

Exclusive Interview

GSK's Vallance says R&D efficiency and transparency are priorities (p6)

Company Focus

Janssen refocuses its R&D efforts on improving convenience and adherence in HIV (p12)

The WORLD Symposium

Updates from the lysosomal diseases meeting in San Diego (p14)

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Celltrion's Truxima First Oncology Biosimilar MAb To Win EU Approval

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Celltrion's version of Roche's MabThera (rituximab), Truxima, has become the first biosimilar anticancer to win marketing authorization in Europe.

A medical milestone was reached Feb. 22 when Celltrion Inc.'s *Truxima* (rituximab), a version of Roche's MabThera, became the first biosimilar to win marketing approval in an oncology indication in Europe, leading a group of novel anticancer bio-copies poised to enter the European market.

Truxima received its EU approval two months after the European Medicines Agency's Committee for Medicinal Prod-

ucts for Human Use (CHMP) recommended it be given marketing authorization for the treatment of non-Hodgkin's lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis, granulomatosis with polyangiitis, and microscopic polyangiitis. The EMA application for Truxima was made by Celltrion Healthcare Hungary. Also known as CT-P10, Truxima binds to the CD20 antigen present on B cells and B cell tumors, leading to the elimination of those cells.

It received regulatory approval in South Korea in November 2016, marking the first approval globally for the product.

Celltrion said it will commercialize Truxima along with its partners across Europe, where it launched the only other approved product, *Remsima*, a biosimilar of Janssen Biotech Inc.'s tumor necrosis factor blocker *Remicade* (infliximab), in 2015. Celltrion's South Korean headquarters told *Scrip* that it plans to launch Truxima first in the UK in the second quarter, rolling out in the rest of Europe through the same existing regional partners as for Remsima.

Mundipharma International Corp. Ltd. has distribution rights for Truxima in the UK, Germany, Italy, Ireland, Belgium, Luxembourg and the Netherlands, and its other partners include Biogaran and Kern Pharma. Celltrion told *Scrip* that it hadn't yet decided on a pricing strategy for Truxima in Europe.

The granting of Truxima's marketing approval in Europe will increase anticipation around other biosimilars under review in the region, comprising two versions of Roche's *Avastin* (bevacizumab) and three of its *Herceptin* (trastuzumab), and at least one other biosimilar of MabThera.

Roche in a statement said MabThera has been used to treat more than four million people with specific blood cancers over the past 20 years.

The South Korean company said it hopes Truxima will win market share quickly, in part due to cost savings that the drug and other biosimilars can offer for healthcare systems, which are under increasing budget pressures, especially in the area of expensive cancer treatments.

"We are excited to offer the first biosimilar MAb in oncology ... For healthcare systems

CONTINUED ON PAGE 7



Gilead's Two PRVs

▶ 5



GSK Entering 'The Cure' Era

▶ 6

from the editor

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So, the first biosimilar anticancer MAb has been approved in Europe. For citizens, the question is how health systems will redeploy savings that biosimilars offer. Will they be used to widen access to those specific therapies, to free up cash for treatments in other areas, or to lower overall drug spending?

For directly affected originator companies, though, the question is whether it will open the floodgates. It's a testing time for Roche, which has for a long time been preparing to shore up its hefty biologics portfolio with next-generation products and formulations. *MabThera*, the drug in the biosimilar firing line, was Roche's best-selling product in 2016, with CHF1.9bn booked in Europe. How much of the market will it lose in 2017?

Merck & Co saw a 29% drop in sales of the inflammatory disease blockbuster *Remicade* (infliximab) in Europe in 2016 (representing a loss of \$526m) thanks to biosimilar competition, notably from Celltrion, also behind the MabThera biosimilar.

It's harder to defend against biosimilars in a continent of health technology value assessment bodies and single-payer systems, compared with the US. This European approval is a bellwether.



exclusive online content

Refocusing Tarveda On Tumor-Targeted Mini-Drug Conjugates

Tarveda Therapeutics has refocused during the past 18 months on its Pentarin technology. The company has raised \$91.8m to date, including a recent \$30m Series D round, which it will use to produce human data that could make it attractive to investors or pharma partners.

<http://bit.ly/2IyaGpe>

AmpliPhi To Address Microbial Infections

Using cocktails of bacteriophages to attack bacterial infections, AmpliPhi has made progress in Phase I studies for its lead program. CEO Scott Salka tells *Scrip* how he is looking to secure sufficient capital to support the Phase II development of AmpliPhi's lead program.

<http://bit.ly/2IM5Yqi>

COVER / Celltrion's Truxima First Oncology Biosimilar MAB To Win EU Approval

- 3 Bayer Bets On Oncology Pipeline, Vows To Increase 2017 R&D Budget
- 4 Breathing Room For BMS In Renal Cancer
- 5 Gilead, With Two PRVs In Hand, Holds Options For Accelerating Late-Stage Pipeline
- 6 **Exclusive Interview:** GSK's Vallance On Efficiency In R&D And Entering 'The Cure' Era
- 8 Novo Sees Brighter China Outlook As Volumes Rise
- 9 Teva's Sol Barer Leads Buyout Of IO Start-up NexImmune
- 10 **Company Focus:** Investors Sound Off On Biogen's Future With Spinraza
- 11 New FDA Revlimid Approval Extends Celgene's Myeloma Empire
- 12 **Company Focus:** Janssen Strives For Simplicity In HIV R&D
- 13 **R&D Bites**
- 14 **The World Symposium Notebook:** New Data In Lysosomal Diseases And A Push For Earlier Testing
- 16 **Policy & Regulation Briefs**
- 17 **Stockwatch:** Alexion, United, Intercept And 'Alternative Facts'
- 18 Novel Antibody Products Ring The Changes In HIV
- 20 Merck's Write-Down Of Phase II Nuc Ill Illustrates Current Reality In HCV
- 21 Billions At Stake As Generic Approvals Open Up Japan Big Sellers
- 22 **Pipeline Watch**
- 23 **Appointments**

Note: in the Orphan Drugs for Rare Diseases infographic published in issue no 3842 we displayed incorrect information about the top 10 originators developing drugs for rare diseases. This is the corrected version of that chart.



Originators Developing Drugs For Rare Diseases²

top 10 order | # of unique drugs | Originator

- | | |
|-------------------------------|------------------------------------|
| 1 98 Sanofi | 6 38 Johnson & Johnson |
| 2 96 GlaxoSmithKline | 7 34 Bristol-Myers Squibb |
| 3 93 Novartis | 8 34 Takeda |
| 4 74 Pfizer | 9 32 Amgen |
| 5 58 Roche | 10 32 AstraZeneca |

Bayer Bets On Oncology Pipeline, Vows To Increase 2017 R&D Budget

Bayer has launched an internal oncology R&D unit to speed up development of its pipeline cancer therapies and ensure the company is first to market with its late-stage treatment candidates, head of pharma Dieter Weinand told Scrip on the sidelines of the pharma's annual results conference.

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Bayer Execs In Leverkusen (L-R): Johannes Dietsch, Werner Baumann, Hartmut Klusik And Michael Preuss

Bayer AG invested around 13% of the group's 2016 sales, or €4.4bn, in research. During the company's Feb. 22 annual results presentation in Leverkusen, Germany, CEO Werner Baumann called innovation the company's core competence – and as such the drug maker has launched a new internal oncology R&D arm, with more autonomy, to speed up decision making and R&D for its pipeline cancer therapeutics.

"Efforts to further strengthen our innovation capability are paying off, as we can see in our development pipelines," Baumann said. He highlighted that within the firm's pharmaceuticals business, for example, Bayer has a series of promising product candidates currently undergoing clinical development. The company estimates that six of them – in the mid- to late-stage pipeline – have a combined peak annual sales potential of at least €6bn.

Bayer's Six Key Pipeline Products For The Future

DRUG NAME	INDICATIONS	CURRENT PHASE
Finerenone	Diabetic Nephropathy	Phase III
ODM-201 (BAY 1841788)	Prostate Cancer	Phase III
Anetumab ravtansine (BAY 94-9343)	Mesothelioma Ovarian Cancer	Phase II Phase I
Copanlisib	Non-Hodgkin's Lymphoma	Phase III
Vilaprisan	Uterine Fibroids Endometriosis	Phase II Phase II
Vericiguat (BAY 1021189)	Congestive Heart Failure (CHF) and Cardiomyopathies	Phase III

Dieter Weinand, head of Bayer's pharmaceutical division, noted that these six key pipeline products, lined up to propel the company's sales in the near future, include a diabetic kidney failure drug, a heart failure compound being developed under a partnership with Merck & Co. Inc., and three cancer therapies.

He noted that the three oncology candidates included in this €6bn forecast are some of the company's products that have recently been moved into a special oncology development arm, known as the Oncology Strategic Business Unit. The oncology development unit, which launched in December 2016, is semi-autonomous, allowing for decisions around clinical progression and resource allotment to be made swiftly. Weinand noted that oncology studies can be different to the traditional pharma R&D model of Phase I, Phase II, then Phase III and registrational studies. "Oncology development is very different: a Phase I trial can very quickly be expanded into Phase II when you see a signal it is working, that Phase II can be used for registration and you can sometimes file on that Phase II study," he said. "In these cases, you can get a quick, conditional approval with a post-marketing commitment to complete your trials to get full approval."

He added that having all its pipeline oncology programs in one new specialist development unit allows Bayer to expand trials rapidly rather than go through the traditional route. "The unit will enable us to get to market first and fast with our oncology products. It is very important to be first to market, otherwise the standard of therapy is changed and your studies were against the old standard of therapy," Weinand highlighted.

The new unit, headed by ex-Bristol-Myers Squibb Co. executive, Robert LaCaze, combines Bayer's oncology groups for experimental medicine, clinical pharmacology, early and late project management,

CONTINUED ON PAGE 4

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strategic regulatory affairs and clinical development all under one strategic unit. Additionally, the new oncology initiative will encompass marketing, pricing and global medical affairs practices for all pipeline oncology products worldwide.

Prior to joining Bayer in 2015 as senior vice president and head of the global oncology therapeutic area within pharma, LaCaze was senior VP and head of product and portfolio strategy at BMS. Most of his career has been spent in oncology, with a focus on global strategy and product launches for small molecules, biologics, and immuno-oncology therapies.

R&D SPENDING

Bayer chief Baumann said during the full-year results presentation that the company had a record year for R&D spending in 2016 and that pharma and crop science accounted for 90% of its €4.4bn R&D costs. He added that Bayer planned to increase its R&D budget again in 2017. "Innovation is our core competence and the foundation of our commercial success. It is based on excellence in R&D – including early-stage research, which serves to safeguard our long-term growth," Baumann said.

Bayer's CEO added that as well as more than 14,000 employees throughout its global R&D network, the German firm is keen to pursue more partnerships with start-ups, biopharmas, academia and public research institutes to remain at the "cutting edge of scientific and technological development." He highlighted Bayer's late-2016 deal with Versant Ventures to launch stem cell company BlueRock Therapeutics as a prime example of the partnerships the company will chase. Bayer and Versant committed \$225m into the BlueRock joint venture, which will focus on clinical programs for cardiovascular diseases, neurological disorders and diseases of the central nervous system.

As well as increased R&D spending in 2017, Bayer issued financial guidance in line with expectations: the big pharma expects to deliver group sales above €49bn in 2017, representing a low-to-mid-single-digit growth and earnings growth in mid-single digits. Its five key marketed drugs in pharma – *Xarelto*, *Eylea*, *Xofigo*, *Stivarga* and *Adempas* – are poised to post over €6bn in aggregated sales in 2017. ▶

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Breathing Room For BMS In Renal Cancer

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Latecomer Tecentriq from Roche has been making solid inroads in the lung cancer space, where it has been scrapping it out with Bristol-Myers Squibb's Opdivo and Merck & Co's Keytruda. However, early data with Tecentriq in the renal cell carcinoma (RCC) space are less than impressive. The news will be welcomed by BMS, which has Opdivo approved in advanced RCC.

Roche's Genentech division presented the first results from the IMmotion150 Phase II study that was investigating *Tecentriq* (atezolizumab, a PD-L1 antibody) alone, and in combination with *Avastin* (bevacizumab) vs standard of care *Sutent* (sunitinib), in first-line metastatic RCC.

In an ITT analysis, the two *Tecentriq* arms did not show significant benefit over *Sutent*. However, when only PD-L1 expressers were considered, the *Tecentriq* + *Avastin* arm did show significant benefit over *Sutent* with median progression free survival (PFS) of 14.7 months vs 7.8 months (HR=0.64), with an overall response rate (ORR) of 46% vs 27%.

Of note, *Tecentriq* alone did not show any benefit over standard of care *Sutent* in monotherapy in PD-L1 expressers. Bryan, Garnier & Co analyst Eric Le Berrigaud wrote in a research note dated Feb. 20 that he found this "surprising."

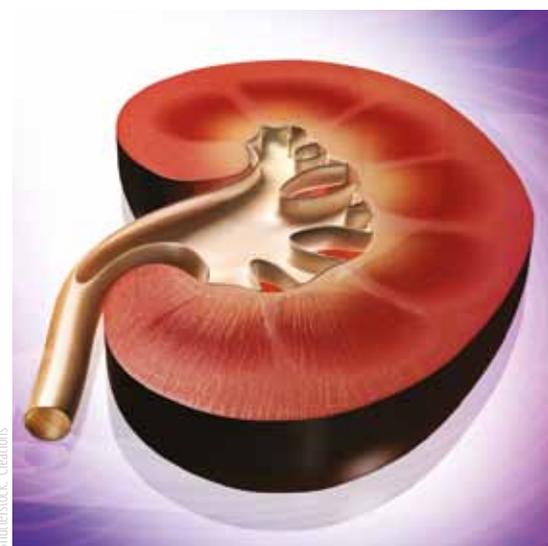
Le Berrigaud highlighted that Bristol-Myers Squibb Co's *Opdivo* (nivolumab, a PD-1 antibody) has shown benefit in RCC (it was approved for metastatic RCC on the basis of the Checkmate-025 trial), so he expected *Tecentriq* to do the same "and that combination with *Avastin* would expand this benefit to a higher level." But this wasn't the case, and while the *Tecentriq* + *Avastin* combination did show a benefit, "it is only in PD-L1 expressers and at the price of some safety issues."

BMS is currently testing a combination of *Opdivo* with *Yervoy* (ipilimumab, a CTLA-4 antibody) in Phase III. Merck & Co. Inc., meanwhile, is testing *Keytruda* (pembro-

lizumab) as a monotherapy in advanced RCC in early stage trials.

SAFETY

There was no difference in the proportion of patients with grade 3/4 adverse events in the two groups in the IMmotion150 trial. However, Le Berrigaud noted that "15% of patients treated with *Tecentriq* + *Avastin* discontinued treatment due to adverse events."



'More clear-cut results are needed if Tecentriq wants to play a role in mRCC'

Median duration of response (DoR) and overall survival (OS) data are not yet mature.

The results were presented at the 2017 Genitourinary Cancers Symposium. Genentech Inc. is currently evaluating *Tecentriq* plus *Avastin* in a Phase III study (IMmotion151) in people with previously untreated, locally advanced or metastatic RCC. Progress will be closely watched. "More clear-cut results are needed if *Tecentriq* wants to play a role in mRCC," warned Le Berrigaud. ▶

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Gilead, With Two PRVs In Hand, Holds Options For Accelerating Late-Stage Pipeline

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Likely candidates for use of Gilead's priority review vouchers include GS-4997, a Phase III candidate for NASH, and bicitegravir, its second-generation integrase inhibitor for HIV. The virology specialist previously used a PRV successfully to accelerate approval of Odefsey.

Sitting on a nest egg of \$32.4bn in cash as of the end of 2016 and needing catalysts to boost sales while revenues from its industry-leading hepatitis C franchise decline steadily, Gilead Sciences Inc. has turned for a third time to the seller's market for priority review vouchers, obtaining Sarepta Therapeutics Inc.'s voucher for \$125m.

Gilead's pipeline lists four Phase III programs with previously unapproved drug candidates, in a variety of therapeutic spaces – HIV, non-alcoholic steatohepatitis (NASH), gastric cancer and autoimmune indications, including rheumatoid arthritis, Crohn's disease and ulcerative colitis. GS-4997, an ASK1 inhibitor for NASH, and an HIV fixed-dose combo containing novel integrase inhibitor bicitegravir seem the likeliest candidates for use of the company's two pending PRVs.

While Gilead has not publicly acknowledged the purchase, Sarepta revealed that it had sold off the PRV it received from FDA upon the approval of *Exondys 51* (eteplirsen) for Duchenne muscular dystrophy last September. That approval qualified the Cambridge, MA-based biotech for a Rare Pediatric Disease Priority Review Voucher – similar vouchers are rewarded to sponsors obtaining approvals for rare tropical diseases, and they can be used by the sponsor or sold off.

Last July, Gilead disclosed during a quarterly earnings call that it had acquired a PRV from an undisclosed company for \$338m, presumably the privately held PaxVax Inc. Bermuda, which received a voucher in connection with its June 2016 FDA approval of a cholera vaccine, *Vaxchora*. In November 2014, Gilead bought a PRV from Knight Therapeutics Inc. for \$125m, which it used to obtain a priority review for *Odefsey* (emtricitabine/rilpiv-

irine/TAF), its next-generation HIV combo drug that contains tenofovir alafenamide (TAF), a successor to the backbone antiviral tenofovir disoproxil fumarate (TDF), which goes off-patent in 2018.

Combo drugs including TAF yielded a 20% year-over-year increase in HIV franchise sales for Gilead during 2016, an important part of how the company hopes to offset declining HCV sales.



With two PRVs in hand, Gilead enjoys significant optionality now for accelerating potential approval of its late-stage pipeline. The Foster City, CA-headquartered firm declined to comment on whether it had purchased the Sarepta voucher – Sarepta issued a press release stating it had sold the voucher to an unnamed buyer on Feb. 21, but also issued an SEC filing indicating that Gilead was the buyer.

Morningstar analyst Karen Andersen suggested that Gilead's three-drug HIV combo comprising bicitegravir, TAF and emtricitabine (aka bicitegravir/F/TAF) is a likely use for one of the two vouchers. She added that GS-4997, a NASH candidate which inhibits the apoptosis signal-regulating kinase 1 (ASK1) pathway, and filgotinib, a Janus kinase 1 (JAK1) inhibitor in Phase III for three autoimmune indications, could be possibilities.

NASH is an unmet medical need and perceived developing epidemic that could yield annual drug sales of \$20bn or more – GS-4997 is the third drug can-

didate to reach Phase III for that indication, after Intercept Pharmaceuticals Inc.'s *Ocaliva* (obeticholic acid) and Genfit SA's elafibranor.

"These vouchers are most valuable when facing a nearly simultaneous launch of a relatively undifferentiated competitor, and that could be the case for both the bicitegravir program (Glaxo-SmithKline PLC's two-drug lamivudine/

dolutegravir HIV regimen could launch in 2019) and the NASH program (Intercept, Genfit, etc. launching by the end of the decade)," Andersen told *Scrip*. "But filgotinib could be facing a competitive JAK market (AbbVie Inc., Eli Lilly & Co./Incyte Corp.) too, so the nature of most of Gilead's key pipeline drugs probably supports the purchase of PRVs."

Another Wall Street analyst, who spoke with *Scrip* on the condition of anonymity, agreed that one voucher almost certainly is targeted for the HIV combo, but said the intended use for the second voucher is unclear.

"I am sure one will be for bicitegravir/F/TAF, which they are eager to get to market as soon as possible," the analyst said. "They may use one for their HIV triple combination to get the product into the market in time for [the] contracting cycle for 2018. It would seem a bit early to be stockpiling a PRV for their NASH program, given a [three-to-four] year period until approval." ▶

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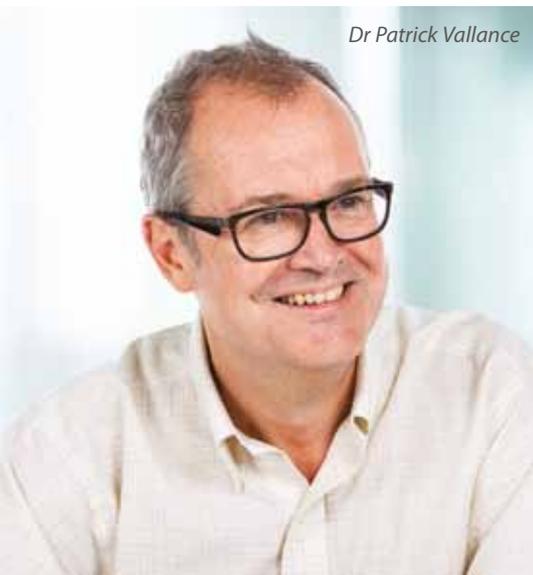
GSK's Vallance On Efficiency In R&D And Entering 'The Cure' Era

Dr Patrick Vallance, president R&D at GlaxoSmithKline, tells Scrip that R&D efficiency is a priority for the company and specifies increased transparency on R&D decision-making and its returns. In a wide-ranging interview, Vallance also discusses the attention GSK's Nucala is garnering within the severe asthma space.

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Dr Patrick Vallance, president R&D at GlaxoSmithKline PLC, was part of a star speaker line-up at BioAsia 2017 in India earlier this month.

Dr Patrick Vallance



In his address at BioAsia in Hyderabad, Vallance touched upon, among other issues, how innovation is only innovation "when it can be afforded," and the value of open innovation is to improve healthcare in a way that is also accessible. "I'm not arguing that there isn't intellectual property that needs to be protected. I'm simply arguing about where and when that happens and the role of openness to try and improve the chances of being successful," he told a packed house at the event.

In an ensuing email interview with *Scrip*, Vallance shared his views on how GSK is focused on improving the efficiency of its R&D and transparency around the returns from research. He also maintained that GSK's "broadest range" of once-daily treatments using a single inhaler platform position it well in the COPD space amid evolving dynamics. Vallance finally referred to medicine entering the era of 'the cure' – changing the paradigm of disease treatment.

ANJU GHANGURDE: *There's significant focus on R&D productivity. In 2014, the Tufts Center for the Study of Drug Development put the cost of developing a prescription drug that gains market approval at \$2.6bn. Can industry afford these cost levels or has technology pruned the figure significantly?*

PATRICK VALLANCE: R&D productivity is certainly a key challenge for our industry and a priority for GSK is to focus on developing innovative medicines with greater efficiency. We're focusing on better trial design, better use of data analytics; we've focused our R&D organization down to two major hubs in order to drive investments in technology and to create the right environments for our scientists to work together.

We also believe it's important to provide a greater level of transparency regarding our R&D decision-making and our R&D returns, so that's why in 2009 we committed to publishing our estimated R&D internal rate of return (IRR) – an important measure of our financial discipline and our strategic progress to improve the economics of R&D. We estimated our IRR to be 11% in 2009, and 13% in 2013. Applying the same methodology, our most recently estimated IRR, in 2015, has remained at 13%.

AG: *At the J.P. Morgan Healthcare Conference 2017, you highlighted how GSK's R&D strategy entails a "reliable fill & flow" with greater novelty and improved return on investment. Could you elaborate on some of the key prongs and whether the DPU [discovery performance units] model is working effectively?*

PV: We're very focused in the discovery organization around our DPU structure, where we bring together our chemists, biologists and other experts to really focus deeply on areas that we want to pursue. About 65% of the new molecules in

our pipeline have come from our DPUs so we're now seeing a very substantial amount of innovation coming forward from these research teams. That's alongside our commitment to external collaboration. The major collaborations we have across leading academia, public-private partnerships, and the links with biotechs and other pharmaceutical companies mean that around 60% of what's in our pipeline comes from homegrown R&D and around 40% is partnered or in-licensed.

AG: *The recent Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations now favor fixed-dose LABA [long-acting beta-agonist]/ LAMA [long-acting muscarinic antagonist] combinations over ICS/LABA combinations in the treatment of COPD - gains for the entire LABA/LAMA class including Anoro, but perhaps underscoring the need for greater differentiation in the backdrop of data like FLAME from Novartis?*

PV: As we saw in the recent revisions to the global GOLD COPD strategy, guidelines are continuing to move towards a more personalized approach to treatment, focusing on reducing symptoms and exacerbation risk. Different patients have different needs, and a range of treatments are needed to address this. This is well-aligned to GSK's strategy and central to our approach to medicines development and evidence generation.

Current evidence demonstrates that dual bronchodilation with LAMA/LABA is the foundation of COPD management for symptom control and that many patients will also need ICS-containing therapy to provide further symptom control and/or reduce their risk of exacerbations. We have the broadest range of once-daily treatments using a single inhaler platform and so are well positioned to meet the different needs of COPD patients and help physicians to select the right medicine for the right patient.

[Ed: In Sept. 2016, Novartis AG said new analyses from the head-to-head FLAME study confirmed that its *Ultibro Breezhaler* (indacaterol/glycopyrronium bromide) is a more effective option for patients at risk of COPD flare-ups than GSK's *Seretide* (salmeterol/fluticasone), across different patient sub-groups.]

AG: *Is Nucala's (mepolizumab) trajectory in line with your expectations so far? What is the broad KOL feedback across the US, Japan, Europe?*

'Lot of attention for Nucala within severe asthma space'

PV: *Nucala is performing well. It was launched in the US very soon after approval, and has now been launched in 16 countries. There has been a lot of attention within the severe asthma space and we see this as an area where we can deliver on an unmet need by decreasing the risk of exacerbations or asthma attacks that these patients all too often suffer from.*

Beyond severe asthma we have a broad development program ongoing for Nucala – we received positive data last year from a Phase III study in patients with eosinophilic granulomatosis with polyangiitis (EGPA), a rare inflammatory disease. And we expect to receive Phase III data from our COPD studies later this year. Studies are also ongoing in atopic dermatitis, hyper eosinophilic syndrome (HES) and nasal polyposis.

AG: *Sirukumab is among the potential launches in 2017 but the competitive landscape appears quite challenging regarding tocilizumab and sarilumab. Is dosing advantage the key?*

PV: Not all patients with rheumatoid arthritis respond the same to available treatments, so it's important to have a range of options available to help them during different stages of their long-term disease. If approved, sirukumab would provide an option delivered every four weeks.

AG: *You've in the past said that rather than "chasing the pack" in the PD-1 space, GSK is working on third generation with leading molecules, combination therapies. Would you say that not being right up ahead in the PD-1 space may even have its own advantages?*

PV: Immuno-oncology is one of our two focus areas within oncology, alongside epigenetics, and we'll begin to see readouts by 2018 from our OX40 and our ICOS agonists. Combining new therapies is certainly a big area of focus for us, exploring the potential to build on the survival advances that we're seeing already from current immunotherapies and also looking at tumor types and patient types where PD-1s/PD-L1s don't work.

AG: *What about potential value from reverse innovation - for example innovations designed and created for emerging markets that perhaps can be brought to developed nations? In the devices space, GE Healthcare has created a portable, rechargeable and low-cost electrocardiogram that was designed to service rural and low-income areas of India but has potential value in several other markets.*

PV: Yes, there is a significant science and technology base in some of the emerging markets, and for a global organization such as GSK it is important that we have a strong presence and are connected to these rapidly evolving areas. Our global reach also allows us to understand and develop medicines and treatment approaches that are suitable for particular groups of patients but could have broader utility; a recent example would be our production of chlorhexidine for umbilical cord sterilization.

[Ed: Last year the EMA's CHMP endorsed an antiseptic chlorhexidine gel to prevent umbilical cord infections (omphalitis) in newborn infants in developing countries, advanced through a partnership of GSK and the charity, Save the Children. It essentially involved innovative reformulation of chlorhexidine in GSK's *Corsodyl* mouthwash.]

AG: *What's the next big thing that you believe could potentially impact, positively, the world of medicine like never before?*

PV: I think medicine is entering the era of 'the cure', when we'll see medicines developed for patients that have the potential to not just alter the fundamental course of disease or modify disease progression but present opportunities to achieve remission and functional cure. That is a huge leap forward in terms of how we treat disease. ▶

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CONTINUED FROM COVER

burdened with high cost oncology treatments, we are pleased to provide an option that has the potential to offer significant savings whilst ensuring patients retain access to high-quality and effective treatments," Jung-Jin Seo, Celltrion's chair, said in a statement.

"Assuming the price of biosimilar rituximab is 70% of the reference rituximab, and the market share of biosimilar rituximab is 30% in the first year, 40% in the second year and 50% in the third year, over this three-year time period the budget savings across the 28 countries of the EU would be around €570m," said László Gulácsi, who heads the health economics department of Corvinus University in Budapest, Hungary. "This equates to 49,000 new RA, NHL and CLL patients who could be receiving life-changing treatment which is clearly a huge aggregate health-gain at both a national and EU level," he added.

Celltrion told *Scrip* that a US approval application for *Truxima* (and Celltrion's biosimilar trastuzumab, *Herzuma*) is expected in the first half of this year, with a goal to get a *Truxima* approval before US exclusivity for original rituximab expires. *Herzuma* was filed for EU approval last October.

'We are pleased to provide an option that has the potential to offer significant savings'

But while Celltrion is collaborating with Pfizer Inc. over a number of biosimilar products, it has decided to team up with Teva Pharmaceutical Industries Ltd. to commercialize *Truxima* in the US and Canada.

If approved by the FDA, *Truxima* will be marketed there by Teva under a deal announced in Oct. 2016 whereby Teva will pay \$160m upfront and will be responsible for all commercial activities; the partners will split profits. ▶

(With contributions from Jung Won Shin in Seoul.)

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Novo Sees Brighter China Outlook As Volumes Rise

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Novo Nordisk says its China business is regaining strength, helped by improved volumes and broad growth in the diabetes sector and despite pricing pressures, and sees a brighter outlook ahead of the local approval of Tresiba.

Emboldened by a 12% local currency increase in sales in China last year to DKK10.46bn (\$1.49bn; +6% in Danish kroner), Novo Nordisk AS president and CEO Lars Fruergaard Jørgensen was confident enough to declare during the Danish company's fourth quarter earnings briefing that there has been a "significant turnaround, rebound of our Chinese business."

Noting that other emerging markets in Africa, Asia, the Middle East, Oceania, Latin America were also now "growing very nicely," the executive said that Novo sees continued opportunities for solid growth in these territories. In China, which has long been an important market and took a 19% share of the company's overall growth in local currencies during the year, "We see a continued strong performance of our modern insulins," he added.

In November last year, Novo said it held a 54% share of the mainland China insulin market (61% of the modern/new insulin sector) based on IMS audit data. Although both figures were down 1% from the same month a year earlier, there was an improved share of volume growth in the modern insulins segment. Fully 98% of the company's insulin volume in China comes from use in devices, primarily the NovoPen system.

While *Victoza* (liraglutide) held 56% of China's GLP-1 market, this class accounted for only around 1% of the total diabetes care sector in the country, as such agents are generally not reimbursed by insurance schemes.

PRICING PRESSURES

Explaining some of the factors behind the improving performance, executive vice president of international operations, Maziar Mike Doustdar, said that the pricing environment in China last year ended up better than the company had planned or hoped for. "We had a minus 1% price decline as a



Novo Nordisk's China Sales

PRODUCT	2016 CHINA SALES (DKK BN)	% CHANGE (LOCAL CURRENCY)
Modern insulins total	4.97	+21
Human insulins	3.36	No change
NovoMix (insulin aspart)	3.36	+17
NovoRapid (insulin aspart)	1.06	+29
Victoza (liraglutide)	0.255	+25

Note: figures for mainland China market only.

result of [prices in] close to 10 of the provinces being negotiated," he noted.

"And as we're moving into 2017, we still believe that, of course, we will be hit by further pricing declines due to the [official] mandate, but perhaps slower than it was initially thought just some 18 months ago. So, it looks in a better shape."

China is rolling out a new simplified and more transparent receipting system in the drug distribution sector, which is expected to add further weight to existing official mechanisms designed to control the rising healthcare and medicines costs in the country.

Doustdar nevertheless remained optimistic, noting during the results briefing that China's diabetes market growth had almost doubled over the last 18 months. "So we've gone from five percentage points volume growth to about 10 percentage points, and our share of the growth has also doubled from 21% to now 45%. We are actually ever more hopeful for the Chinese market turnaround that we have seen [last year] to continue in 2017."

REGULATORY ENVIRONMENT

Novo is currently awaiting the approval in China of the long-acting basal insulin analogue *Tresiba* (insulin degludec). Answering analysts' questions on the general regulatory environment, chief science officer Mads Krosgaard Thomsen commented that although the Chinese FDA has had a major backlog of drug applications due to "being understaffed grossly," the situation is now improving.

"There is actually a collaboration between Novo Nordisk, the Danish Medicines Agency, and the Chinese Food and Drug Administration on how to build world class into all elements of their drug approvals," he added.

"I think we are moving up in the queue [with *Tresiba*] and that we are getting closer to a point in time where we'll hopefully get approval. Could be this year, could also be next year. We're doing everything we can but it is still in the queue, albeit closer to the first position." ▶

From the editors of *PharmAsia News*.
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Teva's Sol Barer Leads Buyout Of IO Start-up NexImmune

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Instead of helping raise a Series A, the Teva chair and others acquire the preclinical company, convinced of its synthetic nanotech promise in immuno-oncology.

NexImmune has not yet reached the clinic but a consortium of blue-chip investors led by Teva Pharmaceutical Industries Ltd. Chairman Sol Barer bought out the Gaithersburg, MD, biotech Feb. 14 for undisclosed terms with the goal of bringing its nanotechnology adoptive cellular therapy into clinical development by the end of 2017.

time. The existing five-member team, including CEO Ken Carter, remains in place at NexImmune.

Barer, also the former chairman and CEO of Celgene Corp., was advising NexImmune on whether to prioritize its cellular therapy candidate or its vaccine, while his son, Joshua Barer, a managing partner at venture capital firm Sunflower Life Sciences, was assisting with a planned Series A financing. The elder Barer pitched an alternative to NexImmune management that a syndicate led by he, his son and former Medtronic PLC

“Our technology, in theory, completely bypasses the role of the host dendritic cell,” he continued. “We have this synthetic nanoparticle that’s our own little dendritic cell that we can program, we can engineer with pharmaceutical precision, literally, to deliver a specific signal, a specific antigen for the patient and also a specific co-stimulatory signal. And so the synthetic nanoparticles do what the host dendritic cell under normal circumstances would do.”

NexImmune believes this approach to cancer immunotherapy can offer risk-benefit advantages over other T-cell stimulating therapies now on the market or in clinical trials. Carmer noted that while chimeric antigen T cell (CAR-T) therapies are producing impressive response rates, they also are presenting significant toxicity in roughly 20% to 30% of patients receiving them. Further, with two-to-three years of clinical practice, the field is beginning to see some relapsing patients.

NexImmune’s goal is to file an investigational new drug (IND) application with US FDA in November or December to begin Phase I studies with its AIM-ACT candidate. “We think that we have the potential – and we’ll only know this by getting into the clinic – that by using natural T-cells [we can] unlock the cancer-killing, the cytotoxic potential of natural T-cells, and to do it in a very antigen-specific way,” Carmer said. “We think this approach has the potential to greatly minimize off-target toxicities that are seen with some of the genetically modified T-cells that are in the clinic. That’s our value proposition – we think that we can enhance the risk-benefit profile by using natural antigens and by using naturally selected T-cells.”

The new NexImmune board will be chaired by former Schering-Plough Corp. Chief Medical Officer Robert Spiegel. Also serving on the board, along with Carmer, will be former Celgene execs Graham Burton and Paul D’Angio, RegenMedTX CEO Timothy Bertram, MedImmune LLC Senior VP of respiratory, inflammation and autoimmunity Bing Yao and Roivant Sciences Ltd. Senior VP-Corporate Development Alan Roemer. ▶

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NexImmune’s pipeline, which includes a preclinical cellular therapy candidate called AIM ACT and an injectable vaccine called AIM101, is based on artificial immune (AIM) technology licensed from Johns Hopkins University. The start-up says this platform creates novel immuno-oncology candidates that can enrich, expand and activate multiple antigen-specific T-cells against either shared tumor-associated antigens or patient-specific neoantigens.

No terms of the sale have been disclosed, but NexImmune Chief Operating Officer Scott Carmer, who takes a seat on the firm’s new board of directors, says Barer’s syndicate bought all outstanding shares and infused the biotech with capital that will allow it to reach a specified milestone. At that point, additional financing will be needed, he said, and the board is mulling how best to proceed at that

CEO William Hawkins would instead buy the company and install a new board, Carmer explained.

The primary benefit of the AIM technology, the exec told *Scrip*, is its ability to create nanoparticle-based, artificial Antigen Presenting Cells (aAPCs) that can bypass the role of dendritic cells in modulating an immune response to a cancer. This is important, he added, because dendritic cells can become dysfunctional and not play their intended role in battling cancer.

“We know that many times, the dendritic cell becomes dysfunctional,” Carmer said. “It often becomes co-opted by the tumor itself to work on behalf of the tumor instead of working on behalf of the host. So, instead of presenting antigens and stimulating T-cells, it actually down-regulates T-cells in an antigen-specific way.”

Investors Sound Off On Biogen's Future With Spinraza

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Entering 2017 with freshly approved Spinraza and new CEO Michel Vounatsos, Biogen still faces challenges and uncertainty. A poll of investors highlights expectations for the company.

Biogen Inc. is one company that doesn't need to beat the drum for investor attention. Ranked a hungry fourth among the top 10 players in biotech, it's a bellwether for what's trendy in market sentiment, with a management team driven by outsized ambition for therapeutic leadership in some of the hardest areas of science. One of the industry's best R&D machines has been built on high risk bets promising equally high rewards against a range of neurological conditions characterized by a grinding lapse in the standard of care.

That's the historical context, but the question now is whether Biogen's latest clinical breakthrough, *Spinraza* (nusinersen), the first treatment for spinal muscular atrophy (SMA), will keep that growth engine humming amidst the threat of payer resistance to a set of dauntingly high price points. Is more great science and an ironclad case for clinical efficacy sufficient to top the guardrails to market access? Or, to paraphrase the PhRMA trade association's new reputational campaign, will payers #GoBoldly in embracing another new agent of progress in the struggle to cure and treat disease? The future of the rare disease model of high prices within a carefully curated patient population may depend on it.

So far, the market appears unconcerned by any downside risk of pricing issues involving Spinraza, with Biogen common shares trading in the \$290 range since the US FDA approved the drug on Dec. 23, 2016. To provide some larger insights, Mizuho Securities, the US arm of the Japanese financial services giant, conducted an anonymous investor survey earlier this month to gauge investor perceptions on Biogen's prospects for 2017. "We look at Biogen as the default player in evaluating everything from the state of biotech science to the overall market's tolerance for risk," Mizuho senior biotech analyst Salim Syed told *Scrip*.

INVESTOR OPTIMISM

Some US 115 investors representing a mix of hedge funds and long term institutional players were polled on expectations around Spinraza, among other things. The topline results:

Spinraza launch year revenues will exceed the sell-side consensus – but won't crush the numbers to justify a surge in Biogen's share price

For 2017, the survey group predicted a weighted average of \$237m in sales against the analyst consensus of \$175m. "The sense is that the clinical profile – both trials in Phase III ended early due to conclusive proof of efficacy – as well as the broad label secured from the FDA will be sufficient to help ease payer restrictions on eligibility for reimbursement over time," Syed said.

"A favorable royalty arrangement with partner firm Ionis Pharmaceuticals means that Biogen retains most of the drug's economics going forward. Spinraza is a breakthrough that promises to extend survival and quality of life for about 9,000 US patients, and about 20,000 patients globally, all of whom have no other options at present."

SPINRAZA – A BLOCKBUSTER

80% of those polled predicted peak year revenues in excess of \$2bn, with the weighted average coming in at \$2.5bn, or slightly higher than the sell-side analyst consensus of \$2.3bn. "The rub is it's going to be a slower build as insurers to date have only seen data published from the infantile study and based on that have set ground rules on which adults and children, at various stages of the disease, will be covered, at what amount and for how long," Syed told *Scrip*.

'Only a few players have resources to take on Biogen's market cap'

MORE DATA ON SPINRAZA ARE NEEDED

Among other things, investors agreed that information on approval for reimbursement under big-ticket state Medicaid programs is sketchy at present. Results of a trial assessing Spinraza's efficacy in the SMA pediatric population, due for release at the 2017 annual meeting of the American Academy of Neurology in April, should yield critical insights around the drug's potential for reducing the societal burden of SMA. According to Syed, "this is a disease where two-thirds of patients are covered by Medicaid, linked to the time commitments of parents and other family caregivers. Quantifying the productivity impact on the mortality and quality of life outcomes from clinical use of Spinraza could buttress Biogen's price/value proposition to payers."

MS COMPETITION IS A WASH - FOR NOW

The survey group was asked about the potential for *Ocrevus* (ocrelizumab), a yet to be approved Roche/Genentech Inc. drug indicated for relapsed and primary progressive MS, in taking market share from Biogen's franchise leaders *Tecfidera* (dimethyl fumarate) and *Tysabri* (natalizumab).

Roche has an active investigational program in neuroscience that includes a commitment to establishing a least a peripheral presence in SMA. FDA approval has been delayed for the first half of this year due to concerns about the manufacturing process that Roche must rectify before obtaining the market license. Nevertheless, those polled basically split in viewing Ocrevus as a wash (45%) or as a negative (46%). "Ocrevus as a competitor to Tecfidera and Tysabri depends heavily on the clarity of the label for the two indications for which it is likely to be approved," observed Syed. "It's also important to figure out where Ocrevus is going to obtain its patient numbers. There is a debate whether it will pull from these two [Biogen] products, and to what extent."

BIOPEN WILL STAY INDEPENDENT IN 2017

Three quarters of those polled rejected the prospect of Biogen being acquired by a big Pharma suitor; of the 24% who did believe M&A targeting Biogen was likely, Merck & Co. Inc. was identified as the top candidate, followed by Pfizer Inc. and Amgen Inc. The cited reason

is Merck has a therapy for Alzheimer's in the works, while Pfizer has a marketing history in the field through its symptomatic drug, *Aricept* (donepezil). Syed comments, "the pricing of any takeover bid is critical. Only a few players have the resources to take on Biogen's market cap and they will want to see progress on the company's high-profile – and expensive – stake in Alzheimer's, with the pending Phase III trial prospects for the key investigational candidate, aducanumab, utmost in mind." News released after the Mizuho survey that Merck has stopped one of two trials of verubecestat, its flagship Alzheimer's candidate, focused on patients with moderate disease (interim results proved negative), simply raises the stakes on Biogen to succeed where others have failed.

BOLT-ON ACQUISITIONS

Another intangible is the transition in top management and the actions of new CEO Michel Vounatsos related to a six-month review of business strategy now underway at the Cambridge HQ.

Beyond Spinraza, the Biogen launch pipeline is basically empty for 2018 and 2019. "The consequences, good or bad, of predecessor George Scangos' high risk/high reward calculation on the Alzheimer's space thus looms large as one of the review's defining questions," noted Syed in his conversation with *Scrip*.

Suggested review priorities offered up by the polling group include a tighter focus on business development in prioritizing new therapeutic segments that can deliver quick results to the bottom line, especially if the big investment in aducanumab tanks.

The poll group selected two small companies as top candidates for a Biogen buy: San Diego-based Neurocrine Biosciences Inc., which has a promising early stage pipeline in neurological and endocrine disorders, and Acadia Pharmaceuticals Inc., whose FDA-approved drug *Nuplazid* (pimavanserin), currently indicated for Parkinson's related psychosis, is emerging as the potential standard of care in treating symptoms of many other neuro-degenerative diseases. The interesting third choice, selected by 10% of the survey: just go and sell yourself, preferably to the highest bidder.

On this, the market always speaks first. ▶
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New FDA Revlimid Approval Extends Celgene's Myeloma Empire

Celgene is finally able to market its mainstay multiple myeloma therapy Revlimid for maintenance use after stem cell transplant, after the FDA further expanded its approved indications. The EU is set to follow suit following a CHMP positive opinion last month.

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The US FDA has expanded the existing indication for Celgene Corp's *Revlimid* (lenalidomide) to include its use for patients with multiple myeloma as maintenance therapy following autologous hematopoietic stem cell transplant (auto-HSCT). The expanded indication makes *Revlimid* the first and only treatment to receive FDA approval for maintenance use following auto-HSCT, the company says.

Revlimid has become a foundational therapy in multiple myeloma since its first approval for this disease back in 2006 in the US for use in combination with dexamethasone in patients who had received at least one prior therapy; similar approvals followed in the EU the following year and in Japan in 2010.

In February 2015, both the FDA and European Commission extended the indication of *Revlimid*. In the US, it was extended to first-line treatment of multiple myeloma patients, and in the EU *Revlimid* was licensed for the first-line treatment of patients not eligible for stem cell transplant.

Its latest approval enables Celgene to market it to patients across the multiple myeloma spectrum. But its use as a maintenance therapy in stem cell transplant patients has taken some time to reach the stage of approvability. Celgene withdrew an EU application for extension of the drug's indication to include maintenance therapy after first-line therapy or stem cell transplant in 2012 after the CHMP requested for more mature data to reach a conclusion on *Revlimid*'s benefit/risk balance.

Revlimid accounts for the lion's share of Celgene's sales: in the fourth quarter they were \$1.8bn worldwide and \$6.97bn for the year, rising 15.9% and 20.2%, respectively. And the multiple myeloma market is growing. Analysts at

Datamonitor Healthcare predict there will be substantial growth in the incident multiple myeloma population in the US, Japan and the five major EU markets between now and 2034. They estimate total incident cases in these markets of 55,450 in 2017 rising to nearly 74,000 in 2034, driven mainly by the ageing population, and the US is expected to see the largest rise.

The newest approval is based on updated data from two Phase III trials, CALGB 100104 and IFM 2005-02. These showed progression-free survival advantages over no maintenance therapy of 3.8 and 1.9 years. Median overall survival for *Revlimid* patients was 9.3 years and 8.8 years, respectively, compared with seven and 7.3 years for no maintenance in a descriptive analysis (the studies not powered for OS).

SECOND CANCER CONCERN

What had most concerned regulators was the risk of developing secondary primary malignancies (SPM) in patients receiving *Revlimid* maintenance therapy. Hematologic SPM occurred in 7.5% of *Revlimid* maintenance patients compared with 3.3% of patients receiving placebo. The incidence of hematologic plus solid tumor (excluding squamous cell carcinoma and basal cell carcinoma) SPM was 14.9%, compared to 8.8% with a median follow-up of 91.5 months.

Patients should be monitored for the development of second primary malignancies, and the benefits and risks need to be considered before treatment.

The EU's CHMP granted a positive opinion for the new *Revlimid* use for the maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation in January. ▶

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Janssen Strives For Simplicity In HIV R&D

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HIV may be effectively treated and managed with available therapies, but there is still great unmet need for a functional cure and better prevention to stop the epidemic.

With HIV now managed as a chronic treatable disease, Janssen Pharmaceutical Cos. has refocused its R&D efforts on improving convenience and adherence, while searching for the holy grail of a preventive vaccine.

Johnson & Johnson established a foothold in the HIV market through the 2002 acquisition of Tibotec Group NV for \$320m in cash.

The company currently markets the non-nucleoside reverse transcriptase inhibitor *Edurant* (rilpivirine), which had worldwide sales of \$573m in 2016, up 39.8%, and the proteasome inhibitor *Prezista* (darunavir), which had 2016 annual sales of \$1.8bn worldwide, up 2.3%. But sales in the infectious disease category, one of J&J's five areas of focus along with immunology, cardiovascular/metabolics, oncology and neuroscience, dropped by 12.3% to \$3.2bn as the company absorbed losses related to the hepatitis C drug *Olysio/Sovriad* (simeprevir), which was down by 82.9% in 2016 to \$106m, a casualty of greater competition in the space.

The company's approach has always been to address the areas of greatest unmet medical need, which in the early days meant developing potent treatments for a drug-resistant virus, Brian Woodfall, head of development and global medical affairs, infectious diseases and vaccines at Janssen, told *Scrip*.

Unmet need has shifted toward developing therapies that work over longer periods of time with safety and tolerability as well as convenience, in particular cutting the dosing intervals and the number of pills patients need to take.

The number one goal of treatment is efficacy – to suppress the virus durably – but adherence affects efficacy and having therapies that are tolerable but also convenient are important for adherence, the exec said.

To that end, the company has a large number of trials exploring various combinations and dosing regimens ongoing.

J&J's latest major HIV release came on Feb. 14 at the Conference on Retroviruses and Opportunistic Infections (CROI) meet-

ing in Seattle, where the company presented data from the SWORD-1 and -2 studies of a single-tablet combination of Edurant with ViiV Healthcare's *Tivicay* (dolutegravir). In the Phase III trials, the two-drug combination was noninferior to three- and four-drug regimens. ViiV, a subsidiary of GlaxoSmithKline PLC that includes Pfizer Inc. and Shionogi Inc. as partners, is set to file a fixed-dose combination of rilpivirine with dolutegravir in the US and the EU this year.

The rilpivirine/dolutegravir combo will face what could be tough new competition from virology powerhouse Gilead Sciences Inc. At the CROI meeting, Gilead presented promising Phase II data for its next generation integrase inhibitor bictegravir vs dolutegravir, both on top of background therapy with Gilead's nucleoside reverse transcriptase inhibitor emtricitabine and TAF (tenofovir alafenamide), a nucleotide analog reverse transcriptase inhibitor. In the trial, the bictegravir arm looked numerically better and analysts are keen to see whether this will turn out to be a statistically significant effect in Phase III. Gilead is set to release Phase III data for bictegravir with emtricitabine and TAF in the middle of this year and could file in the third quarter.

Meanwhile, J&J is awaiting a decision in Europe regarding its September 2016 filing of the combination of its proteasome inhibitor *Prezista* with the boosting agent cobicistat and Gilead's emtricitabine/TAF. This single-tablet combination will be filed in the US this year.

Separately J&J also has a collaboration with GlaxoSmithKline regarding the development of rilpivirine with GSK's investigational integrase inhibitor cabotegravir to allow long-lasting HIV therapy dosing, that is every one or two months. The companies presented long-term Phase IIb data for the combination at CROI and recently started enrolling in Phase III.

IN PURSUIT OF VACCINES

In addition to improving upon the convenience of existing therapies, J&J is actively investigating vaccines – both therapeutic and preventive.

There has been some success for a therapeutic vaccine-based approach it has been

developing with Gilead and Beth Israel Deaconess Medical Center and national agencies, which was effective at stimulating the immune system to control the virus. The partners have created a regimen that combines two therapeutic vaccines – an adenovirus serotype 26 vector vaccine (Ad26) with an MVA vector vaccine (MVA) and a TLR7 agonist, on top of short-term antiretroviral therapy.

The goal is to suppress HIV long-term without the need for antiretroviral medication long-term. The regimen is now in clinical testing.

"We are continuing to move forward looking for ways to advance the therapeutic vaccine as a potential one approach or part of a more general approach to a functional cure for people who are already infected," Woodfall said.

J&J also sees great unmet need for a reliable preventive vaccine. J&J's approach, which it is developing with Beth Israel and other collaborators, involves initial priming of the immune system with the Ad26 vectored vaccine with a different approach as a boost of a purified HIV envelope protein – similar strategies have resulted in strong durable immune responses in other infectious diseases, such as Ebola. The company has noted very positive results in non-human primates and has moved the preventive vaccine into Phase I in healthy volunteers.

"It is the holy grail to have a very effective vaccine that is extremely safe and can be utilized very broadly but there have been many stumbles along the way," as several vaccines failed in larger efficacy studies, Woodfall said.

It's difficult to predict what will happen with the field but there are some signals in early studies that research is moving in the right direction, he said.

"We will get there – it's a bit of a question of when and how will we get there I think," Woodfall said. ▶

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CLICK
View Janssen's HIV
Clinical Trials Overview:
<http://bit.ly/2lqys6p>

Ocular Therapeutix's Lead Product Back On Track

After a rollercoaster ride, the US NDA for Ocular Therapeutix Inc.'s eye insert, *Dextenza* (dexamethasone), has been accepted for review by the FDA for the treatment of ocular pain after ophthalmic surgery, and the company believes there is a significant market opportunity for the extended-release product, its lead candidate. The *Dextenza* insert sits in the canaliculus of the eye, where fluid drains from the surface of the eye, and releases the corticosteroid, dexamethasone, for up to 30 days, while the insert itself is biodegraded. If approved, Ocular Therapeutix says *Dextenza* will be the first non-invasive therapy to provide a full course of pain relief with a single placement. And with four million cataract surgeries performed every year in the US, there will be a significant market for the product. By the year 2020, there will be 30 million Americans with cataracts, the company says. Analysts at JMP Securities pointed out that ocular pain and inflammation are common adverse events to ophthalmic surgery, and with *Dextenza* physicians will be able to control the entire course of therapy, while at the same time patients will be able to avoid daily eye drops, post-operative infections, and co-pays. The NDA acceptance, and the setting of a PDUFA date of July 19, 2017, represents a turnaround for the company that received a complete response letter involving *Dextenza* in the middle of last year because of manufacturing issues.

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Melior, Bukwang Seek Diabetes Edge

Melior Pharmaceuticals Inc. and its partner Bukwang Pharmaceutical Co. Ltd. are gearing up to progress a Phase IIb program with their novel insulin sensitizer MLR-1023 in the US and South Korea this year, following promising earlier clinical results with the repurposed molecule as a potential novel therapy for type 2 diabetes. After gaining a recent green light from South

Novartis Combo On Track To Be First Targeted BRAF NSCLC Therapy

Novartis AG's aim to expand its targeted *Tafinlar* (dabrafenib) and *Mekinist* (trametinib) mixture into cancer indications other than melanoma got a boost Feb. 24 when the European Medicines Agency's advisory panel recommended its use in the region for BRAF-positive non-small cell lung cancer (NSCLC). EMA said its Committee for Medicinal Products for Human Use (CHMP) at its most recent meeting backed recommending approval of *Tafinlar* in combination with *Mekinist* to treat patients with advanced or metastatic NSCLC whose tumors express the BRAF V600 mutation, a niche population. Approval for the combination's use in NSCLC by the EU Commission therefore looks likely within the next few months. Novartis said in a statement that if that's the case, its drugs will be the first targeted therapy for BRAF V600-mutated NSCLC patients. The combo is already approved in Europe, the US and Canada and other countries to treat unresectable melanoma. Datamonitor Healthcare analyst Dustin Phan that the combo's likely first-mover advantage in targeted NSCLC should bring benefits.

sten.stovall@informa.com, 24 Feb 2017

Korea's Ministry of Food and Drug Safety to begin the new trial, Bukwang is going through the institutional review board approval process and plans to start patient screening in April. Results from the study are expected in the first half of 2019. Melior also plans to start its US Phase IIb study in the near future. MLR-1023 is a repositioned small molecule drug candidate discovered through Melior's theraTRACE platform to have potential as a new treatment for diabetes. The compound (formerly known as tolimidone) was previously advanced through Phase II back in the 1980s by Pfizer for the treatment of gastric ulcers but was discontinued due to lack of efficacy in that indication.

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OncoSec Pushes IL-12 Forward In PD-1 Melanoma

OncoSec Medical Inc. says that its approach for delivering the anticancer protein interleukin-12 directly to tumors is likely to work in combination with PD-1 inhibition in melanoma patients who failed a PD-1 inhibitor, based on results from a small, single-

arm Phase II study. It is now planning a registrational trial in PD-1 failures. OncoSec's proprietary ImmunoPulse platform delivers DNA-based therapeutics directly into tumors, eliciting a local but also a systemic approach, according to the company. Its lead "electroimmunotherapy" candidate is a DNA plasmid coding for IL-12 that is delivered using the OncoSec Medical System, a proprietary electroporation device. Melanoma was the first major proving ground for checkpoint inhibitors and the effect was revolutionary, but that doesn't mean there isn't room for improvement. Only about one-third of metastatic melanoma patients respond to PD-1 monotherapy in the frontline setting. Bristol-Myers Squibb Co.'s combination of its PD-1 inhibitor *Opdivo* (nivolumab) with its CTLA-4 inhibitor *Yervoy* (ipilimumab) brings the response rate up to 59% in the treatment-naïve population, but at the cost of high toxicity. OncoSec presented data on Feb. 23 at the ASCO-SITC Clinical Immuno-oncology Symposium in Orlando, showing a 48% objective response rate in patients it says would be less likely to respond to a PD-1 inhibitor.

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New Data In Lysosomal Diseases And A Push For Earlier Testing

The WORLD Symposium Feb. 13 to 16 in San Diego offered everything from basic research through late-stage clinical data in lysosomal diseases, including ArmaGen's blood-brain barrier-crossing treatment for Hurler syndrome and updates from ongoing development programs from rare disease specialists, such as Genzyme, Amicus and Protalix.

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The WORLD Symposium from Feb. 13 to 16 in San Diego brought together academic researchers and biopharmaceutical companies to share emerging research in lysosomal diseases, including next-generation enzyme replacement therapies, gene therapies and tests that identify patients before debilitating effects of the diseases kick in.

Researchers, clinicians and biopharma company scientists presented a range of basic research, preclinical data and clinical trial results for Gaucher, Fabry and Farber diseases, Hunter and Hurler syndromes, and other rare and ultra-rare lysosomal diseases. ArmaGen Technologies Inc., Shire PLC, Sanofi's Genzyme business unit, BioMarin Pharmaceutical Inc. and Amicus Therapeutics Inc. presented data, set up shop in the exhibit hall and sponsored topical seminars, showing how far research has come since the grassroots-organized WORLD (We're Organizing Research on Lysosomal Diseases) Symposium began 13 years ago, while the array of very early disease and therapeutic candidate research served as a reminder of how far the field has to go for many patients.

CROSSING THE BLOOD-BRAIN BARRIER

One of the biggest challenges for many lysosomal diseases – even those with commercially successful treatments – is getting enzyme replacement therapies (ERTs) and other treatments across the blood-brain barrier. Existing therapies often successfully treat or halt progression of somatic symptoms, but don't have an effect on neurological aspects of the diseases.

ArmaGen presented interim results from its ongoing Phase II clinical trial for AGT-181 in Hurler and Hurler-Scheie syndrome (mucopolysaccharidosis type I or MPS I) that showed improvements in somatic and cognitive symptoms in pediatric patients. Hurler syndrome, caused by a lack of the enzyme iduronidase, affects the brain and spinal cord, leading to joint stiffness, loss of physical function and airway obstruction as well as developmental delays and mental decline, among other symptoms.

AGT-181 is an ERT consisting of re-engineered iduronidase as a fusion protein with an immunoglobulin G (IgG) antibody targeting the insulin receptor. ArmaGen's "Trojan horse" technology uses the body's natural system for transporting large molecules across the blood-brain barrier; AGT-181 binds to the receptor that transports insulin into the brain.

Data were presented on Feb. 16 at the WORLD Symposium for the first five patients (age two and older) enrolled in the Phase II study. Results through 26 weeks of treatment showed neurological and cognitive gains for four of the children and stabilization of those symptoms for the fifth child. ArmaGen CEO Mathias Schmidt described the cognitive changes in an interview with



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Scrip as "remarkable" given the children's condition at baseline and the patients' poor prognosis. For instance, a nine-year-old boy severely affected by Hurler syndrome started the study with the cognitive ability of a 16-week-old baby and improved to a nine-month-old child's cognitive ability at week 26 with significant functional gains as well.

A six-year-old boy doubled his cognitive ability; a 15-year-old gained conceptual thinking and the ability to manipulate his clenched hands; and a three-year-old boy who did not improve after a stem cell transplant at six months old stabilized after treatment with AGT-181.

ArmaGen described AGT-181's impact on somatic symptoms as similar to existing ERTs – stabilization of urinary glycosaminoglycan (GAG) levels and stabilization or reduction in liver and/or spleen volume. In terms of safety, there were two infusion site reactions and two hypoglycemic events, which were described as transient and well-controlled by glucose administration.

Enrollment in the Phase II study is complete at 13 patients, including two who dropped out due to the travel burden of getting to the clinical trial site. ArmaGen expects to receive final data in July and may report the full results in August.

"We're already planning very aggressively our Phase III strategy," Schmidt said. "We have various approaches, because MPS I is a very heterogeneous disease, so we may have more than one small Phase III study."

HUNTER CANDIDATES

ArmaGen has a second product candidate in the clinic in partnership with Shire – AGT-182 for Hunter Syndrome (MPS II). Phase I studies in adults are wrapping up and a Phase II program is being planned by Shire, which will take over clinical trial responsibilities for proof-of-concept studies.

Shire also has SHP609, an intrathecal version of its marketed Hunter syndrome ERT *Elaprase* (idursulfase), under investigation in a Phase III clinical trial with data expected in the fourth quarter of 2017. The rare disease and specialty pharma company presented results at the WORLD Symposium for both *Elaprase* and SHP609 as well as observational data about Hunter and Gaucher disease.

ArmaGen has raised \$70m to date, including a \$17m Series A venture capital round in Dec. 2012; the rest is from Shire, other corporate partners and government grants. Schmidt said ArmaGen is talking to potential Series B investors about funding ongoing clinical studies and advancing preclinical programs.

EARLIER DIAGNOSIS FOR PREVENTION

Lysosomal diseases often go undiagnosed until after patients exhibit severe symptoms that cause damage which cannot be undone, so efforts to develop diagnostic tools and implement earlier screening are important to clinicians and biopharma companies.

Shire already works with various academic and other partners to offer early diagnosis and free testing, vice president and head of genetic diseases Hartmann Wellhoefer told *Scrip* in an interview at the WORLD Symposium.

Fabry disease, for instance, typically is diagnosed when patients already are on dialysis for kidney damage rather than during the period when patients experience non-specific pain and gastrointestinal issues; in children, hearing loss and behavioral issues are a concern. Patients with Hunter disease experience bone structure issues and joint damage that could be prevented, at least in part, by earlier treatment.

Amicus hosted a seminar on Feb. 15 to discuss personalized medicine in lysosomal diseases, which highlighted the difficulty of early diagnosis in diseases for which the early symptoms aren't an obvious indication of a particular rare disease.

That's where Ana Jovanovic, a consultant in adult inherited metabolic disorders who works in the Mark Holland Metabolic Unit at the Salford Royal NHS Foundation Trust in Salford, UK, noted that the traditional path to diagnosis requires "a high degree of clinical suspicion" on the part of the treating physician.

Precision medicine – targeted and often personalized treatments based on patient- or subgroup-specific disease targets – is difficult in lysosomal diseases, Jovanovic said, because biomarkers haven't been identified in many diseases and the patient populations are heterogeneous with varying degrees of disease and symptom severity.

Amicus vice president and head of global regulatory affairs Andrew Mulberg noted that a lack of natural history data in many lysosomal diseases also makes personalized medicines and other therapeutic approaches difficult. Data aren't available to compare with biopharma clinical trial results and show that a drug can slow the progression of a disease.

Marc Patterson – a neurology, pediatrics and medical genetics professor who chairs the Division of Child and Adolescent Neurology at the Mayo Clinic in Rochester, Minnesota – said that's why disease-specific organizations should organize patient registries if they haven't already. The information could identify biomarkers and other data to support the development of new diagnostics and treatment options.

Mulberg agreed, noting that "non-proprietary, non-pharma-related natural history data is important," because "we're all then looking at the same apples" rather than comparing apples to oranges.

'We have various approaches, because MPS I is a heterogeneous disease, so we may have more than one small Phase III study'

OTHER DATA AT WORLD SYMPOSIUM

Biopharma companies presented data from a mix of preclinical, early clinical and post-marketing studies at the WORLD Symposium. Some highlights for therapies still in development were:

- Phase Ib data for Sanofi/Genzyme's breakthrough therapy-designated olipudase alfa to treat acid sphingomyelinase deficiency (ASMD or Niemann-Pick type B) showed effects on non-neurological symptoms in adults treated for 30 months.
- BioMarin's and Sanofi/Genzyme's intrathecal version of *Aldurazyme* (aronidase) for the treatment of cognitive decline in Hurler syndrome (MPS I) appeared to be safe in an open label study conducted between 2009 and 2015.
- BioMarin's *Brineura* (cerliponase alfa) significantly reduced the rate of motor and language decline for children with CLN2 disease, a form of Batten disease, who were enrolled in a long-term study compared to a control group; a biologic license application for the ERT is under review by the US FDA.
- A Phase III retrospective analysis showed a correlation between the reduction in disease substrate and reduction in diarrhea for Fabry disease patients treated with migalastat. Amicus will initiate a study in 2017 to confirm the gastrointestinal benefit of the pharmacological chaperone – data that are needed to seek FDA approval.
- Updated and long-term Phase I/II results for PRX-102, a plant-derived alpha-GAL-a enzyme, showed continued benefit for Fabry disease patients; Protalix BioTherapeutics Inc. initiated a Phase III clinical trial in October.
- Abeona Therapeutics Inc. presented additional data from the first dosing cohort of its Phase I/II clinical trial testing the gene therapy ABO-102 in Sanfilippo syndrome type A (MPS IIIA), which showed continued positive effects with some fluctuations; enrollment in the second cohort is under way. A Biomedtracker analysis noted that longer-term data and results from higher doses are needed to confirm what looks to be an encouraging effect on Sanfilippo type A. ▶

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AZ's ZS-9 Nears EU Market

AstraZeneca PLC's investigational hyperkalemia therapy, *Lokelma* (ZS-9, sodium zirconium cyclosilicate), has received a positive opinion from the EU's Committee for Medicinal Products for Human Use (CHMP), and if it is approved, could become a high-selling product through satisfying an unmet need in the therapeutic sector. The UK big pharma spent \$2.7bn on acquiring the US company, ZS Pharma Inc., that initially developed ZS-9, in 2015, and was hoping that it would first be marketed in the US in 2016. But its approval there has been delayed because of a manufacturing issue in a plant in Texas, that resulted in the company being sent an FDA complete response letter. The product now has a PDUFA date in the US of Apr. 18, 2017. In Europe, ZS-9 has been recommended for approval for a relatively simple indication, the treatment of hyperkalemia in adult patients. It has been given the green light as 5 g and 10 g of powder, for formulating into an oral suspension, the CHMP explained on Feb. 24, the day after the end of the committee's monthly meeting.

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New EU Nod For J&J/ Genmab's Darzalex

The EU's CHMP has granted a positive opinion on expanding the approved indications for Janssen Pharmaceuticals Inc./Genmab AS's anti-CD38 monoclonal antibody *Darzalex* (daratumumab; licensed from Genmab) for use in combination with lenalidomide (Celgene's *Revlimid*) and dexamethasone, or bortezomib (Takeda/Johnson & Johnson's *Velcade*) and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. The product was originally granted a conditional approval last May by the European Commission for use as a monotherapy for adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy.

Patient Death Casts Cloud Over Roche

A patient death in the Phase III HAVEN 1 study of Roche's investigational hemophilia A treatment, emicizumab (ACE-910), may have cast a shadow over the product's safety profile, but experts say there is no conclusive evidence that it was related to the drug. Even so, concerns are growing over the investigational drug's side effect profile. Positive top-line data from the ongoing study were reported late last year when they were seen as putting pressure on the hemophilia franchises of the big players in this field, Shire and Novo Nordisk. Emicizumab has been tipped as a potential blockbuster because of the high unmet medical need for prophylaxis treatment in hemophilia A patients, especially for the 30-40% who develop inhibitors and then need to undergo immune tolerance induction therapy to allow clotting factor use, or use bypassing agents such as Baxalta Inc.'s anti-inhibitor activated prothrombin coagulant complex, FEIBA, and Novo Nordisk AS's recombinant Factor VII product, NovoSeven. Both these therapies come with difficulties: FEIBA requires long infusions, while NovoSeven, has to be used every two hours, even during the night, due to its short half-life. Roche's emicizumab is bispecific monoclonal antibody that binds to Factor IXa and Factor X to exert a Factor VIII-mimetic activity and activate the natural coagulation cascade and restore the blood clotting process. Its promise lies in its once-weekly sc prophylactic dosing regimen (a once-monthly regimen is also under investigation) and the fact it works in patients with Factor VIII inhibitor antibodies. It was originally developed by Chugai Pharmaceutical Co. Ltd. and has a US breakthrough therapy designation for prophylactic treatment of hemophilia A in patients over 12 years.

alex.shimmings@informa.com, 24 Feb 2017

The US FDA expanded its original 2015 approval to the second-line setting in November. The new indication, when rubber stamped by the EC in around three months' time, will expand its use into a larger patient population and bring it more into line with Bristol-Myers Squibb/AbbVie's rival MAb product, *Emplixi* (elotuzumab). Multiple myeloma patients often receive several lines of therapy during the disease course, but the population getting earlier-phase treatments is larger, making these indications more commercially important.

alex.shimmings@informa.com, 24 Feb 2017

BMS Given Longer To Make Opdivo Case

NICE, the HTA body for England and Wales, has published draft guidance that does not recommend Ipsen's *Cabometyx* (cabozantinib) for previously treated advanced renal cell carcinoma

(RCC), leaving Bristol-Myers Squibb's *Opdivo* (nivolumab) as the frontrunner for this patient group. NICE recommended *Opdivo* in October last year, but only after an initial rejection on concerns about the drug's cost and its long term survival benefits. Bristol-Myers Squibb Co. turned things around by providing a patient access scheme in the form of a discount on the list price, an updated cost analysis and more clinical data. Ipsen had not responded to *Scrip's* queries on this matter at the time of writing. Fontanilla noted that Novartis AG's *Afinitor* (everolimus) was also not recommended by NICE in this indication following European approval and has only been available through the UK's cancer drugs fund. "Opdivo is likely to gain unrestricted uptake in the UK and will potentially become the second-line standard of care if Ipsen doesn't provide the drug at a discount," she added.

sukaina.virji@informa.com, 21 Feb 2017

Alexion, United, Intercept And 'Alternative Facts'

ANDY SMITH

Mid-cap biotech companies Alexion and United Therapeutics both missed fourth-quarter sales expectations and although Intercept beat analysts' estimates with \$13.4m in sales, does that justify a \$3bn valuation?

If this fourth-quarter earnings season could be likened to the latest results from a soccer league, big pharmaceutical companies seemed to have finished mostly on the losing side while specialty pharmaceutical companies have clawed back the lead before half-time after a late kick-off. Biotech companies have the evening fixtures and have scraped wins on the strength of their non-GAAP financial results, although the number of sendings-off on accounting reconciliations should have left fans feeling bruised.

Alexion Pharmaceuticals Inc. – which is still many investors' archetype for a premium priced orphan drug marketer – did not engender hopes for a biotech renaissance when it reported quarterly sales of \$831m that missed analysts' consensus estimates by \$5m. Non-generally accepted accounting principles (non-GAAP) earnings per share (EPS) did, however, beat consensus estimates by 0.8%. Alexion's non-GAAP EPS of \$4.62 contrasted with its GAAP EPS of \$1.76 and should have pointed investors to the reconciliation part of Alexion's accounts as recommended in Elliott and Schroth's book *How Companies Lie* (I have a signed copy). This attributed much of the difference in GAAP and non-GAAP earnings to write-downs of acquired intangible assets and share-based compensation.

The assets being impaired were *Strensiq* (asfotase alfa), *Kanuma* (sebelipase alfa) and SBC-103, all of which came with Alexion's \$8.4bn acquisition of Synageva BioPharma Corp. Part of Alexion's sales miss was also due to Kanuma, although more worryingly Alexion's weaker than expected full-year 2017 sales guidance probably reflected a minimal contribution from Kanuma, which is experiencing a difference in value perception between Alexion and European payers. While most analysts appeared to be relieved that Alexion was past the difficult fourth quarter, I wondered whether the recent departures of its CEO and CFO had anything to do with the Synageva acquisition and Alexion's "second album" difficulties of finding a replacement for its lead product *Soliris* (eculizumab). In soccer parlance, with *Soliris* sustaining a recent Phase III failure (or soccer injury) the Synageva signing looks likely to be out for the season and should probably have had a more extensive medical before \$8.4bn was handed over.

UNITED THERAPEUTICS

If Alexion's 2017 guidance disappointment was more of a worry than its fourth-quarter sales miss, the tables were turned at United Therapeutics Corp. when it reported sales of \$409m, \$9m behind analysts' consensus estimates. It was fair to say that United Therapeutics' results were not well received since its stock price finished the week down over 12% against a more neutral 0.7% drop for the NASDAQ Biotech Index. The sales weakness in its products *Tyvaso* (inhaled treprostinil) and *Orenitram* (oral treprostinil) was probably due to the recent launch of Actelion Pharmaceuticals Ltd's *Uptravi* (selexipag). *Uptravi* is the only approved selective oral IP prostacyclin receptor agonist for the treatment of pulmonary arterial hypertension (PAH)

and while United Therapeutics and Actelion both have prostaglandin derivatives for the treatment of PAH, Actelion's oral endothelin receptor antagonists and now oral *Uptravi* probably represent a more rounded team franchise for the comprehensive treatment of PAH. This could explain why Actelion and not United Therapeutics is being acquired for \$30bn by Johnson & Johnson. If investors delved deeper into United Therapeutics' fourth-quarter results and reconciled its non-GAAP EPS of \$4.97 against its GAAP EPS of \$2.43, they would have found \$105.3m in share-based compensation, expense which is somewhat typical of United Therapeutics if more than somewhat unpalatable. This nest-feathering took the shine off United Therapeutics' 12% beat of analysts' consensus non-GAAP EPS expectations. As the analysts from Cowen pointed out, even that was driven by share repurchases; they have placed their price target under review. The analysts from Ladenburg Thalmann meanwhile downgraded their recommendation on United Therapeutics from "Neutral" to "Reduce."

Perhaps the biggest investor critique of the week came in response to the fourth-quarter results of Intercept Pharmaceuticals Inc. Loss-making Intercept reported \$13.4m in sales for its recently launched product *Ocaliva* (obeticholic acid) for the treatment of the orphan disease primary biliary cholangitis. The share price of Intercept finished the week down 7.4% and the analysts from Citigroup declared that they could not "see any obvious explanation for the decline." While Intercept tried to console investors with the 55% increase in covered lives in three months, I can think of an easy explanation for the sell-off. For the avoidance of doubt, a good drug launch (without any need to mention of covered lives or physician feedback) was Gilead Sciences Inc.'s first quarter on the market with *Sovaldi* (sofosbuvir), which generated sales of \$2.27bn. Intercept's \$13.4m launch is, by comparison, an embarrassing rounding error for a company with a \$3bn market capitalization.

NEVER SATISFIED

I accept the criticism that CEOs have of investors for never being satisfied if one of sales, earnings or guidance isn't up to what was expected. But a focus on GAAP and non-GAAP reconciliations is pertinent since a study by Citigroup last year illustrated the biggest differences between the two occurred at S&P 500 companies in times of recession. Non-GAAP accounting was called out by Warren Buffet in his address to shareholders this weekend when he used the term "adjusted earnings"; in the parlance of the US administration it could be described as "alternative facts." If we hadn't realized it, contrary to the all-time highs in broad stock markets, we are in a biopharma stock market recession. Missed expectations, big adjusted earnings reconciliations and tiny sales aren't helping. ▶

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Andy Smith gives an investor's view on life science companies. He joined the Commercialization, Pricing and Market Access group of ICON PLC in February 2017. Andy 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.

Novel Antibody Products Ring The Changes In HIV

Two Canadian companies – Theratechnologies and CytoDyn – exploring the use of monoclonal antibodies in the fight against HIV presented data for their novel late-stage candidates at the recent CROI meeting in Seattle. They are aimed at patients experiencing multi-drug resistance and represent a change in this mature therapy area dominated by small-molecule oral products.

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Montreal-based Theratechnologies Inc. is planning a FDA submission shortly, after a three-month delay, for its novel therapy for multi-drug resistant HIV, ibalizumab. Analysts are confident of its quick success at the agency, given the novel product's efficacy and the unmet patient need, which should propel the company to a different league, sales-wise. HIV may have morphed into a long-term illness with the arrival of highly active antiretroviral therapy, but more and more patients are now running through the current treatment options, increasing the demand for novel treatment strategies.

There are about one million HIV patients in the US, of whom between 43% and 63% are on antiretroviral therapy, and analysts at Mackie Research say they believe the MDR population will increase from 10,000 this year to 25,000 patients by 2024. Ibalizumab already has a US FDA breakthrough therapy designation and orphan drug status. "We expect the approval in H2 2017. Ibalizumab should be a transformative product for Theratechnologies and should provide the company with robust long-term growth."

EGRIFTA DWARFED

The analysts predict ibalizumab sales to reach C\$243m, in 2020, dwarfing those of its only marketed product to date, *Egrifta* (tesamorelin acetate) for lipodystrophy, which brought in just over C\$37m last year and is estimated to top C\$58m in 2020. Theratechnologies signed a marketing and distribution deal in the US and Canada from the Taiwanese company Taimed Biologics last March for \$1m in cash with a further \$1m to be paid in shares at the commercial launch. A further \$8.5m will become due at commercial launch, subject to certain conditions.

Ibalizumab is a humanized monoclonal antibody that, unlike other antiretroviral agents, binds primarily to the second extracellular domain of the CD4+ T cell receptor, away from major histocompatibility com-

plex II molecule binding sites. It is thought to prevent HIV from infecting CD4+ immune cells while preserving normal immunological function, and is active against HIV-1 that is resistant to all approved antiretroviral agents.

Theratechnologies released two studies during the Conference on Retroviruses and Opportunistic Infections (CROI) in Seattle – the Phase III trial TMB-301, presented as a late-breaker, as well as another study showing that the product can be delivered intramuscularly (this could improve patient experience by providing another route of administration when IV is not available and may be more convenient in outpatient settings).

The 24-week TMB-301 study showed that patients with multidrug resistant (MDR) HIV-1 infection experienced a mean increase in CD4+ T cell of 48 cells/ μ L after 24 weeks of treatment with ibalizumab plus an optimized background regimen (OBR). These data supplement previously reported findings in November, where 83% of patients achieved a ≥ 0.5 log₁₀ decrease in viral load from baseline seven days after the single intravenous loading dose of 2000 mg of ibalizumab (primary endpoint) and a mean reduction in viral load of 1.6 log₁₀ over the 24-week treatment period with more than 48% of patients experiencing a viral load reduction of more than 2.0 log₁₀.

At the end of the treatment period, the proportion of study participants with undetectable viral load (HIV-1 <50 copies/mL) was 43% (mean viral load reduction of 3.1 log₁₀) and 50% of patients had a viral load lower than 200 copies/mL.

Total CD4+ T cell increases varied according to baseline levels of CD4+ T cells:

- Patients with baseline CD4+ T cells <50 cells/ μ L (17 patients) had an increase of 9 cells/ μ L;
- Those with CD4+ T cells between 50 and 200 cells/ μ L (10 patients) had an increase of 75 cells/ μ L; and
- Those with CD4+ T cells >200 cells/ μ L (13

patients) had an increase of 78 cells/ μ L.

CD4+ cell count has a direct bearing on how well the body can fight infections. "This meaningful increase in CD4+ T cell counts is particularly important for patients with multidrug resistant virus, as they often have the most advanced disease. These data suggest that for these patients, ibalizumab could be an important new treatment option," said researcher Dr. Brinda Emu of Yale School of Medicine.

Similar efficacy was observed in a subgroup of 17 patients infected with HIV-1 that was resistant to all FDA-approved ART and for whom the only other active agent that could be included in the OBR was another investigational drug.

The Mackie analysts added: "It is also interesting to note that 20 HIV patients have been on ibalizumab for seven years – considering that this use is from a clinical trial it indicates the potential patient retention rate could be high," the analysts note.

Safety results were consistent with the Phase IIb trial. Apart from one case of immune reconstitution inflammatory syndrome – an inflammatory response in HIV-infected patients that may be triggered after changing to more active ART – there were no serious adverse events were considered to be related to ibalizumab, and no anti-ibalizumab antibodies were detected.

NOVEL MECHANISM

If it succeeds in getting approved, Dr. Christian Marsolais, Theratechnologies' senior vice president and chief medical officer, said ibalizumab would be "the first antiretroviral treatment with a new mechanism of action to be approved in close to 10 years."

But here it has some competition with Viiv Healthcare's small-molecule product fostemsavir (BMS-663068) – which also is designed to prevent HIV attachment to and entry into CD4+ cells and also has breakthrough therapy status. This prod-

uct was one of two-late stage assets Viiv obtained from Bristol-Myers Squibb Co. in late 2015, and is in a Phase III trial in heavily treatment experienced patients due to complete next year.

CYTODYN'S PRO 140

Meanwhile, Vancouver-based CytoDyn Inc. reported Phase IIb data at the Seattle meeting for its antibody product, PRO 140, showing that it provided maximal virologic suppression and was well tolerated by 10 HIV-infected patients for nearly two years when given as a single agent.

Another breakthrough therapy, PRO 140 is a humanized IgG4 MAb which blocks HIV-1 from entering and infecting immune cells by binding to the CCR5 receptor with high affinity, providing a novel approach to maintaining virologic suppression. Its inventor, Dr. Paul J. Maddon, senior science advisor to CytoDyn, said: "It is exciting that a group of patients self-administering PRO 140 as a monotherapy were able to avoid the potential toxicity of ART, while preserving their option to return to an ART regimen at a later date."

The product was well tolerated with no serious adverse events and no anti-PRO140

antibodies were detected which implies no drug resistance.

CytoDyn believes the data are strong enough to warrant further development as a long-acting, single-agent maintenance therapy in select HIV-1 patients who experience toxicity, intolerance or who find it difficult to adhere to the drug regimen, but the company also has its sights on the MDR population.

Last September, the company raised about approximately \$9.0m to fund clinical trials for its product candidates and for general corporate purposes. It has underway two Phase III trials for PRO 140 in patients with CCR5-tropic HIV-1:

- CD02 trial – in combination with other antiretroviral agents in 30 treatment-experienced adult patients who have documented multi-antiretroviral class resistance and evidence of HIV-1 replication despite ongoing antiretroviral therapy;
- CD03 trial – with PRO 140 as a single-agent maintenance therapy in 300 virally suppressed HIV patients to assess the efficacy, safety and tolerability of PRO 140 as a long-acting, single-agent maintenance therapy for the chronic suppression of HIV. Patients will be shifted from

daily ART regimens to weekly PRO 140 SC injections for 48 weeks.

"We are excited about both Phase III trials with PRO 140," said CytoDyn president and CEO Dr. Nader Pourhassan. "While we believe PRO 140 as a combination therapy offers the compelling advantage of allowing patients to discontinue the most toxic drug in their ART regimen, the results presented today provide sufficient reason to continue pursuing PRO 140 as a single-agent therapy. We are using our ongoing trials to evaluate a number of factors such as patient characteristics and dose levels that may predict PRO 140 treatment success in future studies."

Analysts at Informa Pharma's Biomed-tracker said: "These data support the continued development of PRO 140 as a maintenance monotherapy for patients with CCR5-tropic HIV-1 and we are raising the LOA [likelihood of approval] by 1%. The potential market advantage of this drug is the avoidance of the potential toxicity associated with ART."

There do not appear to be any other antibody-based treatments of HIV in late-stage development. ▶

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Scrip Awards Winner 2016

HUYA Bioscience International's Best New Drug Award

Dengvaxia is the first vaccine against dengue, a disease that affects 390 million people each year. It is indicated to prevent dengue caused by all four of the virus serotypes and is the culmination of over two decades of scientific innovation and collaboration, with 40,000 volunteers participating in the development program.

"Dengue places a heavy burden on individuals and communities in endemic areas around the world. Bringing the first dengue vaccine to the world is consistent with Sanofi Pasteur's vision to be a global public health partner in combatting infectious diseases through vaccination."

David Loew, CEO of Sanofi Pasteur

Sponsored by 



Winner: Sanofi Pasteur's Dengvaxia

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Merck's Write-Down Of Phase II Nuc Illustrates Current Reality In HCV

JOSEPH HAAS joseph.haas@informa.com

While a dwindling patient base and pricing pressures are depleting the market opportunity in hepatitis C, Merck's decision also may result from regulatory dialogue potentially delaying the start of a Phase III study.

Merck & Co. Inc.'s decision to take a \$2.9bn pre-tax intangible asset impairment charge against its 2016 financial results due to a reassessment of the value of Phase II hepatitis C candidate uprifosbuvir (MK-3682) reflects the declining market opportunity in HCV due to a diminishing patient population and the impacts of pricing pushbacks.

In an 8-K filing with the US Securities and Exchange Commission Feb. 23, the firm revealed that it would assess the impairment charge – thereby reducing its earnings-per-share for 2016 – because of “recent changes to the product profile.” After taxes, the charge will amount to roughly a loss of \$1.9bn for Merck, which now values the experimental nucleoside polymerase inhibitor at \$240m, based on market participation assumptions and consideration of different scenarios that could occur in the HCV therapeutic space.

In the filing, Merck stated that “changes to [our] expectations for pricing and the market opportunity, taken together constituted a triggering event that required the Company to evaluate the uprifosbuvir intangible asset for impairment.” Merck said the impairment charge will reduce its fourth quarter EPS from \$0.42 to \$0.22 and its full-year EPS from \$2.04 to \$1.41.

The HCV market overall has been in decline. Market-leading Gilead Sciences Inc. earlier this month slashed its earnings guidance for HCV based on the reduced patient population and pricing pressure.

Merck cited largely the same reasons for the changes in the HCV projections. There has been a reduction in the addressable patient population because the current generation of HCV drugs from Gilead and AbbVie Inc. are curative and have produced high virologic clearance

rates in clinical practice so far. In addition, a pricing environment in which country-by-country negotiation in the EU and the need to provide discounts to obtain favorable formulary positioning from US health plans have diminished the earning power of HCV drugs.

Merck will continue the ongoing development of uprifosbuvir in two Phase II combination studies – one evaluating the “nuc” with the experimental NS5A inhibitor MK-8408 and another investigating triple therapy with those two drugs and grazoprevir, the protease inhibitor approved by FDA in 2016 as one of the two components in Merck's *Zepatier* (grazoprevir/elbasvir). MK-8408 is intended as a follow-on to elbasvir, another NS5A inhibitor.

Merck acquired uprifosbuvir and two other HCV candidates – the nuc IDX-21459 and NS5A inhibitor samatasvir – via its \$3.85bn buyout of Idenix Pharmaceuticals Inc. in June 2014. The other compounds acquired in the sale are not in active development by Merck.

Although uprifosbuvir is not dead yet, the Merck/Idenix deal was one of a trio of high-priced buyouts between 2011 and 2014 motivated almost entirely by companies competing in the HCV space wanting to add a nuc to their pipelines.

GILEAD WON, BRISTOL LOST

The contrasts are stark. Gilead succeeded significantly with its eye-opening \$11bn purchase of Pharmasset Inc. in 2011 on the strength of a Phase II nuc, sofosbuvir, which obtained approval first as solo agent Sovaldi and then as part of the successful HCV fixed-dose combos Harvoni (sofosbuvir/ledipasvir) and Epclusa (sofosbuvir/velpatasvir). According to an assessment by *Scrip* last August based on sales to date and projections of future revenue, that deal will provide Gilead with approximately a 10x multiple on the sales price, still the largest ever paid for a clinical-stage biotech.

A notable contrast to that deal was Bristol-Myers Squibb Co.'s January 2012 acquisition for \$2.5bn of Inhibitex Inc. centered on Phase

II nuc INX-189. The transaction exploded in Bristol's face in less than a year, as it discontinued development of the compound in August 2012 due to cardiotoxicity, and took a \$1.8bn pre-tax impairment charge.

The Idenix buyout has not yet reached that level of disaster, but Merck clearly sees diminishing prospects for gaining market share with a combo containing uprifosbuvir.

POSSIBLE PHASE III DELAY

The biggest issue may be rooted in discussions the pharma has had with FDA; the agency wants to see efficacy data from the Phase II study of the uprifosbuvir/MK-8408 doublet, which is less far along than the Phase II study of the triple combination, before it will okay the initiation of a Phase III trial for the triple, which Merck has touted to investors as its last major prospect in HCV therapy.

This development greatly delays when Merck might be able to bring the triple to market, and Gilead and AbbVie are advancing their final HCV combinations toward regulatory filings as well.

“Merck has been informed by regulators that it will need to complete separate trials, and show an added benefit, with the triple, over its high-dose doublet of MK3683 plus MK8408,” the Leerink note states. “This suggests that the company will need to wait for data from the high-dose doublet (which is further behind in Phase II) and delays the timing of the triple materially.”

Phase II data for the doublet are expected toward the end of 2017, the note adds, but timing for when a Phase III study with the triple combo could begin is unclear. Merck is continuing to enroll patients for both Phase II trials – the triple combo study began in December 2015 with a planned enrollment of 200 patients with genotype 1 or 3 infections who have failed prior therapy with direct-acting antivirals, while the doublet study, initiated this past November, is enrolling up to 250 treatment-naïve or treatment-experienced patients who have not been treated with DAA regimens. ▶

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Billions At Stake As Generic Approvals Open Up Japan Big Sellers

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Japan has approved a new batch of first-time and other generic drugs that will be reimbursed and launched in June, putting at risk several billion dollars' worth of combined sales of some major branded products.

The latest approval of a batch of generic products in Japan opens up to first generic competition a number of big-selling original products in the country, notably in the cardiovascular area, putting at risk several billion dollars' worth of branded sales.

A total of 365 individual generic drugs across multiple active ingredients have been approved by the Ministry of Health, Labor and Welfare for inclusion in the national health insurance reimbursement tariff in June, which will enable commercial launch thereafter.

The lineup notably includes the first generic competition in Japan for Boehringer Ingelheim GMBH/Astellas Pharma Inc's antihypertensive *Micardis* (telmisartan) and related fixed-dose combinations *Micamlo* (telmisartan plus amlodipine) and *Micombi* (telmisartan plus hydrochlorothiazide).

Astellas is forecasting sales of JPY94.7bn (\$834m) for the *Micardis* family in the fiscal year ending March 31, a large pie up for grabs which alone attracted 24 manufacturers and around 100 products in the listing.

ABILIFY, OLMETEC

Among the other major products that will see their first local generic rivals are Otsuka Pharmaceutical Co. Ltd.'s atypical antipsychotic *Abilify* (aripiprazole), with 113 generic preparations due to be listed. Otsuka recently reported Japanese *Abilify* sales of JPY31.7bn in the financial year ended Dec. 31.

Another sartan, Daiichi Sankyo Co. Ltd.'s *Olmotec* (olmesartan), and its fixed-dose combination with azelnidipine, will also see the entry of an authorized generic, potentially undermining the JPY69.0bn in *Olmotec* sales that Daiichi Sankyo is forecasting in its fiscal year ending March 31.

However, the product is being launched by Daiichi Sankyo's own Daiichi Sankyo Espha subsidiary, which also plans to launch in June an authorized generic version of AstraZeneca PLC/Shionogi & Co. Ltd.'s high cholesterol drug *Crestor* (rosuvastatin). Shionogi sees its *Crestor* sales in the fiscal year to March 31 reaching JPY42.9bn.

Put together, these four major active ingredients represent roughly \$2bn in combined annual branded sales that will be put at risk from generic competition (authorized or otherwise) following the June generic launches.

Other listings this time include Towa Pharmaceutical Co. Ltd. with 35 products, Sawai Pharmaceutical Co. Ltd. with 27 (across 10 active ingredients), and Takeda Teva (eight AIs).

POLICY SUPPORT

While starting prices for first-time generics in Japan were reduced last year, the new losses of exclusivity still present a potential bonanza for generics companies, as reimbursement is usually set at 50% of the original drug's current listed official price (40% if more than 10 preparations are listed at once).



AUTHORIZED GENERICS

In a continuation of a trend towards higher numbers of authorized generics in Japan, Daiichi Sankyo Espha is entering the fray through such planned launches as well as conventional generics for the three telmisartan products.

Although less of a factor now, one past hindrance to wider generic uptake in Japan has been prescribers' reluctance to move away from trusted brands, amid lingering concerns over the quality, equivalence and stable supply of generics.

Given this background and that authorized generics, in Daiichi Sankyo Espha's view, can "inherit trust accumulated in medical practice from the original brand drugs," the company says it is planning to pursue more such internal and external launches in the future, following the success of its *Cravit* (levofloxacin) authorized generic launch in Japan in December 2014. The other main generic companies participating in the telmisartan and

The official policies of the past few years to encourage generic uptake, such as revised fee incentives and easier prescriber permission for substitution, also show no signs of abating as Japan continues to grapple with rising healthcare costs from an ageing population and increasing uptake of new, higher-priced therapies for hepatitis C and cancer.

The various policy moves have served to accelerate the erosion of branded sales after patent expiry, and in 2015 the government raised its official target for the volume share of generics in the substitutable market to 80% by March 2021, up from around an actual 56% as of the end of 2015.

Sandoz, for one, said recently that it is expecting to fully double its Japan business over the next five years, boosted by these policies and a series of major opportunities and the planned launch of 70 molecules over the period. ▶

From the editors of *PharmAsia News*.

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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.



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Visit the Pipeline Watch webpage at scrip.pharmamedtechbi.com for all the week's changes to the industry's R&D pipeline

Selected clinical trial developments for the week 17–23 February 2017

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
Phase III Results Published			
Novo Nordisk AS	<i>Victoza</i> (liraglutide)	obesity, prediabetes	SCALE; in <i>The Lancet</i> , Feb. 22, 2017.
Bristol-Myers Squibb Co.	<i>Opdivo</i> (nivolumab)	anal cancer	<i>The Lancet Oncology</i> , Feb. 17, 2017.
Merck & Co. Inc.	<i>Keytruda</i> (pembrolizumab)	bladder cancer	KEYNOTE-045; the <i>NEJM</i> , Feb. 17, 2017.
Updated Phase III Results			
TiGenix NV/Takeda Pharmaceutical Co. Ltd.	Cx601 (allogeneic adipose-derived stem cells)	peri-anal fistula in Crohn's disease	ADMIRE-CD; long-term remission.
Phase III Completed			
ArQule Inc./Daiichi Sankyo Co. Ltd.	tivantinib	liver cancer	METIV-HCC; missed primary endpoint, no effect on overall survival .
Chimerix Inc.	brincidofovir	adenovirus infection in hematopoietic cell transplant	AdVise; suppressed virus, higher rates of survival.
Phase III Interim/Top-line Results			
Celgene Corp.	ozanimod, oral	multiple sclerosis	SUNBEAM; met primary endpoint, annualized relapse rate reduction .
AstraZeneca PLC	<i>Lynparza</i> (olaparib)	BRCA-mutated breast cancer	OLYMPIAD; met primary endpoint, PFS improvement .
Cyclacel Pharmaceuticals Inc./ Daiichi Pharmaceutical Co. Ltd.	sapacitabine	acute myeloid leukemia	SEAMLESS; mixed results, but active and well tolerated .
Trevena Inc.	oliceridine	moderate to severe acute pain	APOLLO-1,-2; met primary endpoint .
Celltrion Inc./Pfizer Inc.	<i>Inflixtra</i> (infliximab-dyyb)	Crohn's disease	Efficacy similar to <i>Remicade</i> .
GlaxoSmithKline PLC/Innoviva Inc.	<i>Breo Ellipta</i> (fluticasone, vilanterol) once-daily	well-controlled asthma	Switch possible from twice daily Seretide Accuhaler (fluticasone, salmeterol)
Phase III Initiated			
Flexion Therapeutics Inc.	<i>Zilretta</i> (triamcinolone acetonide)	osteoarthritis, knee	In 200 patients in the US.
Phase III Announced			
Acea Pharmaceuticals Inc.	AC0010MA	non-small cell lung cancer	Combined with pemetrexed, cisplatin.
Phase II Suspended			
Cidara Therapeutics Inc.	CD101, topical	vulvovaginal candidiasis	RADIANT; not sufficient efficacy.

Source: Biomedtracker

Celgene Corporation's president and chief operating officer (COO), **Jacquelyn Fouse**, will be retiring from the company – effective June 30, 2017. **Scott Smith** has been announced as Fouse's successor and will hold the same title. Smith joined Celgene in 2008 to build and launched the company's I&I franchise. Before this he was global commercial head for Biovail. Meanwhile, **Terrie Curran** has also been promoted to president, global inflammation and immunology (I&I) franchise – effective April 1, 2017. Curran joined the company in 2014 as the US commercial head of the I&I franchise and was later promoted to head of worldwide commercial markets for the I&I franchise. Prior to this, she led Merck & Co.'s global women's health franchise as senior vice president.

YposKesi, a French pharmaceutical company, has appointed **Alain Lamproye** CEO. He joins the company from the biopharma business unit of Novasep, where he was chair since 2012. Previously, he was CEO of Henogen, Novasep's gene therapy focused subsidiary. Lamproye has also worked at Merck Serono, where he held various managerial positions, including site director at Billerica, US. Before this, he was GMP production director at Eurogentec (Belgium) for 14 years.

Sangamo Therapeutics Inc., a company focused on therapeutic genome editing, has appointed chemical engineer **Kathy Yi** senior vice president and chief financial officer. Yi will succeed current CFO **H. Ward Wolff**, who will be retiring from the company this year. Yi has more than 15 years' experience in corporate finance and most recently, she was head of finance for Novartis Pharmaceuticals' global inhalation technical research and development group. Before this, she held financial positions at Life Technologies Corp and Intel Corp.

Gene and cell therapy focused **Oxford BioMedica Plc.** has named **Stuart Paynter** chief financial officer – he relaces Tim Watts, who is retiring from full time executive roles. Paynter is currently finance director, head of business partnering at De La Rue Plc. Before this, he was at Shire Pharmaceuticals, where he held the roles of vice president, head of global audit; senior director, head of internal value management and senior director, head of international speciality pharma finance.

Janet Dorling has joined **Achaogen Inc.** as chief commercial officer and brings more than 14 years of experience in commercial sales and marketing of pharma products to

the company. Most recently, she was the vice president of global product strategy, breast cancer at Roche/Genentech and before this she was vice president of the Lytics Franchise. She has also led the market analysis and strategy group at Genentech.

CRISPR Therapeutics has appointed **Jon Terrett** head of immuno-oncology research and translation. Terrett joins the company from CytomX, a US biotech focused on cancer, where he was vice president oncology discovery. He has previously held various R&D leadership roles in biopharma companies, including Oxford Biotherapeutics, where he was chief scientific officer and has been director at biotech companies including Medarex, CellTech and Oxford Glycosciences.

The biotech company **Onxeo SA.**, focused on orphan diseases, has named **Françoise Bono** chief scientific officer and **Olivier de Beaumont** chief medical officer. Previously, Bono spent 25 years with Sanofi and Evotec and was Evotec's executive vice president, oncology until late 2016. Since 2005, Beaumont was with **Stallergenes Greer** as senior vice president, head of global clinical development, pharmacovigilance and medical affairs and a member of the executive committee.

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