2017 and will pave the way in the establishment of CAR-T centers for these complex therapies that could impact development in larger market indications.

While most CAR-T data are featured at the American Society of Hematology annual meeting, both JCAR015 and CTL019 have abstracts at ASCO as well. JCAR015 is being developed for the adult ALL population, and although top-line results from its pivotal ROCKET study will not be featured at ASCO (probably being held for the next ASH meeting), updated data from the Phase I study are being presented detailing the effect of disease burden at the time of CAR-T infusion on outcomes.

BMT analysts noted: “Not surprisingly, patients with minimal disease fared better across a variety of measures versus patients with morphologic disease. Interestingly, cytokine release syndrome – a major adverse event observed across all CAR-T therapies – was only observed in the patients with morphologic disease. Six-month OS was also higher for minimal disease patients at 73% vs 57% for more severe patients. Of course, the company is promoting these results to suggest earlier frontline use of CAR-Ts, but it may achieve that status on overall efficacy alone which has been strong in ALL.”

8. NOVARTIS’S CTL019 FOR ALL

Novartis’s CAR-T product CTL019 is being featured in several minor abstracts as well. In contrast to JCAR015, CTL019 is being evaluated for the larger pediatric ALL population. Two ASCO presentations (3007 and 3011) feature updated data, but no data from the pivotal Phase II study are expected. Similarly, a presentation of CTL019 for CLL (3009) will feature only updated data from a small Phase II study.

9. ELI LILLY’S ABEMACICLIB

As competition heats up in the CDK 4/6 inhibitor area – with the recent early halting of Novartis’ Phase III MONALEESA-2 study of LEE011 (ribociclib) after it met the PFS endpoint – Eli Lilly & Co. will be unveiling data from the Phase II MONARCH-1 study of its candidate abemaciclib as monotherapy in HR+/HER2- breast cancer, after chemotherapy for advanced disease.

The results are encouraging, BMT analysts said, with an ORR of 17.4%, a clinical benefit rate (CBR) of 42.4% and a median PFS of 5.7 months at an eight-month interim analysis. While the results seem to compare well to the lead product in this class, Pfizer Inc’s Ibrance (palbociclib), they still fell short of some analyst expectations. Nevertheless, dosing interruption and/or dose reductions based on individual safety and tolerability are recommended for Ibrance, whereas abemaciclib’s favorable toxicity profile allows for continuous daily dosing and may allow for differentiation from Ibrance.

Lilly is now conducting two Phase III trials of abemaciclib in combination with hormone therapy, MONARCH 2 and MONARCH 3, with final data expected next year and the opportunity for a positive interim readout later this year.

10. PFIZER’S IBRANCE IN PALOMA-2

For its part, Pfizer will present updated results from the Phase II/III PALOMA-2 study of Ibrance that appear set to shore up its place in the market; the product received an earlier than expected accelerated approval for metastatic breast cancer in February 2015. PALOMA-2 compared Ibrance with letrozole and letrozole alone in postmenopausal women with ER+/HER2- advanced breast cancer. The positive PALOMA-2 data will ensure Ibrance’s conversion from accelerated approval to full approval in the US and support regulatory filings in other markets. The 10-month PFS benefit from the Phase II/III PALOMA-1 trial that led to the accelerated conditional approval of Ibrance was confirmed in this trial (24.8 months with Ibrance/letrozole vs 14.5 months with placebo/letrozole, HR=0.58).
Shire PLC and Baxalta Inc. shareholders have both voted in favor of the latter’s sale to rare disease focused Shire for a price tag of $32bn – closing an almost year-long deal discussion. Both companies held general meetings on May 27 to vote on the proposed merger that will see Baxalta stockholders, who were initially reticent of a merger arrangement, receive $18.00 in cash and 0.1482 Shire ADS per Baxalta share – the deal agreed back in January 2016. Shire CEO Dr. Flemming Ornskov said in a statement, “[We are] grateful that our shareholders have voiced their support by approving this transaction. The combination will allow us to realize our goal of building the leading global biotechnology company focused on rare diseases and other highly specialized conditions...As our teams continue to plan our integration, we anticipate a smooth and timely transition for all of our stakeholders.” The transaction remains subject to certain other closing conditions but the companies expect it will be completed on June 3, 2016. Shire will own 66% of the combined company and Baxalta 34%.

Will Novartis India Buyback Offer Enthusiae?

On May 26, Novartis India approved a buyback proposal for up to 3,820,000 equity shares of INR5 each (representing 11.95% of the total paid-up equity capital), from all the existing equity shareholders of the company on a proportionate basis. The divestment of the Swiss multinational’s OTC and animal health businesses in India is in line with the landmark 2014 deal between Novartis, GlaxoSmithKline and Eli Lilly. The India buyback plan, via the tender offer route, comes at INR760 ($11.3) per equity share, aggregating to about INR2.9bn. Novartis said that the offer price represented a premium of 11.1% over the volume weighted average price of the equity shares on the Bombay Stock Exchange (BSE) for three months preceding the date of intimation to the BSE for the board meeting to consider the buyback plan and 5.0% over the volume weighted average price of the equity shares on the bourse for two weeks preceding the date of intimation to the BSE for the board meeting. A company statement mentioned the “intention” of the parent company to participate in the proposed buyback. Novartis AG currently holds 75% in the Indian arm. The buyback is subject to the approval of shareholders by way of a special resolution through a postal ballot and other applicable statutory approvals.

Operational Fixes At Cipla But All Eyes On Generic Advair

Cipla Ltd. reported a 68.9% slump in profits to INR810m ($11.9m) in the fourth quarter ended March 2016 impacted by one-off costs including those associated with “complexity reduction,” while revenues rose by 5.6% to INR32.67bn. Profits and revenues for the year ended March stood at INR15.06bn (+27.5%) and INR136.78bn (+20.6%) respectively. At the post results investor call, Cipla’s global chief operating officer, Umang Vohra, said that the company was proactively “simplifying” its business in emerging markets, rationalizing markets where necessary and ensuring focus only on high growth markets where it holds a leadership position. Cipla told Scrip that it currently “participates” in over 80 markets, but declined to comment on the optimum number that it was targeting. Cipla expects to retain momentum in South Africa and leadership in key front-ends, such as Yemen, Sri Lanka, North Africa and Iran, with a focus on the respiratory, oncology and global access segments, details in a company presentation said.

Torrent On Course For Buy, US Momentum

At an investor call post the fourth quarter results, Torrent’s management underscored the need to diversify, in the medium term, beyond oral solids and noted that a hospital presence could help make the business “stronger and more sustainable” in the long run. “We are working actively on building our hospital presence. But the current large divestment, which is taking place in India...Torrent is not part of that anymore. So we are not currently pursuing any large injectable acquisition in India, but we remain interested in the hospital space,” Sanjay Gupta, executive director (international business), Torrent, said in response to an analyst’s query. Gupta made no specific reference to Gland, but Torrent was earlier said to be interested in the Hyderabad-based firm. Gland has been on the block for some time now with a clutch of suitors including Baxter International Inc. and private equity investors, Advent International, and more recently China’s Fosun group eyeing the company. The Torrent official maintained that the company’s “sweet spot” for acquisitions was in the $300-600m range, but added that his organization’s “strength and finances” would allow it to target larger acquisitions. “We can even realistically bring about a much larger acquisition.” Torrent earlier this year received shareholder approval to raise INR105bn ($1.6bn) through the issue of shares and certain other securities to finance its growth plans. It explained at the time that, among others, the enabling approvals would help the company take quick and effective action to capitalize on inorganic growth opportunities, as and when available.
Entresto US Sales Barriers Set To Be Removed
By Strong Guidance

STEN STOVALL sten.stovall@informa.com

S sales prospects for Novartis AG’s struggling Entresto have been boosted – especially in the US – by new global cardiology guidelines issued by three organizations containing stronger than expected recommendations for its use in treating heart failure.

Novartis’ novel heart drug, formerly called LCZ696, was given a huge boost when experts from the American College of Cardiology, the American Heart Association and the European Society of Cardiology on May 21 announced that Entresto (valsartan/sacubitril) should replace old ACE inhibitors and ARBs in patients with adequate blood pressure and drug tolerance.

In the US, the twice-a-day medicine is now a standard therapy for heart failure with reduced ejection fraction (HFrEF) as an alternative to an ACE inhibitor or an angiotensin II receptor blocker, given together with a beta blocker and an aldosterone antagonist. In addition, the new guidelines call for doctors to switch HFrEF patients with mild to moderate symptoms from ACEs or ARBs to Entresto.

And in the 28-nation EU, the European Society of Cardiology HF guidelines now recommend that doctors switch HFrEF patients meeting the PARADIGM-HF criteria to Entresto from an ACE or ARB. PARADIGM-HF was a randomized, double-blind, Phase III study evaluating the efficacy and safety profile of Entresto versus ACE inhibitor enalapril and showed Entresto significantly reduced deaths from cardiovascular causes and heart failure hospitalizations in patients with HFrEF, Novartis said in a statement.

GUIDANCE SEEN SET TO BOOST US USAGE

The updated and stronger guidelines could transform the drug’s sluggish rate of uptake in the US, where payers have been slow to cover the drug, and there has been inertia among prescribers to use the new drug when they are accustomed to using older ACE inhibitors and ARBs.

“The updated US and EU guidelines mark a huge success for Entresto, which has so far, struggled to penetrate the chronic heart failure market,” said Datamonitor Healthcare analyst Louisa Joseph. “Entresto has been given the most favorable Class I recommendation in both the US and EU, which will most likely result in greatly enhanced uptake in the CHF indication.”

Entresto has struggled to gain traction within the US CHF market due to reimbursement challenges over its high yearly cost in comparison to the widely genericized ACE inhibitors/ARBs. Despite a heavy build-up, first-quarter sales of Entresto were just $17m and Novartis at its April 27 first-quarter results presentation said it saw only $200m in sales this year. Not surprisingly, consensus estimates for Entresto have been heavily reduced in reply.

That looks likely to reverse now, however.

“The strength of the American College of Cardiology and the American Heart Association treatment guidelines are expected to reduce these reimbursement barriers and increase physician confidence in the long-term cardiovascular benefits of treating HFrEF patients with Entresto,” DataMonitor’s Joseph said.

“Additionally, the US treatment guidelines recommend Entresto to the broadest range of patients, calling for physicians to switch stable HFrEF patients with mild to moderate symptoms from ACE inhibitors/ARBs to Entresto. These strong and broad recommendations completely redefine the standard of care for HFrEF, with Entresto likely to become the first line treatment option in the management of the disease,” she added.

ENTRESTO DOING BETTER IN EUROPE’S SINGLE PAYER SYSTEMS

Entresto has experienced stronger uptake in Europe than in the US, as the European single-payer government funded healthcare systems have been more accepting of Entresto’s clinical benefits and potential for cost-saving. The strong recommendations from the ESC treatment guidelines are expected to further augment uptake of Entresto across the European chronic heart failure (CHF) markets, with sales continuing to grow over the upcoming years.

The European guidelines recommend Entresto to a slightly narrower patient group than the US, focusing on HFrEF patients that fit the inclusion criteria of the PARADIGM-HF trial. The ESC task force agreed that more data were needed before Entresto can be recommended to a broader range of patients.

“Whilst this may slightly limit Entresto’s potential patient population in the EU in comparison to the US, the drug is still expected to experience significant uptake across the European CHF markets,” Datamonitor’s Joseph said.

Analysts had not been expecting a US guideline update on Entresto until the fourth quarter of 2016 and most only expected a class II (moderate) versus the actual class I recommendation made, which are much stronger.

“We expect that this will begin to impact the rate of prescribing of Entresto over the next few months,” Jefferies analyst Jeffrey Holford said in a note. “In turn, this should start the trend towards removal of prior authorization requests by payers over the next 1-2 years. Furthermore, the early guidelines update significantly increases the likelihood that Novartis will enlarge the Entresto sales force to provide a dedicated Primary Care team during the second half of 2016.

To reinforce the new momentum, Novartis has launched an ambitious clinical trial program for Entresto, called FortiHFy, comprised of 40 clinical trials and patients in more than 50 countries. The goal is to generate additional data on Entresto’s clinical outcomes, quality of life benefits and real world evidence within heart failure among the six million HF patients in the US, as well as HF patients in the 56 other countries where Entresto is approved. The overall program will run five years, with some studies ending as early as 2018, while others continue until 2020.

scripintelligence.com
Sanofi, in the midst of another of its own leadership shakeups, clearly has been reviewing a lot of resumes lately, and now the company has recommended new members for Medivation Inc’s board of directors who may support a proposed $9.3bn buyout of the US prostate cancer drug developer.

Pfizer Inc., Amgen Inc., Novartis AG and AstraZeneca PLC – and now also Gilead Sciences Inc. and Celgene Corp. – are rumored to be preparing bids for Xtandi (enzalutamide) co-developer Medivation. But as the only company that has gone public with an offer for the San Francisco-based biotech firm – and the only one whose bid has been publicly rejected – Sanofi is leading the charge to replace Medivation’s board, noting that “we believe that we are in a position to boost its earnings at almost any cost in his latest letter to Medivation’s board with directors “who are willing to fully and fairly evaluate Medivation’s strategic options, including Sanofi’s acquisition offer,” the pharma company said on May 25.

The eight board nominees all appear to be professional corporate and nonprofit board members, each of whom have experience either managing or advising health care, pharmaceutical, medical device, financial, real estate and education enterprises.

Some names that may be recognizable to life science industry insiders include: former Shire PLC business development executive and current AMAG Pharmaceuticals Inc. board member Barbara Deptula; former Beckman Coulter Inc. and Watson Pharma Inc. chief financial officer and current board member at Quidel Corp. and Sequenom Inc. Charles Slack; and retired Abbott Biotechnology Ventures president James Tyree, who now is an independent board director for SonaraMed, Genelux, ChemoCentryx Inc. and Innovia LLC.

SHAREHOLDER SUPPORT?
Sanofi CEO Olivier Brandicourt wrote in a May 25 letter to Medivation’s existing board of directors that the pharma company filed paperwork with the US Securities and Exchange Commission (SEC) to kick off a vote among Medivation shareholders about replacing the biotech firm’s board, “because we believe your shareholders overwhelmingly support the sale of Medivation, and they want Medivation to undertake a sale process and engage with Sanofi.”

Medivation’s board of directors unanimously rejected Sanofi’s offer of $52.50 per share to buy the company for a total of $9.3bn on April 29 and the board has not entered into negotiations with Sanofi to seek a higher bid. Medivation urged its shareholders on May 25 to reject Sanofi’s attempt to replace its board of directors, noting that the current buyout offer “substantially undervalues the company, its leading oncology franchise and its innovative, late-stage pipeline.”

Mediation CEO David Hung praised the company’s board, noting that under their leadership Medivation “has achieved great success and rewarded its stockholders with extraordinary results, delivering total stockholder returns of more than 1,440% since 2009.”

It remains to be seen what shareholders think of Medivation’s current board of directors or Sanofi’s board nominees, but the biotech company’s stock closed down 0.7% at $61.48 per share on May 25 after Sanofi revealed its proposed board member replacements. But the stock’s value remains 17.1% above Sanofi’s offered buyout price, which suggests that Medivation investors believe the company ought to be able to negotiate a higher value from Sanofi or potentially other bidders.

‘A Medivation acquisition would add a product with increasing revenue to Sanofi’s portfolio at a time when the company is battling declining revenue’

AGGRESSIVE MOVES REWARDED
Sanofi’s US shares closed up 1.9% at $40.97, signaling that its investors approve of the company’s recent aggressive moves to shore up its pharma business via management changes and a high-profile purchase.

The company said on May 23 that executive vice president and general manager of diabetes & cardiovascular Pascale Witz would leave the company on June 1 and be replaced by EVP and GM of general medicines and emerging markets Peter Guenter (see p1).

A Mediation acquisition would add a product with increasing revenue to Sanofi’s portfolio at a time when the company is battling declining revenue, especially among its diabetes assets, which have fallen victim to competition in a crowded market. Sanofi said in October that it expects its diabetes sales to decline by 4% to 8% annually between 2015 and 2018.

Brandicourt hinted at the company’s desperation and willingness to boost its earnings at almost any cost in his latest letter to Medivation’s board, noting that “We believe that we are in a position to provide more value than any other party given the strategic importance of the transaction to us.”

And as if Sanofi’s SEC filing to kick off a shareholder vote that could replace Medivation’s board wasn’t enough of a hint, Brandicourt’s letter concluded with a request tied to a threat: “We again request that you engage in good faith with Sanofi as part of a sale process. If you do that, we would not need to proceed with a consent solicitation to remove and replace the Medivation directors.”

Mandy Jackson mandy.jackson@informausa.com
Lilly Playing Catch Up In Oncology

LISA LAMOTTA lisa.lamotta@informa.com

The big pharma is chasing the competition in multiple areas of oncology, bringing forward offerings in CDK 4/6, as well as PD-L1.

Eli Lilly & Co. may be known for its leadership in the diabetes space, but the Indianapolis pharma is quietly building up its presence in oncology hoping one day this franchise will be just as prominent. During an investor meeting have people buzzing about the drug’s potential. Analysts are now debating whether ribociclib or abemaciclib can compete with Ibrance and which is poised to take a larger share of the market. Lilly spent a good chunk of its investor meeting trying to prove that its CDK 4/6 inhibitor is “best-in-class.” It will present additional evidence at the upcoming ASCO meeting, including 12-month data from the Phase II MONARCH-1 study of abemaciclib monotherapy in HR+/HER2- breast cancer, after chemotherapy for advanced disease.

Eight-month data from the MONARCH-1 trial showed an impressive 17.4% overall response rate (ORR). While Lilly execs said they were happy with the data so far, they would not confirm whether the data continued with that trend. “I encourage you to look at the totality of the data when you come to the presentation … for the 12-month data at ASCO and looking at the overall clinical benefit rate as well as the durability of response in patients,” Lilly’s Abemaciclib team leader Colleen Mockbee said.

Lilly is claiming that the drug’s continuous dosing schedule could set it apart from the competition; dosing interruptions and dose reductions are recommended for Ibrance due toxicity issues. “If you do look at the literature, you do see that if you have an inhibition of CDK4 and CDK6 that is sustained over the dosing interval you should expect to get regression of tumors and that’s exactly what we observed in preclinical settings, and it’s translating into the clinic. So again, we believe that that’s the optimal dosing strategy,” said Mockbee.

She highlighted the positive results the company has seen so far for abemaciclib as a single agent, noting that no patients discontinued treatment in early stage trials due to toxicities. Data from the Phase III MONARCH-2 and MONARCH-3 trials will also be presented at ASCO. The company expects to start two other MONARCH breast cancer trials this year and is exploring abemaciclib in non-small cell lung cancer (NSCLC) with the JUNIPER trials. Lilly said there is also the possibility of testing abemaciclib in gastric cancers, brain metastases, pancreatic cancer and mantle cell lymphoma.

“Even though abemaciclib may not have fully met elevated expectations for response rate, the drug clearly is the most active CDK 4/6 as a single agent; regardless of LLY’s decision to file based solely on MONARCH-1, our conviction in the near-term success of MONARCH-3 (abemaciclib + fulvestrant) and ultimately MONARCH-2 (+ aromatase inhibitors) is extremely high,” wrote Leerink Swann analyst Seamus Fernandez in a May 25 note.

EXPLORING IO THROUGH COMBOS

Like all of Lilly’s competitors, combinations are the underpinning of its strategy. Abemaciclib is already being looked at in several combinations including with Lilly’s PI3 kinase mTOR inhibitor LY3023414 and an ERK inhibitor entering the clinic this year, as well as with Merck’s Keytruda. Lilly is also testing its established lung cancer therapies Alimta (pemetrexed) and Portrazza (necitumumab) with Keytruda.

While Lilly knows it’s been left behind in the immuno-oncology space, it is doing its best to catch up, including combination trials with Merck & Co. Inc’s PD-1 inhibitor Keytruda (pembrolizumab) and AstraZeneca PLC’s durvalumab. Lilly is also building an IO pipeline of its own and says it will have five IO candidates in the clinic by the end of the year, including a PD-L1 inhibitor.

“PD-L1, we believe, is key to targeting to immuno-oncology. In fact, this is rapidly becoming a platform upon which oncology might be based,” said Michael Kalos, chief scientific officer of cancer and immuno-oncology, explaining Lilly’s three-pronged strategy to access PD-L1.
Concerned that Americans are no longer revering science the way the country did 50 years ago, Regeneron Pharmaceuticals Inc. leaders Leonard Schleifer and George Yancopoulos decided it was time for the biopharmaceutical industry to do more than just talk the talk in urging youngsters to pursue science, technology, engineering and math careers and have stepped up with a $100m pledge to sponsor the nation’s top high school competition – the Science Talent Search.

If the biopharmaceutical industry wants to be around in the future, drug manufacturers must step up now and help to inspire and support the best and the brightest young minds and capture their imaginations before the current generation is lost to other sectors and careers, said George Yancopoulos, founding scientist and chief scientific officer at Regeneron Pharmaceuticals Inc. and president of Regeneron Laboratories.

Unfortunately, Yancopoulos told Scrip, there are other industries that are grabbing the attention of the young and their heroes in recent years have become the latest reality-TV-made celebrities, rather than the scientists at the heart of some of the greatest emerging discoveries.

“We’ve got to change society,” he demanded, calling on his counterparts at other drug companies to make much more of a serious effort to get involved with mentoring in science, technology, engineering and mathematics (STEM) educational activities.

“We’ve got to focus our attention on the things that really matter,” Yancopoulos said. “We’ve got to get society to recognize the biggest, most important talent search in America is for science because those are the only people who are going to save our world.”

Yancopoulos and his company are not just talking the talk. Regeneron, with the full blessing of its board, just committed $100m over 10 years to support the Science Talent Search (STS) – the oldest and most prestigious STEM competition in the US for high schoolers.

As the new STS sponsor – only the third in the competition’s 75-year history – Regeneron has boosted the top student prize from $150,000 to $250,000. The Tarrytown, New York biotech also doubled the STS awards for the top 300 young scientists and their schools from $1,000 to $2,000 each.

Of the $100m from Regeneron, $30m is expected to be dedicated to “inspirational and aspirational” outreach and equity activities aimed at nurturing students’ interests in science – particularly those in underprivileged communities – support teachers and inspire more youngsters to pursue STEM careers.

Both Yancopoulos and Regeneron president and CEO Leonard Schleifer are STS alumni – participating in 1976 and 1970, respectively.

Yancopoulos actually brought home the fourth-place honors, competing against hundreds of other teenagers.

Yancopoulos pointed out that the STS, which is run by the Washington-based nonprofit Society for Science and the Public, previously was sponsored by Silicon Valley high-tech firm Intel, which held the title from 1998-2016, and nuclear and electronics pioneer Westinghouse Electric Corp., which ran it from its inception in 1942 to 1997, when the company was acquired by American broadcaster CBS. Yancopoulos said when he was a student at the prestigious Bronx High School of Science in New York in the 1970s, a hush would come over the students when a “Westinghouse” winner walked by.

“Legend was that these kids were destined to change the world – invent amazing things, cure diseases win Nobel Prizes,” he said during a ceremony at the American Museum of Natural History in New York where the selection of Regeneron was announced by astrophysicist Neil deGrasse Tyson, who was one of Yancopoulos’ schoolmates at the Bronx school.

And, indeed, they did – with 12 Nobel Prize winners and 11 National Medal of Science recipients counted among the STS alumni.

But, Yancopoulos lamented, society no longer reveres science as an aspirational goal the way it did 50 years ago, when President John F. Kennedy challenged the nation’s scientists to take the country to the moon.

That’s why Yancopoulos said he and Schleifer decided years ago to get more involved in supporting STEM educational activities at their local schools in New York – two of which are now top performers in the STS awards program – and creating an intern program at the company, which now hosts hundreds of students each year.

The decision to compete to become the next STS sponsor, he said, was a “no-brainer” for Regeneron.

“I think Regeneron is the right company at the right time to be taking on this sponsorship, not only because we are reflective of real industry for the next few decades – or maybe the whole century – but also because we’re a company that’s entirely built by scientists, founded by scientists and the board of directors is full of scientists,” Yancopoulos declared.

Read full story at: http://bit.ly/1sInfkr
**Takeda Oncology Hopes Hit By CHMP Ninlaro Rejection**

*Ninlaro* (ixazomib), a drug Takeda is pinning its near-term oncology hopes on and which went on sale in the US in December, has been panned by the European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) due to insufficient proof of its efficacy. The committee considered results from one main study submitted by Takeda involving 722 adults with multiple myeloma whose disease had not responded to or had come back after previous treatment. The study compared Ninlaro with placebo, both taken together with lenalidomide and dexamethasone. The main measure of effectiveness was progression-free survival. The advisory committee could not recommend the oral proteasome inhibitor based on that data, the EMA said in a statement issued May 27, adding: “The CHMP considered that the data from the main study were insufficient to demonstrate a benefit of Ninlaro in the treatment of multiple myeloma.” It said Takeda had proposed restricting the use of the medicine to patients whose disease is more difficult to treat and had come back after one previous treatment, and to those whose disease had come back after at least two previous treatments. But the committee rejected that idea.

**Sandoz Extrapolates Biosimilar Rituximab Data For EU Filing**

Sandoz appears to have taken the lead in the close race to develop a biosimilar version of Roche’s blockbuster TNF-inhibitor *MabThera* (rituximab) for Europe, announcing May 24 that the European Medicines Agency had accepted its regulatory submission for its biosimilar version of rituximab (GP2013) in 629 follicular lymphoma and 173 rheumatoid arthritis patients, but said its approval submission was for all the indications included in the reference product’s labelling, indicating that it is extrapolating the results of the two clinical studies to other indications in *MabThera’s* labelling, principally chronic lymphocytic leukemia (CLL) and B-cell lymphoma. With the filing, Sandoz may have become the favorite to win the race to develop a biosimilar rituximab; other companies nearing the market in Europe include Poland’s biotech start-up Mabion that is completing Phase III studies this summer, and South Korean company Celltrion Inc., that is also evaluating a biosimilar rituximab in Phase III studies. The companies are fighting over a pie that could be as large as CHF1.26bn ($1.27bn) - estimated by applying a 30% discount to Roche’s 2015 European blockbuster sales of *MabThera* of CHF1.8bn, the pricing discount to the innovative product usually applied initially to biosimilars in Europe.

**Lilly Diabetes Extends Feelers Into Other Diseases**

Eli Lilly & Co. is looking to use its strong position in diabetes to segue into other related therapeutic areas, including renal diseases, nephropathy and cardiovascular disease. The Indianapolis company is hoping to offer diabetes patients a continuum of care beyond controlling insulin levels. “Now looking at our strategy from kind of the broadest perspective here, we view diabetes as a systemic multi-organ disorder and one that really goes beyond glucose dysregulation,” David Moller, Lilly’s VP of endocrine research and clinical investigation, said at a May 24 R&D day. “And we are particularly interested in addressing fundamental aspects of pathophysiology, as well as important complications that are closely linked to the pathophysiology and remain inadequately addressed today.” Lilly’s strategy in diabetes is based on three pillars. It will focus on glucose control with new, more convenient solutions to patients that require insulin, as well as metabolic control, working toward disease modification, offering weight-loss solutions and improving cardiovascular risk factors. Moving beyond those more familiar areas, it will also emphasize end-organ protection, looking at drugs that treat cardiovascular disease, nephropathy and non-alcoholic steatohepatitis (NASH). Moller explained that the company already has compounds in its portfolio that address multiple pillars, like *Jardiance* (empagliflozin), which helps with metabolic control and end-organ protection due to its glucose-lowering effects as well as its recently revealed cardio-protective capabilities.

**Minerva Rockets On Positive PhIIb Data**

Minerva Neurosciences Inc.’s schizophrenia drug that targets patients with negative symptoms, an indication with high unmet need and no approved treatments, has met primary and secondary endpoints in a Phase IIb trial – positioning the company well for access to an open market and marking it as an attractive M&A target. Minerva’s stock (NASDAQ) rocketed following the release of topline Phase IIb data for schizophrenia drug MIN-101 – leaping up from its closing price of $3.55 per share on May 25 to a peak of $13.16 per share the following day. Its previous highest price in the last year was just $6.84 per share. There are currently no approved therapies specifically for the treatment of negative symptoms in schizophrenia patients and Minerva’s drug is one of only a handful of products in the pipeline for this particular indication.
Infliximab App Accepted

DONNA YOUNG donna.young@informa.com

If the FDA approves Samsung Bioepis’ and Merck’s biosimilar version of Remicade, known as SB2, which is now under review at the agency, the firms not only will have Janssen Biotech Inc. to contend with, but Celltrion and Pfizer Inc., which won approval last month of the first infliximab biosimilar in the US.

Korean firm Samsung Bioepis Co. Ltd. and its partner Merck & Co. Inc. took a major step forward towards entering the US biosimilars market when the FDA accepted the 351(k) application for SB2, a copycat version of Janssen Biotech Inc’s Remicade (infliximab).

The firms not only will be taking on Janssen, a subsidiary of US powerhouse Johnson & Johnson Inc., but also Celltrion Inc., also from Korea, and its partner drug mammoth Pfizer Inc., who won FDA approval on April 5 of their version of Remicade, dubbed Inflectra – the first monoclonal antibody biosimilar licensed in the US.

Inflectra was only the second biosimilar to gain the FDA’s nod – nabbing that approval a little over a year after Novartis AG unit Sandoz Inc. won the agency’s blessing to market Zarxio (filgrastim-sndz), which was referenced on Amgen Inc’s human granulocyte colony-stimulating factor Neupogen.

But the Celltrion/Pfizer biosimilar has yet to enter the US market – essentially because it’s caught up in a legal dispute with Janssen, which filed its lawsuit at the US District Court for the District of Massachusetts last year. Recently, District Judge Mark Wolf denied Janssen’s motion to stay litigation on its ‘471 patent covering Remicade pending an appeal filed last July by the company of a decision from the Patent Trial and Appeal Board invalidating the patent. The judge declared a stay would undermine the purpose of the Biologics Price Competition and Innovation Act (BPCIA), which gave the FDA the authority to approve biosimilars.

Janssen is insisting that under a ruling last year by the US Court of Appeals for the Federal Circuit involving the BPCIA in another case, Celltrion and Pfizer must wait 180 days before they can market Inflectra.

Samsung Bioepis, which is a joint venture between Samsung BioLogics and Biogen Inc., and Merck could eventually find themselves in the same predicament – caught up in the messy business of the US courts trying to figure out the BPCIA, or what one Federal Circuit judge said was like unraveling “a riddle wrapped in a mystery inside an enigma.”

MARKET PROSPECTS

No matter how the legal battles turn out, biosimilars may struggle with gaining acceptance – at least the early ones coming into the market.

There’s been a lot of skepticism whether the drugs will really provide much cost savings versus the innovators they are trying to emulate.

No matter how the legal battles turn out, biosimilars may struggle with gaining acceptance

Zarxio was priced at only a 15% discount to Amgen’s Neupogen.

SAMSUNG/MERCK PARTNERSHIP

Merck and Samsung Bioepis formed their development and commercialization partnership in February 2013. Samsung is responsible for preclinical and clinical development, process development and manufacturing, clinical trials and regulatory registration, while Merck has full responsibility for commercialization of approved products resulting from the agreement, including SB2.

This past September, Samsung Bioepis and Merck won approval in Korea of their version of Amgen Inc’s Enbrel (etanercept), known as Brenzys, to treat rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis and psoriasis in adults 18 years or older.

The Korean nod was Samsung Bioepis’ and Merck’s first approval under their collaboration.

Then in December, Korean regulators cleared the firms’ version of infliximab, which is marketed as Renflexis.

In January, the European Commission gave its OK to the etanercept biosimilar, also known as SB4, which is sold as Benepali there. The Benepalii approval came two months after the European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) gave the biosimilar a positive opinion on Nov. 20, 2015.

Last month, the CHMP gave another positive opinion to Samsung Bioepis for its infliximab biosimilar, Flixabi, which will be commercialized in Europe by Biogen.

In addition to versions of Remicade and Enbrel, Samsung said it was pursuing around a dozen other biosimilar candidates, including copies of AbbVie Inc’s Humira (adalimumab), or SB5; Roche AG and Genentech Inc’s Herceptin (trastuzumab), known as SB3, and Avastin (bevacizumab), dubbed SB8; and Sanofi SA’s Lantus (insulin glargine), or SB9 – developing those products with either Merck or Biogen, depending on the nation where approval will be sought.

© Informa UK Ltd 2016
Novartis’s FLAME Rockets LAMA/LABAs Into COPD Limelight At GSK’s Expense

SUKAINA VIRJI sukaina.virji@informa.com

Novartis’s recent publication of data from its FLAME study comparing its Ultibro Breezhaler with GSK’s Advair/Seretide in reducing COPD exacerbations could lead to a change in guidelines to favor LAMA/LABAs over ICS/LABA products in patients with severe COPD. Boehringer Ingelheim’s popular Stiolto Respimat will benefit from FLAME’s good will, but GSK’s son-of-Advair, Breo, will likely suffer.

The FLAME study found that Novartis AG’s once-daily Ultibro Breezhaler, which combines the long-acting muscarinic antagonist (LAMA) glycopyrronium with the long-acting beta agonist (LABA) indacaterol, was superior to GlaxoSmithKline PLC’s aging blockbuster Advair/Seretide, which combines the ICS inhaled glucocorticoid fluticasone with the LABA salmeterol, in terms of fewer disease flare-ups.

Of note, Ultibro Breezhaler is not approved in the US. Another product containing the same components but administered twice a day, Utibron Neohaler, was approved by the US FDA in October 2015 but has not yet been launched. AstraZeneca PLC’s LAMA/LABA offering Duaklir has yet to be filed in the US and launch is unlikely before 2019.

Evidence has been available for some time that that LAMA/LABAs are more appropriate for non-exacerbating patients compared to ICS/LABAs. However, Datamonitor Healthcare believes that current treatment guidelines could change to include treatment with LAMA/LABA combinations before the addition of an ICS for patients who remain symptomatic but who are not exacerbators.

Such a change would strongly benefit the LAMA/LABA class as a whole, further driving uptake.

“The exacerbating population type has financial impacts from a payer’s perspective as they are tied to greater use of hospital resources,” explained Datamonitor Healthcare analyst Astrid Kurniawan. “Frequent exacerbators are more likely to be prescribed an ICS as an ICS is expected to be more effective in preventing exacerbation.”

The FLAME data turns this assumption on its head. “The data with Ultibro is significant because Novartis is the only company to have done a head-to-head trial so far on a clinically relevant endpoint – exacerbations - with such a great result,” explained Kurniawan.

LAMA/LABAs face the issue of poor differentiation, notes Kurniawan. There are four of them: Anoro (umeclidinium/vilanterol; GSK), Ultibro (glycopyrronium /indacaterol; Novartis), Duaklir (acridinium/formoterol; AstraZeneca) and Stiolto Respimat (tiotropium/olodaterol; Boehringer Ingelheim GMBH).

“The FLAME data is a point of differentiation for Ultibro from other LAMA/LABAs.”

During Novartis’s first quarter results presentation on April 21, David Epstein – who has since left the company rather ignominiously – commented on a potential US launch of Ultibro Neohaler.

“We are in [partnership] negotiations, to be clear. What’s happened that’s slowed things a down a little bit is when we got this really exceptional FLAME data, it made the asset look even more interesting. And I’m hopeful that we’ll be able to close the deal in the coming month or so.”

STIOLTO SUCCESS

Ultibro Breezhaler’s main competitor is Boehringer Ingelheim’s Stiolto. One of Stiolto’s components is the LAMA tiotropium, the active ingredient in Boehringer’s popular Spiriva product. This familiarity of pulmonologists with Boehringer’s respiratory franchise has been a huge driver for Stiolto’s success.

“While Boehringer conducted a similar head-to-head trial to FLAME, called ENERGITO, the study was only six weeks long and was not specifically targeting patients with a history of exacerbations. The endpoint it looked at was FEV1.”

However, “When guideline changes are made they usually promote a class as a whole rather than advocate for a brand, so Stiolto will benefit from the class-effect of the FLAME result as well,” pointed out Kurniawan.

PRICING EFFECTS

What is still unclear is what effect FLAME will have on payer decisions.

“Many payers have expressed that price will still play a critical role in their decision making, especially since ICS/LABAs are going generic,” noted Kurniawan.

Speaking to Datamonitor Healthcare, key opinion leaders in the pulmonary field have suggested that unless LAMA/LABAs were offered at a price competitive to generic ICS/LABAs, it is unlikely that a significant number of patients would use LABA/LAMAs before the generic ICS/LABAs. The more expensive LAMA/LABAs are more likely to be considered earlier in the therapeutic pathway for severely exacerbating COPD patients as higher costs would be offset by reduced hospitalizations or emergency room visits, according to these KOLs.

“I think that we need to look at the [FLAME] data in more detail, but yes I think it is potentially very exciting because if you take a group of people at risk of exacerbations and that has been one of the problems with the earlier bronchodilator exacerbation studies, people have not really been a high-risk population, but if you take a group that are at risk and you compare the two it seems that LAMA/LABA is better than LABA/ICS, so it is really marginalizing the role of ICS/LABA,” a UK payer-advising key opinion leader told Datamonitor Healthcare.

Kurniawan says that while more research is needed and guideline changes as well as market adoption changes take time, “eventually, LAMA/LABAs will become first line in COPD.” GSK’s revamped its respiratory offering with new products Advair replacement Breo/Relvar (also an ICS/LABA) and Anoro (a LAMA/LABA) but uptake of both products has been slower than expected, although the situation is improving, claims GSK.

Read full story at: http://bit.ly/1qZDLva
While investors were hopeful the FDA’s delay in issuing its verdict for Sarepta Therapeutics Inc’s Duchenne muscular dystrophy medicine eteplirsen may mean the agency is not prepared to reject it, the postponement may create more doubt and uncertainty about the path forward in rare disease drug development in general.

Whether it was a ploy to ensure the start to regulators’ long holiday weekend wasn’t interrupted by a mob of angry protestors showing up on the FDA’s doorstep, the agency has again left another developer of a treatment for a rare and ultimately fatal disease, Duchenne muscular dystrophy (DMD), in limbo land – notifying Sarepta Therapeutics Inc. not to expect a decision on its experimental drug eteplirsen by its May 26 Prescription Drug User Fee Act (PDUFA) action date.

Like in the case of Sarepta, the FDA had postponed making a decision in the midst of the winter holidays for BioMarin Pharmaceutical Inc’s DMD drug Kyndrisa (drisapersen) – informing the biotech on Dec. 18, 2015 not to expect a ruling by its Dec. 27, 2015 PDUFA for the company’s DMD drug Kyndrisa (drisapersen) and avoiding being the Grinch, at least, for a few weeks anyway. BioMarin ended up getting a thumbs-down verdict on Jan. 15.

Whatever the reason for the FDA putting off its final judgment on eteplirsen – or at least, not yet letting Sarepta and the public in on the decision – the postponement may create more doubt and uncertainty about the path forward in rare disease drug development, which already faces high hurdles, including unpredictable markets and reimbursement.

Normally, Wall Street freaks out over such uncertainty. But in Sarepta’s case, investors took the FDA’s postponement as a positive sign – driving shares of the company up about 29%, before closing on May 25 at $23.35, up $4.91, or 26.6%.

An accelerated approval for eteplirsen would certainly provide more confidence for others pursuing Duchenne R&D – or even other rare disease treatments in general. Heidi Chen, an analyst with Citeline, an affiliate of Scrip, said there are at least 118 clinical trials ongoing in Duchenne, with at least 24 companies testing their experimental treatments in the disease.

RW Baird analyst Brian Skorney said he found it particularly interesting the FDA told Sarepta the agency was continuing to have “internal discussions” – which he said was yet another indication there was disagreement between the review team and senior leadership.

“This isn’t language we believe is common in FDA communications about PDUFA delays,” Skorney said.

While the delay “incrementally” increases the probability of an accelerated approval, he said, “more meaningfully,” it decreases the likelihood of a complete response letter that requires a randomized, placebo controlled study of eteplirsen.

With the “band-aid just getting harder to rip off,” Skorney said the worst-case scenario was “looking less and less likely” for the eteplirsen application.

“The longer it takes to reject eteplirsen and request a placebo-controlled study, the harder it is going to be to do that,” he declared.

If anything, Skorney said, “this delay probably increases the probability of some middle ground scenario.”

“Prior delays have allowed sponsors to negotiate restricted labels with FDA facilitating approvals,” said Oppenheimer analyst Christopher Marai.

Analysts at Sagient Research’s BioMedTracker, an affiliate of Scrip, also were optimistic the FDA could still be working out what needs to be done instead of requiring a repeat study or to substantiate an accelerated approval.

They noted that Janet Woodcock, director of the agency’s Center for Drug Evaluation and Research, had made several statements at the April 25 eteplirsen advisory committee meeting stressing the FDA has some flexibility in its ability to approve medicines for rare diseases, particularly those that are for life-threatening conditions.

So, the BioMedTracker analysts said, “there is some possibility” the FDA may overlook the concerns regulators have with eteplirsen and grant it an accelerated approval, “though that is quite uncertain.”

They raised the likelihood of approval for eteplirsen by 2% – from 84% to 86% – although that’s still 3% below average.

VOUCHER WOULD PRECLUDE NEED FOR FINANCING

Oppenheimer’s Marai pointed out that if Sarepta manages to beat the odds and win an accelerated approval for eteplirsen, the company would likely snag a rare pediatric disease priority review voucher, whose market value could be as much as $350m or potentially more – precluding the need for any immediate financing.

The company earlier this month reported it had $140.6m in cash, cash equivalents, short-term investments and restricted cash as of March 31, versus $204m as of Dec. 31, 2015 – a decrease of $63.4m, which used to fund Sarepta’s ongoing operations, commercial launch activities and related inventory build.
India Deliberates Orphan Rules

India is deliberating a string of initiatives to ensure that drugs for rare diseases reach patients faster and are available at “reasonable” prices in the country. The US, EU and Japan, among others, have specific legislation to encourage research of rare diseases and the development of orphan drugs and India’s efforts appear to be early steps in the same direction. India’s plans also come in the backdrop of a 2014 court order against the Government of the national capital territory (NCT) of Delhi where the court noted how the lack of government planning was “pricing out” orphan drugs for rare and chronic diseases like Gaucher’s disease. A recent meeting of the Drugs Controller General of India (DCGI) with key industry stakeholders discussed a host of critical issues including defining rare disease and the criteria for such classification, fast track approvals for drugs for rare diseases and a potentially distinct pricing mechanism for orphan drugs, keeping it “away” from the purview of the country’s apex price regulator, the National Pharmaceutical Pricing Authority (NPPA). The Indian Drugs Manufacturers’ Association (IDMA), in consultation with other institutions, has been tasked with preparing a draft definition of rare disease and the criteria for classification of a disease as rare/orphan, details in the minutes of a May 4 meeting with the Indian regulator said. Senior IDMA officials told Scrip that it is still work in progress and early days to share any details. The Organisation of Pharmaceutical Producers of India (OPPI), which represents leading multinational firms and is part of the joint government-industry endeavor, said that since a majority of patients with rare diseases come quite late for medical care, and most remain undiagnosed, the absolute number of patients suffering from a disease “should not ideally form the yardstick” for a definition.

Black Triangle Warning Dropped From Pfizer’s Smoking Cessation Drug Label

Europe has removed its black triangle warning from the label of Pfizer Inc.’s smoking cessation drug Champix (varenicline; known as Chantix in the US) on the back of new long-term use data. Pfizer said the move by the European Medicines Agency to remove the warning label – which was only imposed in 2013 following new safety monitoring guidelines in Europe – further supports health technology appraisal guidance that recommends Champix as a clinically and cost effective first-line treatment option for smokers wishing to quit. The black triangle warning was introduced to Champix’s labeling because the EMA deemed the product necessary for additional post-approval monitoring. The EAGLES trial (Evaluating Adverse Events in a Global Smoking Cessation Study) was primarily designed to evaluate the neuropsychiatric safety of Champix and bupropion (GlaxoSmithKline PLC’s Zyban), compared with placebo, in adult smokers with and without a history of psychiatric disorder. Zyban is also approved for use in smoking cessation. EAGLES is the first and largest randomized, double-blind, placebo-controlled clinical study of approved smoking cessation medicines to date, including 8,144 adult smokers with and without a history of psychiatric disorder. The results demonstrated that varenicline and bupropion do not significantly increase the risk of neuropsychiatric adverse events in the primary endpoint (a composite measure of moderate and severe neuropsychiatric adverse events), as compared to placebo or nicotine patch (Nicorette), in patients with or without a history of psychiatric disorder. The trial was conducted at the request of both EMA and US FDA regulatory bodies and Pfizer noted that it was in the process of submitting the new data for Champix to regulatory authorities worldwide.

Darzalex March Continues with EU Approval

The European Commission has now granted conditional approval to Janssen-Cilag’s (Johnson & Johnson) first-in-class anti-CD38 antibody Darzalex (daratumumab; licensed form Genmab) for use in melanoma following a CHMP positive opinion in April. The approval, the second for the novel product after it was given an earlier-than-expected go-ahead by the US FDA last November, means it will come to the EU market only weeks after its rival Bristol-Myers Squibb Co.’s SLAMF7 (signalling lymphocyte activation molecule family member 7) protein inhibitor Empliciti (elotuzumab), which was approved in the EU on May 11. In the US, the positions were reversed with Darzalex beating Empliciti to market by two weeks. At present, Empliciti has the edge in terms of indication in the EU, with a label for use earlier in the treatment paradigm in adult patients who have received at least one prior therapy. Darzalex is specifically indicated for the treatment of adults in patients whose previous treatment included a proteasome inhibitor and an immunomodulatory agent and whose disease worsened after treatment, and its approval was based on the Phase II MMY2002 (SIRIUS-US) study. In long term, J&J is banking on broadening the Darzalex label to the second-line setting with the results of its CASTOR study due to be presented at ASCO early next month. The company has also just released top-line data from another study POLLUX, in the relapsed/refractory setting.

scriptintelligence.com
China Sets The Stage For Its Innovation Entrance

JULES QUARTLY

China is coming up fast on the innovation curve as a result of political will and a healthy ecosystem that supports R&D. It will take time to challenge the major players from the US and Europe, but there are few that doubt China can, eventually, do so.

If biotechnology was a race, China is catching up fast to its European and US competitors. It has accelerated pharmaceutical development by moving on from low-risk, low-margin contract work in generics, to producing innovative and novel therapy research, especially in the burgeoning field of biologics.

The fundamentals look sound. China is already the world’s second-largest pharma market, after the US, and is expected to be worth about $200bn by 2020. It is backed by ambitious central government policies, and there is plenty of money washing around. Now the internet bubble is deflating, biotechnology is viewed as an increasingly attractive proposition. There’s a steady swelling of in- and out-licensing transactions, partnering, mergers and acquisitions, while venture capital pours in.

BEHIND THE SCENES

In 2015, there was a big uptick in deals involving China-based R&D companies, such as Shanghai’s Innovent Biologics Inc., which raised $100m to move forward its biosimilars business. Meanwhile, Jiangsu Hengrui Medicine Co. Ltd. penned a licensing agreement with US-based Tesaro Inc., then kept the ball rolling with its announcement in April that it had reached a research agreement with Albert Einstein College of Medicine to improve cancer treatments.

This trend continues in 2016, with Furen Pharmaceutical Group Co Ltd buying Kaifeng Pharmaceutical (Group) Co Ltd for $1.2bn; while New Horizon Capital funneled money to Chinese biopharmaceutical company ZAI Lab Ltd. in January. The month after, Beijing-based cancer drug developer BeiGene (Beijing) Co. Ltd. pulled in $158.4m for its initial public offering on NASDAQ. It held off on celebrating and ringing the bell at the New York Stock Exchange until April, when it released clinical results for its anticancer asset, BGI-183. Meanwhile, Hutchison China MediTech Ltd. is rushing toward its richly anticipated New York stock listing. According to the Financial Times, Jiangsu Hansoh and Simcere Pharmaceutical Group will register Hong Kong IPOs later this year.

China’s emergence as a senior partner in the world of pharma and a cradle for innovation is no surprise to Frank Yu, the founder and CEO of Ally Bridge Group (ABG), a global healthcare-focused investment platform based in Hong Kong, with offices in China and the US.

ABG works closely with WuXi PharmaTech Inc., China’s largest medical contract researcher. ABG helped the company delist from the New York Stock Exchange last year in a $3.3bn management buyout. Then, in January, WuXi broke ground on a $120m biologics center for 800 scientists, in Shanghai. Analysts say a Hong Kong listing of the group worth about $1.5bn is in the works for later this year.

“We know for sure that WuXi’s capabilities have a very high entry barrier, with great quality control and yield. It’s really able to deliver biologics manufacturing to global clients and has come up fast on the innovation curve,” Yu told Scrip. “The fact that China is upgrading into an innovation-based economy, especially in the pharmaceuticals industry, really is no surprise. It’s a must-do. There’s no choice for China, with its 1.2 billion population, they need to do it.”

Yu references the country’s slowing economy (annual growth dropped to 6.7% in the first quarter of 2016) mounting price pressures, the lingering effects of a compliance crackdown and quality issues, as among the reasons why China is forced to move up the value chain. There is also a pressing need to improve healthcare because, as the country becomes richer, people are able to spend more on healthcare; while economic growth, urbanization and an aging population increase the incidence of diseases.

“The ingredients to make this happen are in place. The ecosystem is there and, most importantly, there is a huge talent pool in China. There’s so many biologists, chemists and engineers, many of them trained in the US and Europe. The country has also created a lot of wealth and for innovation you need a lot of money.”

“The government and private industry is putting a lot of money into R&D. At the same time the market is expanding. The new wave of innovation is coming up to global, truly world class standards,” Yu says, adding there are plenty more deals with international companies in the works.

GOVERNMENT’S STARRING ROLE

The big reveal was at the Great Hall of the People in Beijing, at the Fourth Session of the 12th National People’s Congress. It was here in early March that Chinese Premier Li Keqiang rolled out the government’s plans for a “new normal in economic development” (referring to slower growth but greater innovation), including prioritizing “strategic emerging industries” like biomedicine, supported by national development funds. Sydney-based pan-Asian CRO Novotech said at the time that it believes this could be as much as $18bn for the coming 13th Five-Year Plan (2016-2020) – a figure that dwarfs the $2bn biotech cash injection in the previous Five Year Plan.

Encouraging biotech is a policy the world’s largest scientific organization, the Chinese Academy of Sciences (CAS), has been advocating for some time. Five years ago, CAS said the sector had the potential to become a “pillar” of the pharmaceuticals industry, with a market size of around RMB600bn ($92bn) to RMB800bn ($123bn). That figure now looks like it could be an understimation.

Pursuing the future of pharma in biologics would suit China, as it transitions from a labor intensive to knowledge intensive economy for long-term sustainability.
Those That Cannot Be Successful Raise Money

ANDY SMITH

It struck me last week that the quote attributed to George Bernard Shaw – “He who can, does. He who cannot, teaches.” – can be modified to apply to an increasing cadre of small- and mid-capitalization life science companies. Success for these companies that resonates with investors is either to be acquired or to reach a valuation that is too big to be acquired. The opposite of success is not so easy to define since clinical, regulatory or commercial failure usually means coming back to investors for a bail out.

The reputation of AMAG Pharmaceuticals Inc. of regularly disappointing in its earnings announcements was cemented by its first-quarter results which missed analysts’ consensus estimates of sales and earnings. Loss-making AMAG has desperately tried to divert investor attention away from its own developed product – Feraheme (ferumoxytol) for iron deficiency anemia (IDA) and whose quarterly sales have stagnated at $25m a quarter – towards those it acquired in the run up to last summer’s valuation peak. Unfortunately the corporate development prowess at AMAG seems to be on a par with its drug development capabilities. AMAG’s recently acquired product, Makena (hydroxyprogesterone caproate) – which is indicated to lower the risk of pre-term births and was acquired for $750m up front plus $350m in sales milestones – had first-quarter sales of $65m missing consensus estimates after declining 3% from the previous quarter. The analysts from Jefferies pointed out that the delay to the subcutaneous auto injector version could result in an approval just as Makena’s orphan drug exclusivity expires in 2017. AMAG’s catalogue of errors and its $1bn debt saddle do not make it a prime candidate for a dilutive issue of equity, especially in the current environment where fundraisings – like the recent cancelled Bavarian Nordic AS public offering – are shunned. But the issuance of positive research notes from every analyst I follow and an analyst meeting on June 1 may be conspiring to convince investors that night is day, black is white and AMAG is a viable investment proposition.

This mirage making has all happened before when my inbox was deluged with positive research notes on the loss-making diagnostic company Exact Sciences Corp. prior to its $179m share offering in July 2015. Exact Sciences’ first-quarter sales for its colorectal cancer diagnostic test Cologard were an underwhelming $14.8m. The low uptake of Cologard since its launch in August 2014 is not the most damning indictment of its investment proposition. Soon after the share offering, holders were hit with the twin disappointments of Cologard’s status not being elevated in the United States Preventive Services Task Force (USPSTF) guidelines and 2016 test volume guidance that was below expectations. Like AMAG, Exact Sciences’ disappointments were not a one-off as its fourth quarter 2015 results were a drastic preannounced reduction in test volume. The analysts from Jefferies described Exact Sciences’ first-quarter 2016 Cologard volume as “better than feared” but the analysts from Mizuho finally threw in the towel, downgrading their recommendation to “Neutral” and noting the risk to 2016 test volume guidance. Those investors who were taken in by the July 2015 offering at $25.50 saw their shares close last week at $6.50.

Keryx Biopharmaceuticals Inc. seem to be at the stage just before a deluge of supportive sell-side research notes and a share offering cannot be that far away. Loss-making Keryx’s first quarter sales of its product Auryxia (ferric citrate) – an absorbable phosphate binder approved to manage hyperphosphatemia and approved by the FDA in 2014 – were an anemic $5.6m. Sales were slightly ahead of analysts’ consensus estimates of but earnings (or increased loss) missed estimates. Keryx also announced that plans to partner Auryxia in the EU were taking longer than they expected (my guess would be that greater sales would help) and positive Phase III results for Auryxia in iron deficiency anemia (IDA). With $171m in cash at the end of the last quarter and $125m in debt, Keryx’s investors should take into account the commercial performance of Feraheme in IDA and the absence of a licensing deal when the offering is announced.

The inverse correlation between fundraising by a biopharmaceutical company in pre- or early-commercialization of its lead product and the licensing or acquisition of that product was established by Amarin Corp. Loss-making Amarin received FDA approval for its lipid-lowering fish oil extract Vascepa (icosapent ethyl) in July 2012 and in the months that followed expectations rose for either the acquisition of the company or the licensing of Vascepa. These expectations lasted right up until the $100m debt offering in order to fund the launch. Although the Amarin CEO suggested that the fundraising gave the company the resources to sell itself or partner Vascepa, with first-quarter sales of $25.3m, cash of $81.4m and the debt repayment in 2017, no partner has emerged.

Many UK, Australian and Canadian small-capitalization life science companies bemoan their need to frequently raise small amounts of money from their armies of retail investors. The endgame for these companies with non-commercial products or a long or uncertain road to a viable business model is therefore a schedule of dates with underwriters. In the US, investor patience seems to take much longer to run out but when it does, it is more activist and the end result is a different date. With the liquidator.

Andy Smith is chief investment officer of Mann Bioinvest. Mann Bioinvest is the investment adviser for the Magna BioPharma Income fund which has no position in the stocks mentioned, unless stated above. Dr Smith gives an investment fund manager’s view on life science companies. He has been lead fund manager for four life science-specific funds, including Internatinal Biotechnology Trust and the AXA Framlington Biotech Fund, and was awarded the Technology Fund Manager of the year for 2007.
Scrip’s weekly **Pipeline Watch** tabulates the most recently reported late-stage clinical trial and regulatory developments from the more than 10,000 drug candidates currently under active research worldwide.

**Late-stage clinical developments for the week 20-26 May 2016**

<table>
<thead>
<tr>
<th>LEAD COMPANY</th>
<th>PARTNER COMPANY</th>
<th>DRUG</th>
<th>INDICATION</th>
<th>MARKET</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSL Behring</td>
<td>–</td>
<td>Afstyla (CSL627) iv injection</td>
<td>hemophilia A</td>
<td>US</td>
</tr>
<tr>
<td>Braeburn Pharmaceuticals SPRL</td>
<td>–</td>
<td>Probufpime (buprenorphine) implant</td>
<td>opioid dependence</td>
<td>US</td>
</tr>
<tr>
<td>AstraZeneca PLC</td>
<td>–</td>
<td>MEDI-550</td>
<td>pandemic flu vaccine</td>
<td>EU</td>
</tr>
<tr>
<td>Vanda Pharmaceuticals Inc.</td>
<td>–</td>
<td>Fanapt(iloperidone) tablets</td>
<td>schizophrenia</td>
<td>US</td>
</tr>
<tr>
<td>Eli Lilly &amp; Co.</td>
<td>–</td>
<td>Botox Vista (onabotulinumtoxin A)</td>
<td>Crow’s feet lines</td>
<td>Japan</td>
</tr>
<tr>
<td>Chugai Pharma Co. Ltd.</td>
<td>–</td>
<td>Sairamuzar(ramucirumab)</td>
<td>colorectal cancer</td>
<td>Japan</td>
</tr>
<tr>
<td>Johnson &amp; Johnson</td>
<td>–</td>
<td>Invokanet (canagliflozin plus metformin)</td>
<td>diabetes type 2</td>
<td>US</td>
</tr>
<tr>
<td>Seqirus Inc (CSL Ltd.)</td>
<td>–</td>
<td>Flucelvax Quadriivalent</td>
<td>flu vaccine</td>
<td>US</td>
</tr>
<tr>
<td>Janssen-Cilag International</td>
<td>Genmab AS</td>
<td>Darzalex (daratumumab)</td>
<td>multiple myeloma</td>
<td>EU</td>
</tr>
<tr>
<td>Pfizer Inc.</td>
<td>–</td>
<td>Trumenba vaccine</td>
<td>meningococcal group B disease prevention</td>
<td>EU</td>
</tr>
<tr>
<td>Allergan PLC</td>
<td>–</td>
<td>oxymetazoline 1% cream</td>
<td>facial erythema associated with rosacea</td>
<td>US</td>
</tr>
<tr>
<td>Samsung Bioepis Co. Ltd.</td>
<td>Merck &amp; Co. Inc., Biogen</td>
<td>infliximab (SB2)</td>
<td>ulcerative colitis, RA, Crohn’s, ankylosing spondylitis, psoriatic arthritis, psoriasis</td>
<td>US</td>
</tr>
<tr>
<td>Sandoz Pharma Ltd., (Novartis AG)</td>
<td>–</td>
<td>rituximab</td>
<td>non-Hodgkin’s lymphoma, chronic lymphocytic leukemia and RA</td>
<td>EU</td>
</tr>
<tr>
<td>Viamet Pharmaceuticals Holdings LLC</td>
<td>–</td>
<td>VT-1598</td>
<td>antifungal</td>
<td>US</td>
</tr>
<tr>
<td>Akari Therapeutics PLC</td>
<td>–</td>
<td>Coversin</td>
<td>Guillain-Barré syndrome</td>
<td>EU</td>
</tr>
<tr>
<td>Novavax Inc.</td>
<td>–</td>
<td>RSV F nanoparticle vaccine</td>
<td>respiratory syncytial virus infection</td>
<td>US</td>
</tr>
<tr>
<td>Santhera Pharmaceuticals AG</td>
<td>–</td>
<td>omigapil</td>
<td>congenital muscular dystrophies</td>
<td>US</td>
</tr>
<tr>
<td>Relypsa Inc.</td>
<td>–</td>
<td>Veltassa (patiromer)</td>
<td>hyperkalemia</td>
<td>US</td>
</tr>
<tr>
<td>Sarepta Therapeutics Inc.</td>
<td>–</td>
<td>eteplirsen</td>
<td>muscular dystrophy</td>
<td>US</td>
</tr>
</tbody>
</table>

**REGULATORY APPROVAL**

**SUPPLEMENTAL REGULATORY APPROVAL**

**ACCELERATED/CONDITIONAL APPROVAL**

**REGULATORY FILING ACCEPTED**

**ORPHAN DRUG DESIGNATION**

**FAST-TRACK STATUS**

**SUPPLEMENTAL REGULATORY FILING**

**REGULATORY REVIEW EXTENSION**

**PRODUCT LAUNCH**

---

Source: Sagient Research’s BioMedTracker
The global research services provider Envigo has appointed Scott Schulz director of operations for North American research model services. Schulz joins the company from Taconic Biosciences, where he was vice president of operations, introducing lean manufacturing methodologies. Prior to this, he was director of operations at Baxter Health Corporation, before which he was senior director of manufacturing operations at Cardinal Health.

Atlantic Healthcare PLC has named the management team which will lead its newly established US commercial and business development operations, based in North Carolina. The specialty pharma company, which focuses on gastrointestinal disorders, has appointed Sireesh Appajosyula vice president (VP) product commercialisation, Jonathan Drutz VP corporate and business development and Jordan Zwick director of corporate and business development. Appajosyula joins Atlantic from Salix Pharmaceuticals, where he led the company’s inflammatory bowel disease division. Drutz has been involved in a variety of life science ventures, acting as a business development executive, investor and consultant. Zwick most recently led business development and corporate strategy at Chimerix, having previously been at Salix and Medtronic.

Obesity specialist Orexigen Therapeutics Inc. has announced that its co-founder and former chair, Eckard Weber, has stepped down from the board of directors. Weber, who co-founded the company with Michael Cowley in 2002, was chair from 2002 until earlier this year, and also served as interim president and CEO between November 2008 and March 2009. Weber is also a partner at Domain Associates, LLC., a venture capital firm which owns approximately 11.3 million shares of Orexigen common stock.

Alkermes PLC, a global biopharma company focusing on the treatment of central nervous system diseases, has appointed Nancy Snyderman to its board of directors. Snyderman has more than 28 years of experience as a medical journalist, most recently at NBC News, where she was chief medical editor. Prior to her work in journalism, she was vice president of corporate communications at Johnson & Johnson. Snyderman is also a board certified otolaryngologist-head and neck surgeon, and a fellow of the American College of Surgeons.

Regulus Therapeutics Inc. has appointed Allison Way vice president, investor relations and corporate communications. Wey brings over 25 years of experience in investor and media relations to the biopharma company, which specialises in medicines targeting microRNAs. She was previously vice president, investor relations at Durata Therapeutics, before which she held senior roles at Par Pharmaceuticals, Boron LePore and Associates and Edelman Financial Worldwide.

Cancer immunotherapy company Jounce Therapeutics Inc. has appointed Barbara G. Duncan to its board of directors. Duncan has spent the last 7 years at Intercept Pharmaceuticals Inc. where she was chief financial officer and treasurer. Prior to this, she held a number of leadership roles at DOV Pharmaceutical Inc., including chief executive officer. Duncan currently also serves on the boards of Edgemont Pharmaceuticals, LLC., Medgenics Inc. and Adaptimmune.
Maximize Your Reimbursement Potential

The balance of power behind the prescribing decision is changing: payers are ever more in charge. That means that insight into how payers make decisions – how they evaluate drugs, one against another – will be crucial to any successful drug launch.

RxScorecard objectively, authoritatively, and systematically assesses marketed and pipeline drugs in a therapeutic indication from the payer’s point of view. Developed by senior medical and pharmacy leaders from major payers and pharmacy benefit managers, RxScorecard delivers practical and powerful insight into your drug’s reimbursement potential and how you can maximize it.

Transparent, objective, and grounded in payer data, RxScorecard helps you refine your development path, future-proof your market access strategy, and achieve payer acceptance.

Discover RxScorecard today.

Visit https://goo.gl/i0AM2U to review the selection of RxScorecards today. Interact with the data. Compare drugs on clinical, safety, and economic metrics. See the payer perspective.