Which Biopharmas Are Best Positioned For Five-Year Growth?

JOSEPH HAAS joseph.haas@informa.com

Morningstar expects 229% revenue growth during the 2015-2020 period for BioMarin, far stronger than larger competitors. Virology powerhouse Gilead is the only one of the 20 largest biopharmaceutical companies expected to face a decline in revenue over the period.

The brightest picture over the next five years goes to BioMarin Pharmaceutical Inc., and the gloomiest outlook is for Gilead Sciences Inc., according to an analysis of the revenue growth prospects for the 20 largest publicly-traded biopharmaceutical companies during the 2015-2020 timespan by Morningstar.

The investment analyst service also sees strong revenue growth ahead for Bristol-Myers Squibb Co., Eli Lilly & Co. and Roche, but anticipates much less promising near-term performance for Sanofi, Amgen Inc. and AstraZeneca PLC, although Gilead is the only one of the 20 companies examined that is projected to face an overall decline in revenue (see table on p7).

Morningstar’s analysis evaluates the companies’ business performance prospects over the five-year period based on three metrics – new drug sales, sales lost to generic competition and sales from older products not facing generic competition, or “in-line products.” BioMarin benefits from having no products subject to patent expiration during the five-year period, while Bristol, Lilly and Roche will succeed partly on the strength of diversification, Morningstar says.

The true outliers in the report are BioMarin, whose rare disease focus is projected to produce 97% growth for in-line products, 132% growth from pipeline assets and a five-year compound annual growth rate of 229%, and Gilead, whose focus on hepatitis C is facing headwinds from both competition and pricing pressure.

The virology giant is expected to incur a 5% decline in CAGR between 2015 and 2020, spurred by a 41% decrease in revenue from in-line products such as Sovaldi (sofosbuvir) and Harvoni (sofosbuvir/ledipasvir). Patent expiries will cost Gilead an estimated 9% decrease in revenues, while pipeline assets will offer 25% revenue growth over the period, the report states.

The report attributes the expected success of both BioMarin and Roche to in-line product growth and pipeline strength. In particular, Roche has benefited and will continue from the complicated chemical structure of Rituxan (rituximab), which still faces no biosimilar competition despite patent expiration in 2017. Morningstar notes.

“Some complex molecules are difficult to reliably and profitably make, and the manufacturing know-how of branded firms can prevent other firms from entering the market,” Morningstar points out. “We also expect new formulations of these complex
When you think about patient engagement, what do you think of?
I suspect that many in the pharma industry would see it as tied in with commercial and marketing activities, and perhaps also as something that needs to happen to help move a drug towards and through approval.

In this week’s issue, we talk to a communications expert who argues that pharmaceutical companies could and should be pushing the “patient-centric” approach much further upstream, to all phases of clinical development and even product discovery.

Re-engineering your R&D engine so that it is fuelled by real-life patient need rather than by compound discovery capabilities is daunting. Still, making steps in that direction might be just what the doctor ordered for companies in an age when the price a product can command will be increasingly constrained by its ability to meet true unmet need, rather than by its originator’s claims of innovation or R&D investment.

See p20 for Lucie Ellis’s interview with Julie Adrian of InVentiv Health.
GSK Kicks Off Two Large Outcomes Trials In A Competitive CKD Category

The company initiated a Phase III development program for the oral HIF-PH inhibitor daprodustat as a treatment for anemia associated with chronic kidney disease. Two trials will enroll 7,500 patients.

JESSICA MERRILL jessica.merrill@informa.com

GlaxoSmithKline PLC is investing substantially behind the development of daprodustat for the treatment of anemia associated with chronic kidney disease, a competitive therapy area where the big pharma is behind its rivals. The company has initiated two large cardiovascular outcomes trials evaluating daprodustat, which together will enroll about 7,500 patients.

Daprodustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) that works by promoting the production of red blood cells that carry oxygen where it is needed. Anemia arises in patients with kidney dysfunction, because the kidneys no longer produce sufficient amounts of erythropoietin, which stimulates red blood cell production. Early clinical data has shown the mechanism of action could be a promising treatment for anemia in chronic kidney disease (CKD) patients, with the potential for an improved cardiovascular safety profile and oral dosing convenience compared with existing erythropoietin stimulating agents (ESAs).

However, two US biotechs, FibroGen Inc. and Akebia Therapeutics Inc., already are further ahead in development with similar drugs.

FibroGen, which is partnered on roxadustat with AstraZeneca PLC in the US and China, and with Astellas Pharma Inc. in Europe, is running three Phase III trials testing roxadustat for the treatment of anemia in patients with CKD, and has targeted a US NDA filing for 2018. Akebia, meanwhile, also has advanced its candidate vadadustat into Phase III trials in a similar patient population.

Earlier this year, Bayer AG, said it wasn’t sure if it would move forward with development of its own Phase II HIF-PHI inhibitor molidustat, because of the competitive environment. Instead, the company said it might consider out-licensing the drug.

GSK’s Phase III program will include two studies comparing the safety and efficacy of daprodustat versus erythropoietin, Amgen Inc’s Aranesp (darbepoetin alfa). The first trial, ASCEND-D, will enroll approximately 3,000 dialysis patients with anemia associated with CKD switching from an ESA. The second trial, ASCEND-ND, will enroll approximately 4,500 patients with anemia associated with CKD who are not on dialysis and will include patients switching from an ESA or new to treatment.

Published online 28 November 2016

CLICK Read full story at: http://bit.ly/2gUXqfl
The US obesity market is expected to double in size over the next decade with Novo Nordisk’s Saxenda driving the growth – but real progress for the pharmaceutical sector will only come when obesity drugs offer better outcomes than non-pharma methods.

The US obesity market is set to grow from $533m to $1.2bn in the next 10 years, according to Datamonitor Healthcare’s obesity forecast. However, there is room for more dramatic growth long term should more efficacious therapies come to market. Fewer than 1% of treatable patients currently receive a pharmacological intervention for obesity. The market could be worth $11.2bn by 2026 if the proportion of obese patients receiving drug therapy increased to 5%, or $22.4bn if it was 10%.

The predicted boost in the obesity drug market will mainly come from Novo Nordisk’s liraglutide (Victoza/Saxenda).

Increasing sales of Qsymia and Orexigen Therapeutics Inc’s Contrave (bupropion/naltrexone) will also contribute to the obesity market growth over the next few years and will surpass the declining sales of Xenical and Eisai Inc’s Belviq (lorcaserin). Xenical and Belviq are less effective than Qsymia, Saxenda and Contrave, resulting in a reduced patient share and declining revenues. Xenical’s revenue is expected to decrease from $116m in 2016 to $78m in 2026, while Belviq’s will decline from $41m to $18m.

Contrave’s prospects are constrained by Takeda having pulled out of its partnership with Orexigen, leaving the smaller, resource-constrained partner with sole responsibility for marketing the drug. However, sales will grow because physicians are likely to become more accepting of pharmaceutical interventions for obesity. In the DMHC forecast, it says that “physicians are slowly beginning to prescribe pharmacological therapy for weight loss more often as knowledge of the drugs increases and the economic cost of obesity grows.”

Vivus’ Qsymia will likely benefit from Takeda’s abandonment of Contrave, possibly gaining the additional patient share that Contrave will lose. Qsymia already has the largest single share of the obesity market and is expected to remain the most commonly prescribed weight loss drug - its strong efficacy data from clinical studies gives the drug an upper hand over competitor weight loss drugs.

As physicians become more accustomed to drug therapies for weight loss it is expected that more candidates will reach the market. Currently there are 16 late-stage drugs in Phase II development, with pipeline leader Medix planning to initiate Phase III studies for tesofensine before the end of 2016 [see table below].

Datamonitor Healthcare analyst Kevin Shannon, author of the report, highlighted Johnson & Johnson’s Invokana (canagliflozin), currently the leading SGLT-2 inhibitor in type 2 diabetes, and Novo Nordisk’s Victoza/Saxenda follow on, semaglutide (NN9536), as the most significant drugs in the pipeline.

Boehringer Ingelheim GMBH/Eli Lilly & Co’s Jardiance (empagliflozin), another SGLT-2 inhibitor, recently showed a reduction in cardiovascular events in type 2 diabetes in a large scale CV outcomes trial; it is expected that Invokana should follow suit. “This is generally believed to be a class benefit, though we won’t know for certain until Invokana announces the results of its CVOT in 2017,” Shannon noted.

Semaglutide has also demonstrated a CV benefit in type 2 diabetes. Novo Nordisk is working on an oral formulation for the drug, something Shannon believes could be big.

There have also been some trials combining SGLT-2 inhibitors and GLP-1 agonists in type 2 diabetes with a particular interest in the weight loss effect. The results from these studies so far do show impressive...
weight loss, suggesting another option for future treatment in obesity. One such study was AstraZeneca PLC’s DURATION-8 trial, which examined a combination of the SGLT-inhibitor dapagliflozin and the GLP-1 receptor agonist exenatide in patients with inadequately controlled type 2 diabetes; as well as meeting its primary endpoint of HbA1c reduction from baseline compared with either drug alone, it met secondary endpoints including significantly greater body weight reduction compared with either drug alone.

Saniona’s tesofensine and 7TM Pharma AS’ obinepitide are both central nervous system acting drugs, a feature that may actually limit their success in Shannon’s opinion. He noted previous setbacks with this type of drug in the obesity space, including the withdrawal of rimonabant, sibutramine and fenfluramine/phenetermine.

In 2014, the cost of obesity in the US was estimated at $300bn – a price tag that is expected to skyrocket as the proportion of the US population classified as obese rises from 36% to a projected 50% by 2030. With only 1% of the potential patient population actually receiving pharmaceutical treatment, there is room for dramatic expansion of the market by size and value, particularly if more effective therapies are approved.

Challenges for the drug sector though will continue until companies can display strong efficacy results in trials targeting an obesity indication and not a sub-effect from other metabolic clinical studies.

Novo Nordisk is one diabetes company that has recently announced its desire to expand into other metabolic indications; and it is likely other big diabetes firms will follow this route. Increasing competition, a tough drug pricing arena and huge improvements in available treatments effecting cure in certain type 2 diabetes patients will push more companies to seek other therapy areas for R&D. Obesity makes a logical sidestep for former diabetes focused companies and will continue to grow as a competitive landscape over the next decade.

Published online 22 November 2016

Data from Datamonitor Healthcare.


**Late-stage Obesity Pipeline Drugs**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>Phase</th>
<th>Target</th>
<th>Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>IONIS-FGFR4Rx</td>
<td>Ionis Pharmaceuticals Inc.</td>
<td>II</td>
<td>Fibroblast Growth Factor Receptor (FGFR)</td>
<td>Unspecified</td>
</tr>
<tr>
<td>setmelanotide</td>
<td>Rhythm Pharmaceuticals Inc.</td>
<td>II</td>
<td>Insulin Receptor/ Melanocortin (MC) receptors</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>OB-E-100</td>
<td>Medlab Clinical</td>
<td>II</td>
<td>Unspecified</td>
<td>Oral</td>
</tr>
<tr>
<td>EMP-16 (acarbose + orlistat)</td>
<td>Empros Pharma</td>
<td>II</td>
<td>Lipase inhibitor / Cholesterol inhibitor</td>
<td>Oral</td>
</tr>
<tr>
<td>LIK-066</td>
<td>Novartis AG</td>
<td>II</td>
<td>Oral sodium-dependent glucose cotransporter (SGLT)-1 and -2</td>
<td>Oral</td>
</tr>
<tr>
<td>Oral HDV Biotin</td>
<td>Diasome Pharmaceuticals Inc.</td>
<td>II</td>
<td>Unspecified</td>
<td>Oral</td>
</tr>
<tr>
<td>GPP-846</td>
<td>Gene PreDiT</td>
<td>II</td>
<td>Nucleotide polymorphisms (SNPs) of GP0044 gene</td>
<td>Oral</td>
</tr>
<tr>
<td>MB-11055</td>
<td>KT&amp;G Life Sciences</td>
<td>II</td>
<td>AMP-activated protein kinase</td>
<td>Unspecified</td>
</tr>
<tr>
<td>langlenatide (SAR-439977; HM-11260C; LAPS-Exd4)</td>
<td>Hanmi Pharmaceutical Co. Ltd.</td>
<td>II</td>
<td>Glucagon-like peptide 1 (GLP-1) receptor</td>
<td>Injectable, subcutaneous</td>
</tr>
<tr>
<td>Invokana (canagliflozin)</td>
<td>Johnson &amp; Johnson</td>
<td>II</td>
<td>sodium-dependent glucose cotransporter (SGLT)</td>
<td>Oral</td>
</tr>
<tr>
<td>obinepitide</td>
<td>7TM Pharma AS</td>
<td>II</td>
<td>Neuropeptide Y (NPY)/Peptide YY (YY) Receptors</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>SAR439977 (efpeglenatide)</td>
<td>Sanofi</td>
<td>II</td>
<td>Glucagon-like peptide 1 (GLP-1) Receptor</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>tesofensine</td>
<td>Saniona AB in collaboration with Medix Inc.</td>
<td>II [plans to initiate Phase III]</td>
<td>Dopamine/norepinephrine (Noradrenaline)/serotonin receptors</td>
<td>Oral</td>
</tr>
<tr>
<td>Sarconeos BIO-101</td>
<td>Biophytis</td>
<td>II</td>
<td>MAS receptor</td>
<td>Oral</td>
</tr>
<tr>
<td>Oral HDV-1</td>
<td>Diasome Pharmaceuticals</td>
<td>II</td>
<td>Insulin Receptor</td>
<td>Oral</td>
</tr>
<tr>
<td>Semaglutide (NN9536)</td>
<td>Novo Nordisk AS</td>
<td>II</td>
<td>GLP-1 Receptor</td>
<td>Subcutaneous</td>
</tr>
</tbody>
</table>

Source: BioMedTracker and Citeline Pharmaprojects

Physicians are beginning to prescribe pharma therapy for weight loss as knowledge of the increases
Actelion Could Succumb To Big Pharma’s Charms

JOHN DAVIS john.davis@informa.com

News that Europe’s largest biotech Actelion is in preliminary discussions with Johnson & Johnson about a transaction has been viewed favourably by investors, and could see the return of mega-merger activity to other big pharma companies.

Switzerland’s Actelion Pharmaceuticals Ltd. has been a reluctant M&A target in the past, unmoved by unconfirmed approaches from several big pharma companies that most recently included Shire PLC in 2015, but this time around worries about growing competition to its key pulmonary arterial hypertension (PAH) therapies might make it more receptive to a deep-pocketed suitor.

Confirmation from the Basel-based biotech on Nov. 25 that it was in preliminary “transaction” talks with Johnson & Johnson were received in a favorable light by analysts and investors, with Actelion’s share price rising 16.8% during that day to CHF184.50 ($182).

Indeed, the idea that other companies might be flushed out to hold M&A discussions with Actelion has also taken hold, with European big pharma’s like Sanofi being mentioned. Because Basel is also the location for the headquarters of Roche and Novartis AG, those companies might be interested in Actelion too, it has been suggested.

Actelion is Europe’s largest biotechnology company and has carved out a lucrative niche for itself over the past decade, developing several drugs for PAH. But it is facing the loss of marketing exclusivity in the US to its top-selling PAH product, Tracleer (bosentan), in 2017.

The Swiss company is currently in the launch phase with two newer PAH therapies, Opsumit (macitentan) and Uptravi (selexipag, in collaboration with Nippon Shinyaku Co. Ltd.). In the first nine months of 2016, sales of the newer PAH therapies were catching up with those of Tracleer; Opsumit and Uptravi sales were CHF596m and CHF160m, respectively, while revenues from Tracleer were down by 18% at CHF790m.

Tracleer is already facing competition from generic bosentan in some European markets, for instance in Spain where pricing competition has led to an 82% decline in Tracleer sales, Actelion reported during its 2016 third-quarter earnings call with analysts on Oct. 20. Loss of marketing exclusivity is expected in other European countries in August 2017, following the expiry of six months of market protection because of pediatric use. And in the US, generic bosentan is expected to enter the market in the first quarter of 2017, where “aggressive net pricing” is expected by generic manufacturers, Actelion noted.

On the face of it, Johnson & Johnson seems an unlikely acquirer; it has not engaged in a Pharma-based mega-merger for some time, preferring to acquire products rather than companies, or smaller biotechs with a handful of promising products. But as Swiss newspapers commented over the weekend, J&J has been an active acquirer in the country’s medical technology space, buying the Swiss/US orthopedics company Synthes Inc. in 2011 for €1bn, and it is the largest US employer in the country.

The CEO and co-founder of Actelion, Jean-Paul Clozel, has expressed in the past an unwillingness for the company to lose its independence. But there have been signs Actelion might be facing a more uncertain future than previously thought. Increasing competition in the PAH market from Gilead Sciences Inc’s Letairis (ambrisentan) and from generic bosentan was the subject of questions from analysts during the third-quarter earnings call.

Still, Actelion is seen as a desirable target. “The highly profitable and long life-cycle PAH franchise is likely attractive,” said analysts at Jefferies in a Nov. 28 note. The robust long-term data, established patient base, orphan indication, and potential use in niche indications of its PAH drugs could all mitigate the impact of generic erosion. There might also be overlooked pipeline opportunities, they add. The lowest takeout value of Actelion could be more than CHF240 per share.

Others put the emphasis on the Swiss company’s R&D efforts. J&J may have seen value in Actelion’s R&D pipeline beyond PAH, that might have triggered the merger interest from the US company, Deutsche Bank analysts said. During Actelion’s 2016 third-quarter call, Clozel said the company’s strategy of diversifying its activities into new therapeutic areas was bearing fruit, and in a few years, “you will see a different Actelion than what we have today.”

Clozel pointed to the investment the company has made in discovery, including new laboratories and a clinical development engine.

Published online 28 November 2016
molecules to slow biosimilar erosion to a limited extent, such as Roche’s subcutaneous Rituxan and Herceptin formulations, and Amgen’s wearable delivery of Neulasta.”

Roche’s top-three sellers – Rituxan, Herceptin (trastuzumab) and Avastin (bevacizumab) – all are expected to face biosimilar competition by 2019, Morningstar states, but the Swiss pharma is “doing an excellent job of extending franchises with new products” including Perjeta (pertuzumab) and Gazyva (obinutuzumab).

Meanwhile, Morningstar cites a widely promising pipeline, led by immuno-oncology with Tecentriq, which the report says will battle earlier entrants Opendo (nivolumab) and Merck & Co. Inc.’s Keytruda (pembrolizumab) with first-to-market positioning in bladder cancer, as well as reasons for optimism in other therapeutics areas such as multiple sclerosis with Ocrevus (ocrelizumab), hemophilia withemicizumab and geographic atrophy with lampalizumab.

Morningstar attributes some of BioMarin’s strength to “intangible” patent protection that results from the small patient bases and, therefore, sales potential of its enzyme-replacement therapies, such as Vimizim (elosulfase alpha) for Morquio A Syndrome, as well as the fact that such products are less susceptible to patient switching due to their life-saving nature and the typically strong relationship between company and patient.

The report concedes that Sanofi and Shire PLC also benefit from these factors, but only a portion of their portfolios enjoy this set of protections, whereas BioMarin’s entire portfolio to date fits into that footprint.

While Sanofi will enjoy the protected position of the rare disease drugs from its Genzyme Corp. division, Morningstar projects modest five-year growth for the French pharma due to the patent exposure of diabetes blockbuster Lantus and a late-stage pipeline centered on two assets viewed as offering modest sales potential – the Phase III atopic dermatitis candidate Dupixent (dupilumab) and sarilumab, a rheumatoid arthritis candidate that received an FDA complete response letter in October.

**INLINE PRODUCTS VS. PIPELINE**

Bristol’s main strength is inline business; Morningstar sees Bristol’s five-year prospects tied primarily to its PD-1 inhibitor Opendo (nivolumab) and anticoagulant Eliquis (apixaban). Despite its clinical failure in first-line non-small cell lung cancer this past October, Opendo will be the core driver of revenue during 2015-2020 as it adds indications and starts to be used in combination regimens, while Eliquis will increase market share due to best-in-class characteristics, the report says.

Those two drugs, however, will have to stave off the impacts of several pending patent expirations for Bristol – Baraclude (entecavir) in 2016, and in 2017 Sustiva (efavirenz) and Reyataz (atazanavir) – as well as a relatively thin late-stage pipeline. “With all the focus on Opendo, Bristol’s remaining pipeline is minimal,” the report says. “For a company of Bristol’s size, the high concentration on one drug is concerning, and increases the company’s uncertainty.”

At Lilly, the prognosis is somewhat reversed. Although the Indianapolis pharma does face a host of near-term patent expirations, such as Cialis (tadalafil) and Straterra (atomoxetine) next year, Morningstar sees the pipeline as the source of growth. The near-term pipeline includes the recently approved psoriasis drug Taltz (ixekizumab), under Morningstar’s definition, with baricitinib bolstering the immunology strength suggested by Taltz. Morningstar’s projections, however, also include significant hopes for Lilly’s Alzheimer’s disease candidate solanezumab, which suffered a massive failure since the report was compiled.

A broad-based diabetes franchise, however, should offer Lilly some revenue stability among inline portfolio assets, Morningstar suggests. “The insulin franchise and animal health sales drive steady growth, and impressive outcomes data for Jardiance should drive leadership in the increasingly important SGLT-2 class,” the report says. “Also, Lilly is the only firm with drug representation across all major diabetes classes, which may help in contract negotiations with payers.”

**PATENT CLIFF STILL IN ACTION**

Amgen’s five-year prospects are hindered by headwinds from the 2015 patent expirations of its three-drug erythropoietin franchise – EpoGen, Neupogen and Neulasta – which Morningstar predicts will lead to $5bn in potential revenue losses to biosimilar competition during 2015-2020. On the positive side, the big biotech could bring in $2bn over the five years from its own biosimilars products – of Roche’s Rituxan and Herceptin, with potential EU launches in 2017, and of AbbVie Inc.’s Humira (adalimumab) in 2018.

AstraZeneca is being buffeted by the worst of its patent cliff at present but Morningstar projects its revenue situation to stabilize by 2018. This will be bolstered by a pipeline derived both internally and via business development, which has been focused on oncology, immunology and respiratory therapies, the report says.

---

Large-Cap Biopharmas’ Prospects For Growth, 2015-2020

<table>
<thead>
<tr>
<th>COMPANY</th>
<th>INLINE PRODUCTS</th>
<th>PATENT EXPOSURE</th>
<th>PIPELINE</th>
<th>FIVE-YEAR REVENUE GROWTH %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BEST-POSITIONED</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BioMarin</td>
<td>97</td>
<td>0</td>
<td>132</td>
<td>229</td>
</tr>
<tr>
<td>Bristol-Myers Squibb</td>
<td>86</td>
<td>–21</td>
<td>3</td>
<td>68</td>
</tr>
<tr>
<td>Eli Lilly</td>
<td>32</td>
<td>–28</td>
<td>41</td>
<td>45</td>
</tr>
<tr>
<td>Roche</td>
<td>23</td>
<td>–17</td>
<td>25</td>
<td>32</td>
</tr>
<tr>
<td><strong>WORST-POSITIONED</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sanofi</td>
<td>16</td>
<td>–14</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Amgen</td>
<td>16</td>
<td>–23</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>18</td>
<td>–34</td>
<td>19</td>
<td>3</td>
</tr>
<tr>
<td>Gilead</td>
<td>–41</td>
<td>–9</td>
<td>25</td>
<td>–5</td>
</tr>
</tbody>
</table>

- Columns depict change in revenue from 2015 to 2020 as a percentage of 2015 revenue.
- Inline products defined as those launched before 2016 and not facing patent expiry during 2015-2020.
- Pipeline depicts revenue from products launched during 2016 or later.

Source: Healthcare Observer, November 2016, Morningstar Institutional Equity Research
Pfizer’s Avelumab Poised For Speedy Review By FDA

Avelumab could be the fourth PD-1/L1 inhibitor to reach the market now that the US FDA has accepted Pfizer’s and Merck KGaA’s BLA for priority review in the treatment of metastatic Merkel cell carcinoma.

JESSICA MERRILL jessica.merrill@informa.com

Pfizer Inc. and Merck KGAA’s PD-L1 inhibitor avelumab appears on track to be the fourth anti-PD-1/L1 antibody to reach the market and the first for metastatic Merkel cell carcinoma. The companies announced Nov. 29 that a BLA for avelumab was accepted for priority review for the treatment of metastatic MCC, positioning the cancer immunotherapy for FDA approval in the first part of 2017.

Avelumab is the cornerstone of Pfizer’s strategy to become a leader in the field of immuno-oncology and getting the drug on the market next year is an important catalyst for the initiative. Pfizer is studying avelumab in dozens of clinical trials in as many as 15 indications, including gastric, ovarian, renal and lung cancer. The company’s long-term focus is on combinations involving avelumab as a backbone, the area in which Pfizer believes it can catch up to immuno-oncology leaders like Merck & Co. Inc., Bristol-Myers Squibb Co. and Roche. Pfizer has said it expects to have a total of 10 IO assets in clinical development by the end of the year.

The FDA has approved three other PD-1/L1 inhibitors and multiple new indications for the treatments under the six-month review clock established for priority reviews. Opdivo, Merck’s Keytruda (pembrolizumab), and Roche’s Tecentriq (atezolizumab) are the first PD-1/L1 inhibitors to reach the market. Together, they are approved across a range of indications including metastatic melanoma, non-small cell lung cancer, classical Hodgkin’s lymphoma, renal cancer and bladder cancer. In lung cancer – considered to be the largest single potential indication for cancer immunotherapy – Merck’s Keytruda has recently gained the upper hand with FDA approval Oct. 24 for first-line NSCLC.

When it comes to combinations, however, the only approved PD-1/L1 combination, is for certain melanoma patients who may be treated with Opdivo and Bristol’s other checkpoint inhibitor, the CTLA4 inhibitor Yervoy (ipilimumab).

Approval for avelumab under a six-month priority review would position Pfizer and Merck KGaA ahead of AstraZeneca PLC, which is developing durvalumab and had hoped it might be the fourth PD-1/L1 inhibitor available in the US. The UK-based big pharma ran into trouble with its immunotherapy combination strategy with a recent clinical hold on a head and neck cancer study.

Now avelumab appears poised to enter the already crowded market, though the initial approval would be for a rare and aggressive skin cancer that impacts only 2,500 people in the US each year. There are currently no approved treatment options for MCC. The filing is based on the JAVELIN Merkel 200 clinical trial, a Phase II study that enrolled 88 patients who were treated with avelumab. Median PFS in the trial was 2.6 months and the PFS rate at six months was 36%.

Pfizer has made substantial strides in oncology, part of a strategy that has evolved over nearly 10 years with the establishment of a dedicated oncology unit in 2008. The company has had success with targeted drugs, like Sutent (sunitinib) for kidney cancer and Xalkori (crizotinib) for a limited set of ALK-positive NSCLC patients.

The company acquired rights to avelumab, then in early clinical development, through a deal signed with Merck in November 2014, under which the company agreed to pay $850m up front plus $2bn in potential milestones.

Avelumab appears poised to enter the already crowded market, though the initial approval would be for a rare and aggressive skin cancer

But it was the launch of Ibrance (palbociclib), the first-in-class CDK4/6 inhibitor that launched in early 2015, that marked a turning point for Pfizer’s oncology efforts, with the drug on its way to becoming a blockbuster in its first full year on the market.

The company gained another blockbuster oncology franchise earlier this year with the $14bn acquisition of Medivation Inc., which added the prostate cancer drug Xtandi (enzalutamide) to the portfolio, though it shares rights with Astellas Pharma Inc.

Despite its acquisitions, development wins and its new blockbuster franchise, succeeding in immuno-oncology is a notch Pfizer still needs to add to its belt to convince skeptics that the company, with a history and reputation of working in primary care, has the focus and expertise to lead in oncology. Pfizer recently decided against breaking up the company too, so it needs to show that size won’t inhibit the company from working quickly and nimbly in the fast-paced field of immuno-oncology.

Published online 29 November 2016
Trump Win Is False Security For Drug Makers, Allergan CEO Warns

JESSICA MERRILL jessica.merrill@informa.com

Industry should act on drug pricing now while there is a post-election reprieve, Allergan CEO Brent Saunders said during the Forbes Healthcare Summit. Trump is a populist who will jump on the next big pricing scandal, he said.

Allergan PLC CEO Brent Saunders warned pharmaceutical manufacturers not to let the election of Donald Trump as president of the US to result in a false sense of security across the industry when it comes to the public controversy over high drug prices.

"I worry today that the pharma industry has a very false sense of relief or security because of a Trump administration and Republican-controlled Congress," Saunders said, speaking during a panel on drug pricing during the Forbes Healthcare Summit in New York City Dec. 1.

Trump won the election on a populist campaign and the drug pricing issue is a populist issue, he reminded industry. Debate over the cost of pharmaceuticals is not likely to abate because many Americans are "rightfully angry," Saunders said.

"To think President Trump isn’t a populist, that he won’t jump on the next Epipen scandal and tweet more on a pricing scandal than Hillary Clinton tweeted or anybody else…you are fooling yourself," he said.

What the drug industry does appear to have won is a short reprieve to address drug pricing without government intervention, Saunders added.

"We have a little bit of time to solve it ourselves, but we don’t have a lot of time," he said. "The next big scandal will revive the debate."

The Allergan chief executive also published a corresponding article on Forbes’ website advocating for self-governance, outlining an expansion of Allergan’s previous-announced social contract with patients that will increase eligibility in its patient assistance program for more than 40 medicines to include patients earning up to four times the federal poverty level and five times the poverty level for certain complex medicines.

Allergan has been one of the more vocal drug manufacturers when it comes to addressing the issue of high drug costs. In September, the company vowed not to engage in predatory pricing and promised to limit cost increases to single-digit percentages taken no more than once per year.

But while Saunders urged other drug makers to develop their own social contracts, he said that is only part of the solution.

“All participants in the pharmaceutical distribution chain and the larger health care chain have to step back and look at what can they do to honor what they believe their social contract is,” he said.

Express Scripts Holding Co. chief medical officer Steve Miller was the other participant on the stage and he agreed that the steps Allergan has announced are just the beginning. Meanwhile, Saunders called out pharmacy benefit managers like Express Scripts to do their part too.

The two discussed whether the use of rebates to negotiate drug prices and secure premium real estate on formularies has changed in a way that should be reevaluated. Drug manufacturers provide rebates to insurers that reduce the list price of their drugs but also results in a lack of transparency about the actual cost of medicines.

“It works most of the time,” Miller said of rebates. "The trouble is when you have a high deductible health plan." Then, patients have to front the initial cost under their deductible, which can be thousands of dollars. "High deductible plans are created for rich people and they are sold for poor people," he said.

Saunders said rebates, over the last decade, have morphed into something beyond their initial function. "Do we need to step back and look at that system and say is it functioning as we intended? Absolutely," he said. But he added that the system is not fundamentally broken.

Published online 1 December 2016

AstraZeneca Puts Bicycles To Work In Multitarget Deal

Bicycle Therapeutics Ltd., led by ex-Pfizer executive Kevin Lee, will be using its bicyclic product platform to identify ‘Bicycles’ for an undisclosed number of targets specified by AstraZeneca PLC. The big pharma will be responsible for further development and product commercialization. The targets will cover respiratory, cardiovascular and metabolic diseases.

If all planned programs reach the market, Bicycle is eligible for over $1bn in payments, including an upfront, R&D funding, development, regulatory and commercialization milestones. Bicycle would also be entitled to royalties.

Bicycle’s core focus is on oncology, so expanding outside this area is good for the small biotech. In addition, this is the biotech’s first major collaboration and brings its technology validation. “This collaboration is a testament to the broad applicability of Bicycles and the robust platform we have created,” said Lee. “This is a broad partnership between two entrepreneurial and innovative companies, as illustrated by the collaborative deal structure we have put in place. Bicycle’s focus so far has been in oncology and bringing AstraZeneca’s expertise in respiratory, cardiovascular and metabolic disease to their platform substantially expands its potential,” added Kumar Srinivasan, Vice president, Scientific Partnering and Alliances, Innovative Medicines and Early Development Biotech Unit at AstraZeneca.

Bicycles are small molecules which exhibit an affinity and target specificity usually associated with antibodies, while a low molecular weight enables quick and deep tissue penetration enabling more efficient tumour targeting, according to Lee. Their peptidic nature provides a “tunable” pharmacokinetic half-life and a renal route of clearance, avoiding the liver and gastrointestinal tract toxicities often seen with other drug modalities.

sukaina.virji@informa.com, 2 Dec 2016
Merck’s Keytruda Wins NSCLC Edge Over BMS’ Opdivo

New draft guidance from NICE, the health technology appraisal institute for England and Wales, recommends Merck & Co. Inc.’s PD-1 inhibitor Keytruda (pembrolizumab) for some non-small cell lung cancer patients. The news could put Keytruda ahead of its rival and fellow PD-1 inhibitor from Bristol-Myers Squibb Co.’s, Opdivo (nivolumab), which has so far failed to secure a positive recommendation from the institute. NICE is now recommending Keytruda for treating locally advanced or metastatic PD-L1-positive non-small-cell lung cancer in adults who have had at least one chemotherapy (and targeted treatment if they have an epidermal growth factor receptor or anaplastic lymphoma kinase positive tumor). The recommendation, however, depends on a confidential discount on Keytruda’s list price. In addition, treatment with Keytruda must stop after two years if the patient’s disease has not worsened. The guidance is to be reviewed again in two years when more data is available. In October, NICE had rejected the drug because its appraisal committee was concerned that there were not enough “robust” data on the drug’s long-term benefits. It also pointed out that the company was assuming that patients stopped using Keytruda after two years if their disease has not worsened. NICE thought that in clinical practice this would be very unlikely, which meant the drug would not be cost-effective. “Even when making assumptions about the value of using pembrolizumab beyond two years, our lowest estimates showed it would be over the range of what we normally consider cost-effective,” said director of the centre for health technology evaluation Carole Longson at the time. However, Merck came back with more analysis of trial data, and crucially, a further discount on the drug. “The company put forward a fairly priced proposal that reflected the benefits their drug offered. If companies work with us to price drugs reasonably and manage any uncertainties in the evidence base, we can continue to recommend patients have routine access to the treatments they need,” said Longson.

NICE Gives Nucala Initial OK In Severe Asthma After GSK Offers Price Cut

An undisclosed price discount offered by GlaxoSmithKline PLC has opened the way for severe asthma patients in England and Wales to access Nucala (mepolizumab), the first biologic treatment to target specific white blood cells called eosinophils which are responsible for symptoms in thousands of asthma patients. The Dec. 1 announcement by the UK HTA reverses NICE’s earlier stance when its independent appraisal committee declined to recommend Nucala on evidence presented by GSK “suggesting the drug would be used in less severe cases of asthma and would not therefore be cost effective,” the National Institute for Health and Care Excellence said in a statement. But the UK’s biggest drug maker then provided further analyses on its use, alongside an additional price reduction, which clinched this latest backing. The director of NICE’s center for health technology evaluation Carole Longson said some 100,000 people in England and Wales suffer from severe asthma which cannot be controlled with current regular medicines. Some have their condition caused by high levels of eosinophils, producing the signal molecule IL-5 which in turn protects and promotes creation of eosinophils. Nucala (mepolizumab) stops IL-5 from working and thus helps reduce the number of eosinophils in the airways. “Many of these people will soon have access to an extra treatment option to help them take control of their asthma,” Longson said, indicating an assumption that NICE is now minded to give Nucala final approval. GSK welcomed the news.

Shionogi/Merck HIV Patent Tussle Set To Go Another Round

A continuing spat in Europe over HIV drug-related intellectual property involving Japan’s Shionogi & Co. Ltd. and Merck & Co. Inc. is showing no signs of resolution following the first court decision in the affair. A UK patent court ruled on Nov. 25 that Shionogi’s UK patent number UK 60242459.3 was not valid “due to not satisfying the description requirement.” Such descriptions generally form an important basis for granting protection as they describe in detail the innovative and distinguishing nature of the invention. The intellectual property involved is possessed solely by Shionogi and not related to that held jointly with HIV partner GlaxoSmithKline PLC for the marketed integrase inhibitor Tivicay (dolutegravir), the Japanese company stressed, without providing further details. Its contretemps with Merck began in August last year when Shionogi filed a patent infringement action in a district court in Dusseldorf, Germany against Merck Sharp & Dohme Ltd.’s German subsidiary and European group companies, claiming that the US company’s marketed integrase inhibitor Isentress (raltegravir) infringed Shionogi’s German patent DE 60242459.3. A few days later, MSD in the UK than brought a suit in the UK patent court seeking revocation of Shionogi’s patent in that country. Shionogi responded with a counter-claim in the same court this May alleging that Isentress infringed the patent.
GOLD Pushes LABA/LAMAs In New COPD Update

New guidelines for the treatment of COPD could change the way this serious condition is managed, with knock-on effects for pharma companies with respiratory franchises.

SUKAINA VIRJI sukaina.virji@informa.com

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has published its first update in five years on treatment recommendations. It now favors fixed-dose LABA/LAMA combinations over ICS/LABA combinations in the treatment of COPD.

The previous GOLD guideline, published in 2011, recommended the use of either a LABA/LAMA or ICS/LABA in the majority of COPD patients.

Novartis AG’s publication of data from the FLAME study comparing its Ultibro Breezhaler with GlaxoSmithKline PLC’s Advair/Seretide in reducing COPD exacerbations was likely a significant catalyst in changing the guidelines.

The FLAME study found that Novartis’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 GSK’s aging blockbuster Advair/Seretide, which combines the ICS inhaled glucocorticoid fluticasone with the LABA salmeterol, in terms of fewer disease flare-ups.

Evidence has been available for some time that that LABA/LAMAs are more appropriate for non-exacerbating patients compared to ICS/LABAs.

“We have long highlighted our preference for the LABA/LAMA class [and] questioned the chronic use of ICS in COPD patients with a lung function exceeding 60% of the expected. It has only proven beneficial in the most severely affected patients,” Dr Jens Lindqvist, an analyst with N+1 Singer, told Scrip.

There are four LAMA/LABAs on the market, and they often face differing dose regimens. This first regulatory submission of our closed triple therapy brings us a step closer to providing a once-daily treatment in a single Ellipta inhaler as an alternative option for those patients who require multiple therapies.”

A GSK spokesperson added: “What we have taken from this is that GOLD are moving towards a broader definition of COPD that recognizes the heterogeneity in how people with COPD present to their doctor and how their condition progresses. In this update GOLD recommend an individualized treatment approach, based on assessment of patient needs and not a one-size fits all approach.”

The spokesperson continued: “In their [new] guideline, GOLD have highlighted the role of spirometry - using FEV1 to inform diagnosis and prognosis, but not to inform the patient classification grid (A, B, C, D) which is based on level of symptoms [using mMRC and CAT scores], and exacerbation risk. This continuing move to a more personalized approach to treatment, focusing on reducing symptoms and exacerbation risk, is very aligned with our strategy at GSK.”

Datamonitor Healthcare analyst Christina Vasiliou told Scrip that, “Generally, physicians note that there was a lack of clarity in the previous GOLD recommendations, which led to mixed implementation of the guidelines and prescribing practices.” She believes that the new GOLD strategy will drive the use of LABA/LAMA therapies, especially among physicians that were previously skeptical about the role or positioning of these therapies in the management of COPD.

Published online 28 November 2016
Celebrating the best in health

A momentous night for the pharma and biotech industry - the 12th annual SCRIP Awards, held on 30th November at Grosvenor House Hotel, Park Lane, London.

We would like to thank everyone who attended. The night, hosted by broadcaster Jeremy Vine, was a great celebration of success stories and was enjoyed by over 400 guests from across the pharma and biotech community.

The Scrip Awards provides the industry with an opportunity to acknowledge and applaud its highest achievers across all parts of the value chain, and to recognise both corporate and individual achievement.
The winners

**Lifetime Achievement**
Raymond Schinazi

**PPD’s Pharma Company of the Year**
Shire

**HUYA Bioscience International’s Best New Drug Award**
Sanofi Pasteur’s Dengvaxia

**Management Team of the Year**
Genmab’s Core Leadership Team

**Executive of the Year**
Brent Saunders, president and CEO of Allergan

**Licensing Deal of the Year**
Galapagos and Gilead Sciences for filgotinib in inflammatory diseases

**Community Partnership of the Year Award**
GlaxoSmithKline’s Newborn Survival Project

**WuXi AppTec’s Biotech Company of the Year Award**
Genmab

**Best Partnership Alliance**
(Associated with INC Research)
AstraZeneca and Human Longevity’s genomic partnership

**Best Company in an Emerging Market**
(Sponsored by ICON)
Mundipharma Singapore (Singapore)

**QuintilesIMS’ Clinical Advance of the Year Award**
Summit Therapeutics’ Phase II CoDIFy study of ridinilazole in Clostridium difficile infection

**Financing Deal of the Year**
(Sponsored by EBD)
Immunocore’s $320m series A financing

**Best Contract Research Organization**
(Niche providers)
Altasciences Clinical Research

**Best Contract Research Organization**
(Full service providers)
QuintilesIMS

**Best Technological Development in Clinical Trials**
(Sponsor-focused)
Medidata Solutions’ Medidata Payments

**Best Technological Development in Clinical Trials**
(Patient-focused)
AiCure’s artificial intelligence DOT smartphone app

**Best Company in an Emerging Market**
(Sponsored by ICON)
Mundipharma Singapore (Singapore)

**Executive of the Year**
(Sponsored by Lachman Consultants)
Brent Saunders, president and CEO of Allergan

**Licensing Deal of the Year**
(Sponsored by Worldwide Clinical Trials)
Galapagos and Gilead Sciences for filgotinib in inflammatory diseases

**Community Partnership of the Year Award**
(Sponsored by Medidata)
GlaxoSmithKline’s Newborn Survival Project

**WuXi AppTec’s Biotech Company of the Year Award**
Genmab
A National Health Service spending report reveals the top 20 most expensive NICE approved drugs in England for 2016.

AbbVie Inc’s Humira (adalimumab) has topped NHS England’s drug spending charts for the 2015/2016 period, with a £416.6m price tag. The drug is used in England to treat autoimmune disorders, such as arthritis, psoriasis and Crohn’s disease. Within just the primary care setting the most expensive medicine for the NHS from 2015/2016 was Bayer AG’s Xarelto (rivaroxaban). Humira added the greatest cost in the secondary care setting and was the most expensive drug prescribed in hospitals but dispensed in the community – adding to its high overall cost to the national health body.

The table below shows the top 20 medicines positively appraised by NICE with the greatest total cost – combining primary care, secondary care and community prescription costs in 2015/2016. Seven of the top 20 most expensive drugs for the NHS have cancer indications listed as their most recently recommended uses, as assessed by NICE. Some novel cancer therapeutics have struggled in recent years to get listed on the NHS for regular use due to their high costs.

### NHS SPENDING TRENDS

In total NHS England expenditure on medicines increased 8%, to reach £16.8bn, for the 2015/2016 period compared to the prior year, according to data released in a new NHS Digital report titled *Prescribing Costs in Hospitals and the Community*.

Broken down, this figure would mean around £307 was spent per person over the 2015/2016 period; the population of England is approximately 54.7 million according to 2015 government statistics.

NHS drug spending has been steadily increasing in England: for the 2010/2011 period the national health body spent £13bn on medicines; this rose to £15.5bn by 2014/2015. Of this year’s total £16.8bn spent on pharmaceuticals, almost half (£7.6bn) was for hospital use, while £9bn was spent on primary care prescribed medicines and £150m was spent on hospital prescribed medicines dispensed in the community.

### Top 20 NICE-Approved Medicines By Greatest Total Cost 2015/2016

<table>
<thead>
<tr>
<th>DRUG NAME</th>
<th>ORIGINATOR COMPANY</th>
<th>MOST RECENTLY APPRAISED INDICATION</th>
<th>SECTOR WHERE HIGHEST COST IS INCURRED</th>
<th>TOTAL COST (£K)</th>
</tr>
</thead>
<tbody>
<tr>
<td>adalimumab</td>
<td>AbbVie</td>
<td>ankylosing spondylitis and nonradiographic axial spondyloarthritis</td>
<td>secondary care</td>
<td>416,647.8</td>
</tr>
<tr>
<td>ranibizumab</td>
<td>Roche</td>
<td>choroidal neovascularisation associated with pathological myopia</td>
<td>secondary care</td>
<td>248,975.9</td>
</tr>
<tr>
<td>etanercept</td>
<td>Amgen Inc.</td>
<td>ankylosing spondylitis and nonradiographic axial spondyloarthritis</td>
<td>secondary care</td>
<td>230,588.3</td>
</tr>
<tr>
<td>aflibercept</td>
<td>Sanofi/ Regeneron Pharmaceuticals Inc.</td>
<td>diabetic macular oedema</td>
<td>secondary care</td>
<td>198,268.4</td>
</tr>
<tr>
<td>infliximab</td>
<td>Johnson &amp; Johnson</td>
<td>rheumatoid arthritis</td>
<td>secondary care</td>
<td>178,179.2</td>
</tr>
<tr>
<td>rituximab</td>
<td>Roche</td>
<td>anti-neutrophil cytoplasmic antibody-associated vasculitis</td>
<td>secondary care</td>
<td>155,893.3</td>
</tr>
<tr>
<td>trastuzumab</td>
<td>Roche</td>
<td>metastatic gastric cancer</td>
<td>secondary care</td>
<td>152,037.6</td>
</tr>
<tr>
<td>lenalidomide</td>
<td>Celgene Corp.</td>
<td>myelodysplastic syndromes</td>
<td>secondary care</td>
<td>141,840.4</td>
</tr>
<tr>
<td>Xarelto (rivaroxaban)</td>
<td>Bayer</td>
<td>acute management of acute coronary syndrome</td>
<td>primary care</td>
<td>106,586.8</td>
</tr>
<tr>
<td>imatinib</td>
<td>Novartis AG</td>
<td>gastrointestinal stromal tumors</td>
<td>secondary care</td>
<td>89,067.7</td>
</tr>
<tr>
<td>enzalutamide</td>
<td>Astellas Pharma Inc.</td>
<td>metastatic hormone-relapsed prostate cancer</td>
<td>secondary care</td>
<td>86,360.4</td>
</tr>
<tr>
<td>insulin glargine</td>
<td>Sanofi</td>
<td>type 1 and type 2 diabetes</td>
<td>primary care</td>
<td>81,629.9</td>
</tr>
<tr>
<td>ledipasvir-sofosbuvir</td>
<td>Gilead Sciences Inc.</td>
<td>chronic hepatitis C</td>
<td>secondary care</td>
<td>81,054.7</td>
</tr>
<tr>
<td>buprenorphine</td>
<td>multiple forms used</td>
<td>drug misuse</td>
<td>primary care</td>
<td>76,728.9</td>
</tr>
<tr>
<td>abiraterone</td>
<td>Johnson &amp; Johnson</td>
<td>second-line castration-resistant metastatic prostate cancer</td>
<td>secondary care</td>
<td>74,148.7</td>
</tr>
<tr>
<td>sofosbuvir</td>
<td>Gilead</td>
<td>chronic hepatitis C</td>
<td>secondary care</td>
<td>73,443.0</td>
</tr>
<tr>
<td>tacrolimus</td>
<td>Astellas</td>
<td>renal transplant</td>
<td>secondary care</td>
<td>71,435.0</td>
</tr>
<tr>
<td>docetaxel</td>
<td>Sanofi</td>
<td>breast cancer</td>
<td>secondary care</td>
<td>66,654.8</td>
</tr>
<tr>
<td>dimethyl fumarate</td>
<td>Biogen Inc.</td>
<td>relapsing-remitting multiple sclerosis</td>
<td>secondary care</td>
<td>64,178.5</td>
</tr>
<tr>
<td>paclitaxel</td>
<td>Celgene</td>
<td>ovarian cancer</td>
<td>secondary care</td>
<td>61,298.3</td>
</tr>
</tbody>
</table>
MedImmune, Abpro’s Unspecific Plans For Bispecific Antibody Collaboration

Possibly reflecting a tightening of focus at MedImmune LLC, the biologics division of AstraZeneca PLC announced an agreement Nov. 29 with Abpro Labs to co-develop a preclinical bispecific antibody that targets both angiopoietin-2 (Ang2) and vascular endothelial growth factor (VEGF). No financial terms were disclosed and the companies aren’t talking about specific indications for the MedImmune-discovered antibody. The agreement will establish a spinout called AbMed, to be operated on a day-to-day basis by Woburn, Mass.-headquartered Abpro, whose focus is on synthetic biology. In an interview, Abpro CEO Ian Chan said the goal is to advance the antibody into Phase I studies by the end of 2017 or early 2018 by applying his firm’s DiversImmune technology platform to optimize the candidate for development. He would not specify which indications AbMed will investigate with the antibody, saying only that the new company would focus on “some of the largest indications that have an impact on the quality of life for patients. There is a very large number of indications that the molecule can be applied to.” “This is a great way for both companies to really maximize resources and combine them in a very collaborative manner,” he told Scrip. “It allows us to have greater focus than a traditional kind of structure.”

joseph.haas@informa.com, 29 Nov 2016

SillaJen IPO Priced Low But Hopes High As Pexa-Vec Progresses

SillaJen Inc. has priced its shares at the bottom of the proposed band for a domestic initial public offering but has nevertheless drawn robust interest from retail investors who are counting on the potential of the South Ko-

Bussiness Bulletin

New CNS-Focused Biotech Cerevance Launches With Takeda Backing

Cerevance – a company focused on novel therapeutics for neurological and psychiatric disorders – has launched with operations in the US and the UK, after securing investment from Takeda Pharmaceutical Co. Ltd. and Lightstone Ventures. Takeda has granted the startup its recently shuttered Cambridge, UK laboratory site to progress several preclinical and early stage assets targeting central nervous system (CNS) indications. Cerevance, which is based on technology created in the Howard Hughes Medical Institute laboratory of Dr Nathaniel Heintz at the Rockefeller University, has already secured $36m in funding – including a $21.5m series A financing investment from Takeda and Lightstone Ventures, with a representative of each company joining Cerevance’s board of directors. Takeda is also providing other non-cash supports to the company. Takeda said it was “jumpstarting” the new company by supplying a 25-person neuroscience research team from its Cambridge, UK site; including industry veteran Dr Mark Carlton. Takeda is also contributing a fully equipped laboratory space and licenses to a portfolio of preclinical and clinical stage drug programs.

lucie.ellis@informa.com, 2 Dec 2016

The P5 Partnership Starts First Phase III HIV Vaccine Study

When the results of the just-initiated South African study of a combination of Sanofi Pasteur’s and GlaxoSmithKline PLC’s potential HIV vaccines become available in late 2020 or in 2021, it will have taken more than 11 years to confirm and move beyond the results of a moderately successful clinical study of a vaccine approach to preventing AIDS/HIV. But considering the history of other disappointing HIV/AIDS vaccine research stretching back decades, it could be considered time and money well spent. The previous study, the RV144 study, announced modest results in 2009, having been conducted in Thailand by the US Military HIV Research Program and the Thai Ministry of Health. The vaccines used in the RV144 study had an efficacy rate of 31.2% in the 3.5 years of follow-up. The new study aims to build on those results, and will enroll 5,400 men and women in South Africa.
View From The Top: Growing Grünenthal

JO SHORTHOUSE jo.shorthouse@informa.com

As he leaves after 23 years at the firm, outgoing CEO Eric-Paul Pâques talks about Grüntenhal’s growth and strategic priorities under his leadership while its new head, Gabriel Baertschi, brings his own brand of energy.

JO SHORTHOUSE: Has your leadership style changed over the time you’ve been with Grünenthal GMBH?

ERIC-PAUL PÂQUES: My style changed over time simply because I was getting older. I started in an executive position when I was 40; you learn a lot in 30 years and you adapt your behaviors and beliefs. You can be very dogmatic as a young guy and then life teaches you a thing or two and you change. But something of my style which remains is an emphasis on credibility and authenticity.

I believe if we are not credible as leaders, if we are not authentic we will not endure. I ask everybody to be anti-dogmatic. People follow the mainstream so easily and I say, “We have a brain and a gut, and we need to use our brain as far as possible, but when we come at the end of what we can do with our brain then we need to trust our gut.”

JS: What’s been the biggest impact you’ve made on the company in the last three years as CEO?

EPP: Currently 60% of our revenues are generated by products we have discovered and/or developed at Grünenthal. We have been working with partners in the US, we had a very long partnership with Johnson & Johnson and then we moved to Depomed Inc., which is now selling our major product in the US and Canadian markets, tapentadol.

‘I met with Gabriel [Baertschi] and I am very much impressed, not only by his international experience, but also by his energy’

That being said we have decided to move Grünenthal in a direction where, due to our size, we concentrate our action on focused label products. We are not going to go in large broad label indications in moderate to severe pain anymore. These days in Europe, you don’t get a decent reimbursement for that, so that’s why we sharpened our strategy. We are going to focus on small indications in pain, for example Complex Regional Pain Syndrome (CRPS), which has an orphan status with an extremely high medical need.

We want to remain a pain company worldwide while focusing on the non-addressed pain status. And there is a huge need. Look at non-responders: can you imagine that almost half of the patients receiving pain analgesics are poor or non-responders? That’s kind of things we want to address.

The future of a company like Grünenthal is based on innovation. We are not a generic company; we do not want to be a generic company. Since we are a midsize company we can only innovate in very focused areas. We have decided to double our investment in R&D for next year, just to demonstrate that we are highly committed to innovation.

I used to say research is a promise where we very rarely deliver, it’s the nature of R&D in pharma. But despite that, the commitment to invest is extremely high because that’s the only avenue we see for our company.

JS: What achievement are you most proud of at Grünenthal?

EPP: Among other achievements, I’m very proud about having identified the need for abuse deterrent technology in the US. One day I was in New York and in the New York Times there was a big article on misuse of opiates. I returned to Germany and said that we needed to find a solution, and today we cover something like 80-85% of the slow release opiate market in the US with our technology, INTAC.

I’m also very proud about how we have developed our Latin American markets. A few years ago LatAm was one tenth of our sales and now LatAm really is exploding, numerically. These days we are roughly at €500m in terms of revenues and we are moving to bring LatAm at the same level as Europe in terms of top line and bottom line. We want to partner with big pharma in Latin America. We are in many countries which are not of interest for big pharma, and Grünenthal is reliable company there.

JS: What’s your biggest frustration at work within Europe or European healthcare systems?

EPP: My frustration is with the [European healthcare] authorities. The Eu-
Gabriel Baertschi: My Strategic Priorities

“Grüenthal will lose the exclusivity for some core products within the next 10 years, starting with INTAC and ending with Palexia (tapentadol). To compensate this, we must seek to develop a sustainable, risk-diversified innovation portfolio. Grüenthal will keep building up in pain and beyond and close gaps in the pipeline by pursuing external growth. To go beyond pain means to develop additional therapeutic fields and Grüenthal is currently evaluating inflammation, late stage Parkinson’s and several technology platforms. It is essential to keep reaching out to biotech companies, universities and industrial partners. The cooperation with a reliable partner network is crucial if we want to enrich our innovation portfolio.

Business-wise, Grüenthal will strengthen engagement in Latin America. Recently we integrated the Laboratorios Andromaco in Chile and the Almirall portfolio in Mexico. That has given us an even stronger basis in this region and it is our aim to make as much revenue in Latin America as in Europe.

Last, but not least, I want to foster our commercial partnering for the US business and have a closer look at our geographical footprint.

I strive to guide the company through these processes and enable the development of game changing innovation in catastrophic diseases. Grüenthal already achieved to be a more than €1bn company in terms of revenues. It is my goal to work together with my team and all employees to make it a €2bn company.”

ropean Medicines Agency (EMA) has evolved rapidly in a good direction, I’m very pleased about that. Now what’s frustrating all of us is the pricing authorities. Each single country has a different pricing authority and different metrics. What is good in Germany is bad for the French authority, and so on and so forth. It’s frustrating for companies and it’s not good for the patients. If you look at the main drug we have put onto the market in the last three years; Tramal (tramadol), we have been fighting with the authorities in France for four years to get a reimbursement.

**JS:** How involved were you in looking for your replacement and what was the executive board looking for in a new CEO?

**EPP:** I met with Gabriel [Baertschi] and I am very much impressed, not only by his international experience, but also by his energy. We are just starting the implementation of the science base of our strategy and I think it’s time to have a change of generation. We need somebody in the company who will be there in 10 years from now and will make sure that we consistently implement the strategy. We need somebody who will learn the positive and the negative side of each implementation. So I think that now is a really good time to do it, it needs to be done by a young, very dynamic person and I think that’s what we have with Gabriel.

**JS:** What are your hopes for the company as it goes off without your influence?

**EPP:** There are three dimensions. Firstly; I’d like it to keep the pace of the last three years. We have been growing by 15% and we need to keep that going. Secondly; if we do keep growing, then we can invest in R&D as much as we need. In the foreseeable future we should be able to invest at least €400m in R&D. And thirdly; we need to continue to sharpen our R&D effort on focused label indication. We are not big pharma, we cannot go for big indications and there’s plenty of space and plenty of needs which are underserved. That’s where Grüenthal should focus on.

**JS:** What would you like your Grüenthal legacy to be?

**EPP:** I would like to be remembered as somebody very committed. This company has been somehow my life, I have been fighting a lot for this company and I want to be recognized as loyal servant.

Published online 29 November 2016

**BI/Lilly’s Jardiance Is First Diabetes Drug With CV Benefit Claim**

Boehringer Ingelheim GMBH and Eli Lilly & Co. will promote the first-of-its kind cardiovascular mortality risk reduction claim for their type 2 diabetes drug Jardiance (empagliflozin) with a combination of unbranded and branded consumer awareness campaigns and professional detailing to cardiologists.

On Dec. 2, the US FDA approved Jardiance, an SGLT-2 inhibitor, to reduce the risk of cardiovascular death in adults with type 2 diabetes and CV disease.

The supplemental approval makes Jardiance the first type 2 diabetes drug to be labeled for CV risk reduction, giving it a leg up not only on other SGLT-2 inhibitors but also drugs in other antidiabetic classes. The new indication is based on the results from the 7,000-patient EMPA-REG trial, in which empagliflozin demonstrated a 38% reduced risk of CV death and a 32% reduced risk of all-cause mortality.

BI and Lilly have already begun laying the groundwork to promote the new claim. On Nov. 22, the companies launched an unbranded educational campaign about the link between diabetes and heart disease.

Published online 29 November 2016

sue.sutter@informa.com, 2 Dec 2016
MiNA Pursuing The Other Side Of RNA Interference

London biotech MiNA Therapeutics is aiming high with its novel small activating RNA (saRNA) therapeutics, going after the toughest possible patient base in liver disease because, as CEO Robert Habib put it, soaring ambition should be the very purpose of novel technology – to produce transformational results. The privately backed start-up is hoping to offer a therapeutic option for the sickest liver disease patients with a novel technology that has the reverse effect of RNA interference: its small activating RNA (saRNA) therapeutics in theory will up-regulate genes that are turned off, rather than silencing genes as RNAi approaches attempt. During the American Association for the Study of Liver Diseases conference last month in Boston, Habib said MiNA’s lead candidate - Phase I MTL-CEBPA, intended to turn on the CEBP (CCAAT-enhancer binding protein) alpha gene – could provide a therapy for hepatocellular carcinoma patients who also have decompensated cirrhosis. These are patients progressing from liver dysfunction to liver failure who face grim survival prospects. This focus gives MiNA an area of differentiation beyond its novel technology, as most companies addressing nonviral liver disease are focused on addressing fibrosis. A therapy that can halt, slow down or even turn back fibrosis would be of no benefit for the type of patients MiNA hopes to treat, Habib said.

Pfizer’s Herceptin Biosimilar Moving Forward

Pfizer Inc. Dec. 1 said it was “encouraged” by good top-line results from its Phase III pivotal comparative REFLECTIONS B3271002 study of its PF-05280014 biosimilar for treating patients with HER2-positive metastatic breast cancer. The 690-patient study met its primary endpoint and was designed to measure the safety and efficacy of the biologic follow-on versus Genentech Inc.’s Herceptin (trastuzumab). Pfizer, which is seeking new sources of revenue growth, said the Phase III trial showed equivalence in the primary end point versus trastuzumab taken in combination with paclitaxel. That primary endpoint was objective response rate (ORR) by week 25 of study treatment. ORR is defined as the proportion of patients with tumor size reduction of a predefined amount and for a minimum period of time. A separate comparative, randomized, double-blind clinical trial in early breast cancer patients dubbed B3271004 also met its primary endpoint of steady-state C-trough concentrations in patients treated with PF-05280014 and trastuzumab, the company added without elaboration. Herceptin, which generated some $6.6bn in sales for Roche in 2015 is currently approved in the US, EU and other markets for HER2-positive breast cancer and gastric cancer. PF-05280014 is a monoclonal antibody (mAb) that is in development as a potential biosimilar for all currently approved indications of Herceptin.

Arrowhead Misfires: Abandons Clinical Programs

Arrowhead Pharmaceuticals Inc. says it is shifting its focus to programs developed with its subcutaneous platform after abandoning its lead hepatitis B vaccine ARC-520 and two other related intravenous products amid regulatory concerns about toxicity. The company announced late on Nov. 29 that it was dropping development of three clinical intravenous candidates – ARC-520, ARC-521 and ARC-AAT – and refocusing efforts on subcutaneous and extra-hepatic delivery programs. The company now intends to advance two previously unannounced HBV and alpha-1 antitrypsin deficiency (AATD) programs using its subcutaneous platform. Arrowhead said that in light of the platform changes the company will cut its workforce by 30%, including the elimination of its clinical team and part of its research and development team. “These changes will enable us to continue to move quickly with our subcutaneous and extra-hepatic programs and the partnerships that are based on them while extending our cash runway into 2019,” CEO Christopher Anzalone said during a Nov. 29 investor call. FDA placed a clinical hold on Heparc-2004, Arrowhead’s Phase IIb study of ARC-520 in early November. The hold was prompted by deaths at the highest doses in an ongoing non-human primate toxicology study using EX1, Arrowhead’s intravenous, liver-targeted delivery vehicle. This delivery vehicle also is used in ARC-521, which was in Phase I/II for HBV, and ARC-AAT, which was in Phase II for liver disease associated with alpha-1 antitrypsin deficiency. Arrowhead’s stock price tanked on Nov. 30, closing down 67.2% at $1.44 per share. This wasn’t the first time the company ran into trouble with the FDA over ARC-520. The agency put a partial clinical hold on Heparc-2004 in 2015 that was lifted after four months. The decision to discontinue development of EX1-containing programs was based on a number of factors. First, discussions with regulatory agencies and outside experts made it clear that there would be substantial delays in all clinical programs based on EX1 as Arrowhead sought to determine the cause of deaths in the primate study. Anzalone said during the investor call that the company does not know why some primates died at the highest dose of ARC-520 tested in the preclinical study.

sukaina.virji@informa.com, emily.hayes@informa.com, 30 Nov 2016

stcn.stovall@informa.com, 2 Dec 2016
Watson Health And Pfizer Partner To Harness Big Data For Drug Discovery

The advanced data analytics provider IBM Watson Health has signed its first big pharma partner – Pfizer – for a new drug discovery tool, with a focus on immuno-oncology.

JESSICA MERRILL  jessica.merrill@informa.com

T
he advanced data analytics provider IBM Watson Health has signed its first big pharma partner, Pfizer Inc., for a new computational tool called Watson for Drug Discovery. Pfizer will use Watson’s new cloud-based data analytics tool to discover new drugs faster in the area of immuno-oncology, with a focus on discovery of new and unexplored drug targets, potential combination therapies and patient selection strategies.

The companies announced the collaboration Dec. 1 at the Forbes Healthcare Summit in New York City.

Watson Health, established in Cambridge, Mass. in April 2015, has developed analytics solutions for six business areas – life sciences, oncology and genomics, imaging, value-based care, government and Human Health and Services, and consumer health, according to Innovation & chief science officer Shahram Ebadollahi.

The company has announced collaborations with other large pharma partners including Johnson & Johnson, Celgene Corp. and Teva Pharmaceutical Industries Ltd. in other areas and has also aligned with major academic centers including Memorial Sloan Kettering Cancer Center and MD Anderson.

The new drug discovery tool uses natural language processing and cognitive technologies to bring human-level analysis to broad data sets, according to the company.

“If you take any researcher or scientist, the best ones, they probably can read 300 to 400 publications per year, [but] the number of scientific articles are doubling every 18 months,” Ebadollahi said in an interview. “There is no human who can keep up with the volume of such scientific publications.”

Watson for Drug Discovery includes 25 million Medline abstracts, more than 1 million full-text medical journal articles, 4 million patents and is continually updated. It can also incorporate an organization’s private data, so researchers can look both inside and outside the company. “We are empowering the human expert, the scientist who is working on drug discovery type scenarios in immuno-oncology with the capability to let the machine read, distill information and highlight hypotheses that may take the human expert, and a lot of them, a long time to come up with,” Ebadollahi said.

In a statement, Pfizer’s worldwide president R&D Mikael Dolsten said, “With the incredible volume of data and literature available in this complex field, we believe that tapping into advanced technologies can help our scientific experts more rapidly identify novel combinations of immune-modulating agents.”

While the initial partnership with Pfizer is focused on immuno-oncology, Ebadollahi said the applications for Watson for Drug Discovery could be expanded more broadly.

Watson Health’s other pharma collaborations are around other healthcare computing services. For example, the company’s partnership with Celgene is focused on analyzing high volumes of data from sources like electronic medical records and medical claims databases to establish an outcomes and evidence-based drug safety system. The deal with Teva is focused on using Watson’s computing technology to evaluate drugs for repurposing.

And with Johnson & Johnson in January, Watson Health began working with the biotech company’s veterans on a broad initiative to identify, develop and test new treatments for Alzheimer’s disease.

“Together with JNJ, we can look at all the data currently available, as well as what’s available in the future, and use these insights to potentially find a novel approach that could benefit Alzheimer’s patients,” Ebadollahi said.

Watson Health’s other collaborations are focused on areas such as personalized medicine, predictive analytics in clinical trials and lower the cost of care.

All of the currently approved treatments for AD possess a symptomatic mode of action in that they target the cognitive and functional deficits from which patients suffer. Due to the limited efficacy of this approach, there is a high unmet need for more effective treatments that address the actual underlying causes of the disease.

Through the “homing effect,” one of the unique characteristics of stem cells, Nature Cell’s injected autologous cells migrate to the affected AD lesion to directly differentiate and interact with the area, causing trophic or paracrine effects.

Amid Failures

Nature Cell’s Alzheimer’s Therapy Advances Amid Failures

Nature Cell is set to begin a groundbreaking clinical trial in the US of a novel autologous stem cell therapy for Alzheimer’s disease, a new approach likely to gain attention amid other high profile failures in the challenging indication.

The South Korean bioventure Nature Cell Co. Ltd. has received IND approval from the US FDA to start a Phase I/II clinical trial with its novel stem cell-based therapy for Alzheimer’s disease (AD) AstroStem, taking a step forward to challenge a major indication where many multinationals have failed in their race to market a disease-modifying therapy. The new trial will mark the world’s first in which autologous (self-sourced) adipose tissue-derived stem cells will be repeatedly intravenously injected into patients with AD, Nature Cell noted.

The venture plans to begin recruiting patients at two US hospitals from late 2016 and the stem cell research institute of South Korea’s Biostar Group - Nature Cell’s parent company - will manufacture the cells to be used in the US trial.

All of the currently approved treatments for AD possess a symptomatic mode of action in that they target the cognitive and functional deficits from which patients suffer. Due to the limited efficacy of this approach, there is a high unmet need for more effective treatments that address the actual underlying causes of the disease.

Amid Failures

Therapy Advances

Alzheimer's

Nature Cell's

autologous stem cell therapy for Alzheimer's disease, a new approach likely to gain attention amid other high profile failures in the challenging indication.

The South Korean bioventure Nature Cell Co. Ltd. has received IND approval from the US FDA to start a Phase I/II clinical trial with its novel stem cell-based therapy for Alzheimer’s disease (AD) AstroStem, taking a step forward to challenge a major indication where many multinationals have failed in their race to market a disease-modifying therapy. The new trial will mark the world’s first in which autologous (self-sourced) adipose tissue-derived stem cells will be repeatedly intravenously injected into patients with AD, Nature Cell noted.

The venture plans to begin recruiting patients at two US hospitals from late 2016 and the stem cell research institute of South Korea’s Biostar Group - Nature Cell’s parent company - will manufacture the cells to be used in the US trial.

All of the currently approved treatments for AD possess a symptomatic mode of action in that they target the cognitive and functional deficits from which patients suffer. Due to the limited efficacy of this approach, there is a high unmet need for more effective treatments that address the actual underlying causes of the disease.

Through the “homing effect,” one of the unique characteristics of stem cells, Nature Cell’s injected autologous cells migrate to the affected AD lesion to directly differentiate and interact with the area, causing trophic or paracrine effects.
Patient Engagement: How Soon Do You Start?

Julie Adrian, European managing director of inVentiv Health Communications, outlines the greatest barriers preventing companies from engaging patients earlier in drug development and highlights the greatest benefits on offer to those that can successfully implement patient-centric drug discovery models.

LUCIE ELLIS lucie.ellis@informa.com

The pharmaceutical industry has got a handle on new patient engagement models when it comes to marketed drugs, but the sector has more work to do prior to drug approval according to healthcare marketing communications veteran, Julie Adrian, European managing director of inVentiv Health Communications.

According to an Oct. 2015 survey conducted by Accenture Life Sciences and cited by inVentiv Health, which included responses from 200 pharma executives, 85% of those asked have piloted “patient-centric” models within their businesses. 51% said their companies have since widely adopted a patient-centric approach and more than 80% noted that they are continuing to develop their commercial models in this area and are increasing investment in patients services, including new staff hires, investment in analytic services and establishing more partnerships with customers.

InVentiv Health, a global provider of healthcare and pharma consulting to biopharmaceutical clients, believes that patient-centric models will help to bridge the historical gap in biopharma companies between their clinical and commercial activities; and enhance pharma’s reputation among the general public.

However, Adrian told Scrip in a recent interview that biopharma companies still need to increase their levels of patient engagement during clinical development – instead of focusing just on patient-centric commercialization models for new drugs. “We are seeing a tectonic shift in thinking within big and small pharma towards getting the patient voice into development, even as early as product discovery,” Adrian said. She noted this push was coming from clinical teams within biopharma companies: “It’s not the marketing guys, the communications people or the commercialization teams: we are hearing more and more from preclinical people. This is a change in thinking for these teams, they are now talking about involving patient voices very early in drug discovery and development,” Adrian said.

The Clinical Trials Transformation Initiative, a public-private partnership that includes international government and industry representatives, estimates that 80% of biopharma companies are already engaging with patient groups during the later stages of drug development, Phase III and Phase IV. However, this percentage drops significantly as you move back up the development chain. Approximately 62% of biopharma companies covered by CTTI’s data are engaging with patient groups in the Phase II setting and only 35% of companies consult with patient groups at the Phase I/proof-of-concept stage for drug development. For drug discovery only 15% of companies analyzed by the CTTI are deemed to be working with patient groups.

CTTI highlights that the top five major barriers for pharma companies not pursuing patient-centric models are:

• Insufficient tools

• Warn on how to engage with patient groups

• Internal resistance

• Lack of funding

• Absence of sophisticated patient groups

Adrian believes the wider healthcare system is evolving to replicate the business models of companies like Amazon and Zappos – which she says are very transparent and treat their customers like partners. Traditionally, she noted, the patient voice hadn’t been heard by pharma groups until the later stages of drug development, when these companies were focusing on commercialization strategies. “While the industry is getting better at being more interactive and transparent, patients are still demanding involvement earlier,” Adrian said, noting that concerns around access to novel therapies was driving this evolution.

Adrian highlighted some of the key benefits of involving patient groups during drug discovery and earlier stages of development as:

• The ability to build long-standing relationships, which she noted was particularly important in the rare disease space where patient numbers are small

• The opportunity to plan along the continuum for a drug from development into commercialization, which helps to connect clinical insights with commercial models

• A chance to break down internal silos that have historically divided clinical and commercial activities

• The ability to develop an early understanding of patient needs within a disease space

• The opportunity to relay these insights to regulators

Adrian believes that patient engagement in the clinical setting has been promoted in recent years by companies and patient groups in the rare disease field. “There are a number of things we have taken from a lot of our work in the rare disease space that we have translated to things like diabetes or Alzheimer’s disease. Advocacy groups are absolutely critical, especially in rare diseases,” she said.

In this early drug development setting Adrian noted there is a stronger focus on just the disease and the unmet needs, rather than a specific compound.

Published online 30 November 2016

http://bit.ly/2h5pZ7u
Bluebird, Arrowhead And Short Memories

ANDY SMITH

Last year’s platform failure of bluebird bio was all forgotten last week as data on a few patients treated with its CAR-T therapy were released. It seems that investors are quick to forget similar failed or problematic products at Arrowhead, uniQure and Juno.

When I arrived at 3i Group plc in 2000 there was a legendary piece of internal research that classified CEOs that had been successful at 3i investee companies into either first-timers or repeat CEOs. There was no difference in success rates between the two groups. Perhaps the better piece of research in order to increase the chances of success would have been to stratify and exclude those CEOs who had been previously unsuccessful, because two CEOs last week demonstrated that failure often has a habit of making repeat visits.

Continuing the dire year-end news flow in life science companies, Arrowhead Pharmaceuticals Inc. followed up on the FDA’s clinical hold on its lead interfering RNA (RNAi) program ARC-520 for chronic hepatitis B virus (HBV) infection by canceling all its clinical programs. Investors were clearly shocked by the news and Arrowhead’s shares plunged more than 68% on the week against the backdrop of the NASDAQ Biotech Index’s more sedate 4.3% fall. Arrowhead’s investors only had themselves to blame as the nucleic acid drug space had already suffered a number of setbacks this year. They should have taken heed of the fact that Arrowhead’s platform comprises the cast-offs from Roche and Novartis AG that were acquired in 2011 and 2015 respectively, for a total of only $10m in cash and various stock and promissory note considerations. For example, presided over the failure of Envyseive Pharmaceuticals Inc’s only drug. Such an introspective is almost certainly going on at Amgen Inc. as its recent collaboration with Arrowhead now looks on a par with last year’s deal between uniQure NV and Bristol-Myers Squibb Co. for a business development lemon of the year award.

Investors in bluebird bio Inc. also seemed to have forgotten that it showed the same back-to-the-drawing-board status in gene therapy as Arrowhead has in RNAi when bluebird’s issues of gene therapy efficacy in some beta-thalassemia genotypes and duration of response in sickle cell disease (SCD) emerged at last year’s American Society of Hematology (ASH) conference. Side-stepping these thorny platform issues, bluebird presented interim Phase I results last week for its anti-BCMA CAR-T engineered cell therapy (bb2121) in nine out of a planned enrolment of 50 refractory multiple myeloma patients. Most analysts were bullish on the data – which “delighted” those from Cowen – and described the 78% overall response rate in six patients as “impressive” or “striking.” The analysts from Leerink Partners were more cautious, probably because they remember that bluebird’s past “impressive” reports have tended to look less impressive over time. They cautioned that “the data are still somewhat immature.” The bluebird stock price finished the week up just under 12% despite social media comments that one of the patients in the earliest and lowest dose cohorts had already relapsed. If past behavior is a good predictor of the future, then the warm-blooded bluebird is likely to go into hibernation for a year on bb2121 in the same way it did on beta-thalassemia and SCD. At the latest ASH conference, bluebird’s Dec. 3, 2016 press release presented data on four beta-thalassemia patients and one SCD patient – exactly the same numbers of patients in those indications that had been press released at the ASH conference on Dec. 6, 2015.

Certainly bluebird should be allowed to move on from its first missteps in beta-thalassemia and SCD gene therapy where the analysts from Leerink Partners suggest it is “still struggling to optimize its LentiGlobin platform”, and last week’s data from its first foray into CAR-T cell therapy are indeed interesting if early. However, one case of cerebral edema has already been reported in another BCMA-targeted CAR-T study and CAR-T companies like Juno Therapeutics Inc. had treated many more patients over longer periods of time than bluebird before observing drug-related patient deaths and clinical holds.

Perhaps investors should wonder if – to paraphrase Michael Bublé – bluebird just hasn’t treated enough patients yet.

In Joseph Kanon’s historical novel The Prodigal Spy, the real-life American Appenben dynasty was discussed. Patriarch Moses Appenben built a very successful publishing empire that included The Philadelphia Inquirer, but he later pleaded guilty to income tax evasion, was fined $8m in 1940, sentenced to three years’ imprisonment and died in 1942. In 1969 his son Walter, who had taken over the family business, was appointed as US Ambassador to the UK – a move that prompted one of the characters in the book to suggest that the US is “a wonderful country. Nobody remembers anything.” Short memories also seemed to characterize investors last week.

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

SELLING ARROWHEAD

I managed a fund that inherited a holding in Arrowhead in 2012 and spent those first few months selling the stock as quickly as I could because unlike its more recent investors I took into account the cumulative failures of Arrowhead’s technologies at big pharmaceutical companies. While the reasons for Arrowhead’s failures are still undisclosed – leaving the prospect for repetition – perhaps investors should have examined the track record of their investments’ management more closely. Arrowhead’s chief operating officer, for example, presided over the failure of Envyseive Pharmaceuticals Inc’s only drug. Investors often has a habit of making repeat visits.


*Scrip's weekly Pipeline Watch* tabulates the most recently reported late-stage, Phase III clinical trial developments for the more than 10,000 drug candidates under active research worldwide. To see changes to the progress of product candidates further back in the development pipeline, and a table of the week’s product approvals, please visit our Pipeline Watch webpage at scrip.pharmamedtechbi.com.

**Selected clinical trial developments for the week 25 November – 1 December 2016**

<table>
<thead>
<tr>
<th>LEAD COMPANY/PARTNER</th>
<th>COMPOUND</th>
<th>INDICATION</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase III Results Published</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Johnson &amp; Johnson/ International Partnership for Microbiocides</td>
<td>dapivirine vaginal ring</td>
<td>HIV/AIDS</td>
<td>In the Dec. 1 issue of the NEJM.</td>
</tr>
<tr>
<td>Tesaro Inc.</td>
<td>niraparib</td>
<td>ovarian cancer</td>
<td>NOVA; in the Dec. 1 issue of NEJM</td>
</tr>
<tr>
<td><strong>Phase III Results</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cosmo Pharmaceuticals NV/ Dr. Falk Pharma GMBH</td>
<td>Zemcolo (rifamycin SV)</td>
<td>traveller’s diarrhea</td>
<td>ERASE &amp; Phase III; met primary endpoints, better than placebo, non-inferior to ciprofloxacin.</td>
</tr>
<tr>
<td>CytrRx Corp.</td>
<td>aldoxorubicin</td>
<td>sarcoma</td>
<td>PFS significantly improved over other therapies.</td>
</tr>
<tr>
<td>Nymox Pharmaceutical Corp./ Recordati Industria Chimica &amp; Farmaceutica SPA</td>
<td>fexapotide (NX-1207)</td>
<td>benign prostatic hyperplasia</td>
<td>Phase III results confirm superior efficacy versus controls.</td>
</tr>
<tr>
<td><strong>Phase III Interim/Top-line Results</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novo Nordisk AS</td>
<td>Tresiba (insulin degludec)</td>
<td>type 2 diabetes</td>
<td>DEVOTE; long-term cardiovascular safety and fewer hypoglycaemia episodes versus insulin glargine U100.</td>
</tr>
<tr>
<td>Momenta Pharmaceuticals Inc.</td>
<td>biosimilar adalimumab (M923)</td>
<td>psoriasis</td>
<td>Met primary endpoint, 75% reduction in psoriasis area and severity index.</td>
</tr>
<tr>
<td>Pfizer Inc.</td>
<td>biosimilar trastuzumab</td>
<td>breast cancer</td>
<td>REFLECTIONS B327 1002; showed bioequivalence.</td>
</tr>
<tr>
<td>Aradigm Corp./Grifols SA</td>
<td>Pulmaquin (inhaled ciprofloxacin) one-daily</td>
<td>bronchiectasis, non-cystic fibrosis</td>
<td>ORBIT-3 &amp; -4; in patients with chronic P. aeruginosa infections.</td>
</tr>
<tr>
<td>Santen Pharmaceutical Co. Ltd.</td>
<td>Opsiria (sirolimus), intravitreal injection</td>
<td>non-infectious uveitis of posterior segment</td>
<td>SAKURA Program; reduced intro-ocular inflammation.</td>
</tr>
<tr>
<td>Recro Pharma Inc./Alkermes PLC</td>
<td>meloxicam intravenous (N1539)</td>
<td>post-surgery pain</td>
<td>Met primary endpoint of reducing pain, well tolerated.</td>
</tr>
<tr>
<td>Pfizer Inc.</td>
<td>Lyrica (pregabalin)</td>
<td>adjunctive therapy of pediatric epilepsy</td>
<td>PERIWINKLE: met primary endpoint, reduced partial seizures.</td>
</tr>
<tr>
<td><strong>Phase III Initiated</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GlaxoSmithKline PLC</td>
<td>daprodustat (GSK1278863)</td>
<td>anemia</td>
<td>ASCEND-D, -ND; in chronic kidney disease.</td>
</tr>
<tr>
<td>Aimmune Therapeutics Inc.</td>
<td>AR101</td>
<td>peanut allergy</td>
<td>ARTEMIS (Europe); in children and adults.</td>
</tr>
<tr>
<td>Alder BioPharmaceuticals Inc.</td>
<td>epinephrine (ALD403)</td>
<td>migraine</td>
<td>PROMISE-2; its second pivotal Phase III study.</td>
</tr>
<tr>
<td>Nuvo Research Inc.</td>
<td>Pennsaid 2% (diclofenac) topical</td>
<td>acute pain</td>
<td>Patients with acute ankle sprains in EU, Canada, Australia.</td>
</tr>
<tr>
<td>Amgen Inc. /Cytokinetics Inc.</td>
<td>omecamtiv mecarbil</td>
<td>congestive heart failure</td>
<td>GALACTIC-HF; a cardiovascular outcomes study.</td>
</tr>
</tbody>
</table>

*Source: Biomedtracker*
Ian C. Read, Pfizer’s CEO and board chair, has been elected president of the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) for a two-year term. Read will take over from Stefan Oschmann, chair of the executive board and CEO of Merck KGaA, Darmstadt, Germany.

AstraZeneca’s former senior vice president and head of infection, global medicines development, John H. Rex, has been appointed F2G Ltd’s chief medical officer (CMO). Before AstraZeneca, Rex was professor of medicine at the University of Texas Medical School, Houston. He has also been the industry representative on the US FDA anti-infective drug advisory committee and has served as chair of the consensus committee on microbiology for the Clinical Laboratory Standards Institute. Rex is a member of the Wellcome Trust seedung drug discovery committee and serves on various editorial boards.

In other AstraZeneca news, the company’s UK and Ireland president, Lisa Anson, has been named the next president of the Association of the British Pharmaceutical Industry (ABPI). Before AstraZeneca, Anson gained experienced from a California based healthcare company and was also a management consultant at KPMG. She joined the ABPI board in January 2012 and will take over from the current ABPI president, John Kearney, general manager at Amgen, at the end of April, 2017.

Myokardia Inc., a company focused on heritable cardiovascular diseases, has named Marc Semigran chief medical officer. Most recently, Semigran led the Massachusetts General Hospital Heart Failure and Cardiac Transplant Program as section head and medical director. He was principal investigator of the Harvard Regional Clinical Center of the National Heart, Lung, and Blood Institute Heart Failure Network. With over 140 peer-reviewed papers in cardiomyopathy, heart failure and cardiac transplantation, Semigran was editor for a leading textbook on heart failure.

Colin Goddard has been appointed non-executive chair for Mission Therapeutics – effective Jan. 1, 2017. Goddard joined Mission’s board as non-executive director in July 2015. The company’s current and founding chair, Michael Moore, will continue on the board and transition to the role of deputy chair. Previously, Goddard was CEO of OSI Pharmaceuticals having joined that company in 1989 as a research scientist. Prior to this he worked at the National Cancer Institute, Bethesda. Currently, he is chair and CEO of US based biotech, Blink-Bio Inc. and on the board of Endocyte Inc.

Arquer Diagnostics Ltd. has appointed Nadia Whittley CEO of the company. Recently, Whittley was partner and managing director, Europe, of Tefen Management Consulting. Previously she was CEO at Allium Medical Ltd.; managing director medical devices EAME at Allergan Inc.; marketing director EMEA for interventional cardiology at Boston Scientific International; and a non-executive board member at Peptonic Medical AB.

Former president and CEO of the Canadian Cancer Society, Pamela Fralick, has joined Innovative Medicines Canada as president – effective immediately. Previously Fralick spent five years as CEO of the Canadian Healthcare Association and six years as CEO of the Canadian Physiotherapy Association. She was also chair of the Health Action Lobby (HEAL) and co-chair of the Canadian Coalition for Public Health in the 21st Century (CCHP21).