Scrip
23 November 2018
No. 3932
scrip.pharmaintelligence.informa.com
Pharma intelligence | informa

R&D Heads At GSK & AZ Say Key To Success Lies In Smart Risk Taking

STEN STOVALL sten.stovall@informa.com

The raison d'être of any R&D chief is finding a way to increase the successful translation of innovation into a rejuvenated pipeline and successful new drug launches. The R&D heads of Britain's two biggest pharma companies were asked at a recent London conference what they believe the secret in doing that is – and both agreed that in large part it lies in creating a smarter, more focused risk-taking culture within their teams.

AstraZeneca PLC's Mene Pangalos and **GlaxoSmithKline PLC**'s Hal Barron were featured speakers at this year's FT Global Pharmaceutical and Biotechnology Conference in London. Each heads R&D teams that have had their share of disappointments.

AstraZeneca's recent rebound in pipeline productivity and product launches contrasts markedly with a dire position of just a few years ago. Pangalos, in concert with AZ's CEO Pascal Soriot, has overseen that rebound.

Hal Barron was brought in this year to shake up and improve GSK's R&D efforts by the company's recently installed CEO Emma Walmsley. *(Also see "For GSK R&D Head Hal Barron 'There's No Place Like Home' For Seeding Innovation" - Scrip, 25 Jul, 2018.)*

ASTRAZENECA'S PANGALOS RELATES R&D JOURNEY

Pangalos, who joined AstraZeneca in 2010 when the company was struggling with an anemic pipeline, has since overseen a transformation of its R&D productivity resulting in a greater than four-fold increase in success rates compared with industry averages.

"We spent quite some time in the early years trying to understand what it was about our decision making that had made us, by one measure, as being the most productive pharma company in the world measured by the number of things that we did, while at the same time – and more importantly – the fact we were one of the least productive companies when it came to the launch of new drugs," the scientist explained.

"As a consequence of that analysis, we changed the internal culture of the company, moving away from the volume and quantity of the things that we did to one where we were fundamentally asking whether we believe in the programs that we're working on are based on sound science and biology, do we understand what the key experiments are, the patient populations that are most likely to respond, and why anyone would care to reimburse the medicine," Pangalos told the conference.

He said AstraZeneca's R&D scientists were receptive to the changed approach, and haven't looked back since. "The R&D organization at that time felt pretty beaten up, and rightly so because they weren't delivering differentiating medicines back then that were being launched and being successful," he explained.

"So when we shifted the culture to one that was really being science-led and patient-led and putting the science at the forefront of the decisions that were being made to progress a program it changed the way science was used in the company and as we began to finally find nuggets it elevated the quality of the pipeline and it also elevated how the people felt about being in R&D. And it really positioned the R&D organization as a

CONTINUED ON PAGE 4

BROUGHT TO YOU BY THE EDITORS OF **PHARMASIA NEWS, START-UP** AND **SCRIP INTELLIGENCE**

A Fishy Tale

Vascepa's game-changing data questioned by cardiologists (p4)

The American Dream

Sobi and Grunenthal make moves to gain market share in the US (p8 & 18)

A Deal To Be Had

Alnylam in pricing talks in the EU for breakthrough drug Onpattro (p21)

from the editor

eleanor.malone@informa.com

This week's cover story looks at the R&D decision making process at the UK's two biggest pharma companies. It is a popular trope that decisions by committee are poor decisions, and slow to be reached. In trying to please all constituents they may fail to be sufficiently bold, or conversely, they may be swayed by dominant members. GlaxoSmithKline's new R&D head Hal Barron's philosophy is that decisions need a single, accountable decision maker.

Among the many academic studies into decision making, some support his view and others find that groups are just as good if not better. In general, having a single decision maker may accelerate decision-making but it doesn't guarantee responsible or well-informed decision making. However, nor does group decision making guarantee the latter. The information and analytical processes used in decision making, the openness to varied expert input and the strategic alignment with a company's mission are all key to the quality of a final decision, whether it is made by an individual or a group. It is important that an organization guards against its decision makers developing a God complex, but committees can also be at risk of bias and complacency.

Barron is not advocating autocracy in any case: decision makers are selected depending on the decision to be made, and are counter-balanced by others adopting the role of challengers. In making them completely accountable, they are highly motivated to decide well. It will be interesting to see how Barron's approach plays out at GSK, and whether he will be able to replicate his prior success at Genentech.

Scrip

LEADERSHIP
Phil Jarvis, Mike Ward, Karen Coleman

SUBSCRIPTIONS
Dan Simmons, Shinbo Hidenaga

ADVERTISING
Christopher Keeling

DESIGN SUPERVISOR
Gayle Rembold Furbert

DESIGN
Paul Wilkinson

EDITORIAL OFFICE
Christchurch Court
10-15 Newgate Street
London, EC1A 7AZ

CUSTOMER SERVICES
US Toll-Free: +1 888 670 8900
US Toll: +1 908 547 2200
UK & Europe: +44 (20) 337 73737
Australia: +61 2 8705 6907
Japan: +81 3 6273 4260
Email: clientservices@pharma.informa.com

TO SUBSCRIBE, VISIT
scrip.pharmaintelligence.informa.com

TO ADVERTISE, CONTACT
christopher.keeling@informa.com

All stock images in this publication courtesy of www.shutterstock.com unless otherwise stated

exclusive online content

AstraZeneca: DECLARE-TIMI Outcomes May Support Competitive Claim For Farxiga In Heart Failure
https://bit.ly/2AadRMd

Lack of significant reduction on cardiovascular deaths or a composite of major events may have been due to enrolment of a healthier population relative to other studies, said investigators from the DECLARE-TIMI 58 outcomes study, which was reported at the AHA meeting.

AI-Powered 'Doctor' Adds Fuel To China Digital Health Investment Fire
https://bit.ly/2QabByx

China's artificial intelligence-powered healthcare ambition takes a new form, a 24-hour health clinic complete with a medicine dispenser that may eventually be coming to a city corner near you. Pharma companies are also continuing to build digital health services in the country as part of the health technology push.

UniQure Hemophilia B Gene Therapy AMT-061 Has Early Phase IIb Success
https://bit.ly/2PEkFfE

Early positive data from a Phase IIb dose-confirmation study showed AMT-061 achieved and sustained therapeutic levels of Factor IX (FIX) activity in all three participating patients at six weeks after a single administration of the investigational AAV5-based gene therapy.

Madrigal Cements Case For Hepatic Fat Reduction, Other NASH Benefits With MGL-3196
https://bit.ly/2S4VoYR

Madrigal's selective THR beta agonist continues to demonstrate hepatic fat-lowering abilities in 36-week data, along with lipid-lowering characteristics. The company hopes to initiate a Phase III study in early 2019.

Back In Fashion? Boston's CBO Talks Turkey On Reinvigorating Pharma's Unwanted Assets
https://bit.ly/2FxYseH

Constantine Chinoporos, Boston Pharmaceuticals' CBO, talks to *Scrip* about its deal strategy and how it intends to build its pipeline over the next few years, liberated from the constraints of portfolio management.

Glenmark Re-Evaluates Complex Generics Basket, Won't Be Part Of The 'Crowd'
https://bit.ly/2PJLoaA

Glenmark has ended development of certain in-licensed complex generic assets including generic versions of Abraxane and Suboxone in view of the extremely competitive landscape in the US. The Indian firm says it would rather focus on products where it is an early entrant.

inside:

@PharmaScrip /scripintelligence
/scripintelligence /scripintelligence

CONTINUED FROM COVER

foundational driver for future growth of the company because without a pipeline you can't grow the business."

He added that there was still much to do to improve AstraZeneca's success rate. "Our success rate has risen from 4% to 20% but we mustn't become complacent. A 20% success rate still means you are failing eight out of ten times, so we're very used to picking ourselves up, dusting ourselves down and trying again," he quipped.

REVOLUTION BASED ON 'ACCOUNTABILITY'

Hal Barron, GSK's head of R&D as of March, told the London conference that he hopes to rejuvenate R&D efforts at Britain's biggest drug maker by injecting smarter risk-taking and clear accountability at each level of decision making.

"Science, science technology, and R&D culture are critical for the equation needed to get medicines to patients. The piece of culture that's really important is decision making," the American said.

"If we leverage the great science that's happening within GSK, put a lot more energy behind it along with the advanced technologies that might drive innovation in the future, and mold this new culture to take advantage of these opportunities while incorporating some new approaches in decision making and risk-taking, then we could take a very good portfolio and make it an outstanding one," Barron said.

AstraZeneca's R&D chief Mene Pangalos

GlaxoSmithKline R&D head Hal Barron

He noted that 90% of all molecules that enter the clinic fail to create medicines for patients. "There's a lot of reasons for that. But my experience has shown me that consensus can really kill innovation. The best possible decision is rarely one that everyone can live with. So one of the key components of the new culture is to have a single accountable decision-maker for every decision that's needed," Barron said.

"We're trying to create a culture where everyone is opinionated. That means finding the best person to take an individual decision. And my experience is that when done well it's rarely the most senior person in the room. And when done by the most appropriate people, we find that these decision makers, because they know that they're completely accountable for making good decisions, they perform incredibly well."

"Often times people will experience this culture as one where individuals making decisions have never before been listened to more intently. So it creates a very dynamic organization and one that I think will make better decisions," Barron concluded.

Published online 15 November 2018

Amarin's REDUCE-IT Data For Vascepa May Be Game-Changing, But Not Without Controversy

MANDY JACKSON mandy.jackson@informausa.com

Amarin Corp. PLC has the first successful cardiovascular outcomes trial for a drug added on to statin therapy in the REDUCE-IT trial of the company's fish oil-derived *Vascepa* (icosapent ethyl), but an increase in LDL cholesterol in the placebo arm has raised some concern about the full data presented at the American Heart Association (AHA) annual meeting.

Vascepa, indicated for the treatment of hypertriglyceridemia, showed a 25% relative risk reduction in cardiovascular events in the outcomes trial known as REDUCE-IT, including a 20% reduction in CV death.

The highly anticipated cardiovascular outcomes trial (CVOT) results revealed in a late-breaker presentation at the AHA Scientific Sessions on Nov. 10 in Chicago showed dramatic reductions in major cardiovascular events (MACE) and nearly all components of the primary endpoint. However, placebo results raised a few eyebrows as cardiologists and others digested the data, since LDL cholesterol increased in patients who received mineral oil as a placebo instead of Vascepa. REDUCE-IT investigator Michael Miller, University of Maryland Medical Center, acknowledged the controversy, but told *Scrip* that there are several factors that keep the mineral oil-induced LDL rise in the placebo group from invalidating the CVOT trial's results.

For one thing, the reduction in CV risk was so large that the results still are significant even taking the relatively small LDL increase into account, Miller noted in an interview, echoing the sentiment of a *New England Journal of Medicine* publication concurrent with the AHA presentation. He was one of the NEJM paper's authors.

Miller said the REDUCE-IT results were "unprecedented" for cardiologists, because "we really haven't had an effective or proven therapy for a very vexing problem, which is a patient which has cardiovascular disease, for who LDL has been controlled with a statin and still has residual elevation in triglycerides. REDUCE-IT, in this high-risk population, demonstrated pretty dramatic results."

CVOT RESULTS DISTINCTIVE ACROSS ENDPOINTS

Vascepa is a prescription-strength pill consisting of the omega-3 acid known as eicosapentaenoic acid (EPA). Amarin contends that over-the-counter (OTC) omega-3 dietary supplements are not as potent as the company's purified EPA product, which does not include docosahexaenoic acid (DHA), and has sued to keep supplement makers from using the REDUCE-IT data as marketing material for their OTC products. *(Also see "Amarin Says REDUCE-IT Results Are Off Limits To Omega-3 Supplement Claims" - Pink Sheet, 5 Nov, 2018.)*

"The results of REDUCE-IT stand apart from the negative findings of several contemporary trials of other agents that also lower triglyceride levels, including other n-3 fatty acids, extended-release niacin, fenofibrate, and cholesteryl ester transfer protein inhibitors. It is not known whether the lack of benefit from n-3 fatty acids in previous trials may be attributable to the low dose or to the low ratio of EPA to docosahexaenoic acid (DHA)," Deepak Bhatt of Brigham and Women's Hospital Heart and Vascular Center, and Harvard University, et. al., noted in the NEJM publication.

Amarin reported in a top-line release on Sept. 24 that 4 mg of Vascepa (2 mg twice daily) reduced MACE by 25% relative to placebo (HR=0.75; p<0.001) in REDUCE-IT – a CVOT that enrolled 8,179 adults with elevated triglyceride levels between 150 mg/dL and 499 mg/dL even though they were able to keep LDL cholesterol at healthy levels on statin therapy. About 59% of trial participants had type 2 diabetes and about 71% had established cardiovascular disease, so were at high-risk for MACE.

Jefferies analyst Biren Amin in a Nov. 12 report noted that cardiologists and key opinion leaders have indicated that they are more likely to treat hypertriglyceridemia in statin-controlled patients who have diabetes and/or are obese with metabolic syndromes, "which is a sizeable number of patients, but smaller than the total population with hypercholesterolemia."

Amarin plans to submit a supplemental new drug application (sNDA) to the US FDA in early 2019 based on the REDUCE-IT results; Vascepa's current label allows for treatment of patients with triglyceride levels at 500 mg/dL.

The first occurrence of MACE for the primary endpoint was a composite of cardiovascular (CV) death, non-fatal myocardial infarction (MI or heart attack), non-fatal stroke, coronary revascularization and unstable angina requiring hospitalization (*see box for secondary endpoint details*). A key secondary endpoint assessing the first occurrence of CV death plus non-fatal heart attacks and strokes showed a 26% relative risk reduction (RRR) for Vascepa versus placebo (HR=0.74; p<0.001).

Individual REDUCE-IT Endpoints

CV Death or non-fatal MI:
25% RRR (HR=0.75; p<0.001)

Fatal or non-fatal heart attack:
31% RRR (HR=0.69; p<0.001)

Urgent or emergent revascularization:
35% RRR (HR=0.65; p<0.001)

CV death: **20% RRR (HR=0.80; p=0.03)**

Hospitalization for unstable angina:
32% RRR (HR=0.68; p=0.002)

Fatal or non-fatal stroke:
28% RRR (HR=0.72; p=0.01)

Total mortality, non-fatal heart attack and non-fatal stroke:
23% RRR (HR=0.77; p<0.001)

Total mortality (CV and non-CV death):
13% RRR (HR=0.87; p=0.09)*

**This endpoint that was not statistically significant*

"For cardiologists, what was really embraced was the reduction in cardiovascular deaths. That has been really difficult to show in other clinical trials with statin therapy as the background," Miller said.

He noted the three major CVOTs that have shown a CV risk reduction beyond statins, none of which have shown a reduction in CV deaths: IMPROVE-IT for **Merck & Co. Inc.**'s cholesterol absorption inhibitor *Zetia* (ezetimibe), and the FOURIER and ODYSSEY-OUTCOMES studies for the PCSK9 inhibitors *Repatha* (evolocumab) from **Amgen Inc.** and *Praluent* (alirocumab) from **Sanofi** and **Regeneron Pharmaceuticals Inc.**, respectively.

REDUCE-IT "is the first study that showed a 20% reduction in cardiovascular death, [which is] both statistically significant and what we would view as clinically significant," Miller said.

Jefferies analyst Amin pointed out Vascepa is not likely to steal hypercholesterolemia market share from the PCSK9 inhibitors, because it would be reserved to treat its indicated population of patients with hypertriglyceridemia.

His Jefferies colleague Michael Yee said in a Nov. 11 note that 87% of physicians responding to a survey during the AHA late-breaker session that included REDUCE-IT said they'd prescribe Vascepa for all of their high-risk cardiovascular disease patients with moderate hypertriglyceridemia.

MINERAL OIL LDL CONTROVERSY

Miller noted five different factors that should set minds at ease in regard to placebo results in REDUCE-IT. First of all, he said, "it is not unusual in a large clinical trial for a placebo group to have some mild increases in LDL. There are a number of studies that have demonstrated that. The 5 mg/dL difference between the groups is within what we traditionally see as far as clinical trials."

The median change in LDL cholesterol from baseline in REDUCE-IT was an increase of 3.1% (2 mg/dL) in the Vascepa group and an increase of 10.2% (7 mg/dL) in the placebo group – a 6.6% (5 mg/dL) difference (p<0.001).

Secondly, Miller said, the MACE rate in high-risk patients on placebo also was similar in REDUCE-IT to what has been observed in other CVOTs. Third, patients on placebo in the Vascepa study whose LDL cholesterol increased did not have worse outcomes than those whose LDL was stable, he said.

The NEJM publication similarly noted that "if mineral oil in the placebo affected statin absorption in some patients, this might have contributed to differences in outcomes between the groups. However, the relatively small differences in LDL cholesterol levels between the groups would not be likely to explain the 25% lower risk observed with [Vascepa], and a post hoc analysis suggested a similar lower risk regardless of whether there was an increase in LDL cholesterol level among the patients in the placebo group."

Fourth, Miller said, the FDA was aware of mineral oil effects in other cardiovascular studies and let REDUCE-IT move forward with mineral oil as the placebo. Finally, he continued, some of the cardiologists raising concerns about the mineral oil effects in the CVOT have conflicts of interest due to their participation in other trials of triglyceride-lowering treatments.

Jefferies analyst Yee said he is not concerned about the "noisy mineral oil debate." He noted that "the overall absolute rate of MACE in placebo was similar with other historical studies, so it wasn't like the event rate was abnormally high and driving the results

... regarding the LDL increase in placebo – [Amarin] management noted an analysis was done on the 8%-10% LDL increase showing magnitude of effect on MACE was same in those who raised LDL at one year versus placebo who declined ... so change in LDL had no impact on results."

SAFETY DATA SHOW NO BIG SURPRISES

Adverse event rates in REDUCE-IT were described as similar across the Vascepa and placebo arms of REDUCE-IT. Pneumonia was the only serious adverse event that occurred in more than 2% of patients – in 2.9% of those who took Vascepa and in 2.6% of placebo patients. Adverse events observed in 5% or more Vascepa-treated patients were peripheral edema (6.5% versus 5% for placebo), constipation (5.4% vs. 3.6%) and atrial fibrillation (5.3% vs. 3.9%).

Rates of treatment-emergent adverse events (TEAEs) leading to withdrawal of study drug were 7.9% in the Vascepa arm and 8.2% in the placebo arm of REDUCE-IT, while rates of serious TEAEs leading to withdrawals were 2.2% in both arms. Series TEAEs leading to death were observed at rates of 2.3% for Vascepa and 2.5% for placebo.

Serious bleeding events happened more frequently in the Vascepa group (2.7% versus 2.1% for placebo), but there were no fatal bleeds in either arm of the study with no significant difference in hemorrhagic stroke, serious central nervous system bleeds or gastrointestinal bleeding events between the two arms. Miller said it was reassuring that there were no intracranial bleeding events.

With respect to the 1.4% difference between Vascepa and placebo for atrial fibrillation, he said this result "was statistically significant, but we would not consider this to be clinically important."

"The two prime members of the data safety monitoring board were electrophysiologists and they weren't concerned about this," Miller continued. "Ventricular arrhythmias were reduced, but atrial arrhythmias were not. We're not exactly sure why, but we don't think it's clinically relevant with respect to the study."

Amarin described the REDUCE-IT safety results are consistent with clinical experience with omega-3 acids and FDA-approved labeling for such products.

Published online 12 November 2018

EDIT-101 To Be First In Vivo CRISPR Gene-Editing Therapy In Clinic

STEN STOVALL sten.stovall@informa.com

Editas Medicine Inc.s CEO Katrine Bosley says the US-based CRISPR gene-editing specialist had a particularly good third quarter, notably because its IND filing made in October puts its investigational candidate EDIT-101 on track to be the first of its kind tested in human clinical trials.

That milestone followed September's ruling by the US Court of Appeals for the Federal Circuit that affirmed an earlier US Patent and Trademark Office decision that ended the interference concerning foundational patents that have been exclusively licensed to Editas, lifting a heavy cloud hanging over the Boston-based group's strategic investment in intellectual property.

EDIT-101 IND

Editas' therapy, which is globally partnered with **Allergan PLC**, aims to treat patients suffering from blindness-causing rare disease Leber's congenital amaurosis 10 (LCA10), a monogenic disorder caused by mutations in the *CEP290* gene.

With the IND submitted, "EDIT-101 is poised to be the first in vivo CRISPR medicine administered to people anywhere in the world. This is the first product candidate to emerge from our platform and it's just the beginning as we continue to work to fulfill the promise and potential of the field, Bosely told an analysts call when presenting the third-quarter update Nov. 7.

Editas has developed a comprehensive data package supporting EDIT-101. Elements of that were presented at the European Society of Gene and Cell Therapy meeting in October demonstrating several important attributes of EDIT-101.

"First, it has a rapid onset of editing on the order of a few weeks to few months, both in non-human primates and mice," the CEO said.

"Second, it's well tolerated in non-human primates at AAV doses that are predicted to be therapeutically relevant in people."

"Third, it's a highly targeted and specific medicine with editing restricted to photo-

Editas Medicine Inc. CEO Katrine Bosley

receptors and no detectable off-target activity. And fourth, neither pre-existing nor induced immunity to either AAV5 or *Staph. aureus* Cas9 impacted productive editing with EDIT-101."

Bosley said the data set underpinned the decision by Allergan to exercise its option to develop and commercialize EDIT-101 globally.

"We continue to work hard to put the pieces in place to dose patients following the clearance of the IND. We're pleased that the National Institutes of Health determined that a Recombinant DNA Advisory Committee meeting was not necessary and our Phase I/II protocol is now registered with the NIH," Bosley said.

Once the IND is cleared, Editas will seek approval of the protocol from the Institutional Review Boards and the Institutional Biosafety Committees at its clinical trial sites after which the sites can begin to screen patients into the study.

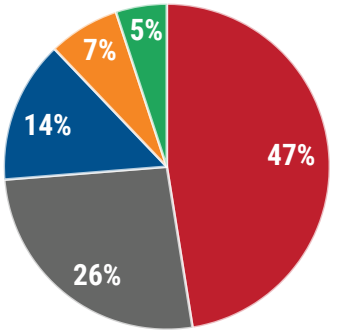
The Phase I/II trial of EDIT-101 will be an open-label, dose-escalation study, with primary endpoints designed to as-

CONTINUED ON PAGE 8

Sweden's Vibrant And Growing Life Sciences Landscape

Geographic concentrations of biopharma enterprises

Two major clusters - Stockholm-Uppsala and then Malmo-Lund in the south – have strong links to Denmark and are increasingly looking to the US to set up operations and collaborations and missing out the UK due to uncertainty over Brexit.



- Stockholm/Uppslala Region
- Malmö/Lund Region
- Göteborg Region
- Umea Region
- Linköping Region

The Swedish government is strongly committed to supporting continued rapid development in the life science sector. In February 2018, a government Office of Life Science was established.

Analysts describe the Swedish precision medicine sector as booming. Start-ups are increasingly raising seed captal on Sweden's NASDAQ First North and the smaller SPOTLIGHT stock markets, which are aimed at small-cap companies and growth firms.

76
Recently formed companies active within precision medicine

50%
of them are associated with incubators or science parks

72%
are spin-offs from academia

77%
of the companies plan to recruit more R&D staff

47%
plan to increase their number of specialised consultants/contractors

61%
of the 76 companies have less than 50 employees

Sources: SwedenBIO

CONTINUED FROM PAGE 6

sess safety and tolerability and secondary endpoints measuring efficacy, Bosley said.

"We expect to enroll 10 to 20 patients, starting with a low, but potentially efficacious dose in adults with severe vision loss. We will then progress to higher dose levels in adults with a broader range of vision loss," she said.

"Then, following a review of safety data by an Independent Data Monitoring Committee, pediatric patients with a broad range of vision loss will be included. Because the dose response curve is expected to be fairly sharp based on our preclinical data, we anticipate testing only a few dose levels," the CEO said.

LEGAL RELIEF

Bosley and her management team used the third-quarter update to voice relief over the September ruling by the US Court of Appeals for the Federal Circuit affirming the earlier US Patent and Trademark Office decision that ended the interference concerning foundational patents exclusively licensed to Editas.

The legal dispute pitted the University of California, the University of Vienna, and scientist Emmanuelle Charpentier, against the Broad Institute, Inc. concerning certain CRISPR/Cas9 patents that Editas Medicine exclusively licenses from the Broad Institute.

In its September ruling, the US Court of Appeals for the Federal Circuit affirmed the Patent Trial and Appeal Board (PTAB) ruling from February 2017 of no interference-in-fact with regards to the Broad Institute's patent claims for the use of CRISPR-Cas9 in eukaryotes.

The University of California (UC) had claimed that Broad's patents were an obvious extension of the UC's work in prokaryotic cells. Editas licenses CRISPR IP from the Broad Institute, whereas **CRISPR Therapeutics AG** and **Intellia Therapeutics Inc.** license patents from UC, who appealed the February 2017 PTAB ruling alongside the University of Vienna and CRISPR pioneer Emmanuelle Charpentier.

"This is a highly favorable decision," Bosley said, as access to those foundational patents is essential to her company, and anyone else seeking to commercialize CRISPR/Cas9 gene editing medicines.

Still, the legal dispute continues outside the US. In March 2017. The European Patent Office indicated it favored the University of California's argument that its discovery covers CRISPR use in both prokaryotic and eukaryotic systems. *(Also see "Editas Competitor CRISPR Therapeutics Hails European Patent Decision" - Scrip, 29 Mar, 2017.)*

SUPREME COURT APPEAL?

Speaking to *Scrip*, Bosley said an appeal of the PTAB ruling from the UC side is possible in theory if done within the next half-year or so – and if made to the US Supreme Court.

Bosely sounded doubtful that would occur, however. "The only step left for the other side in the US is to appeal the federal circuit decision and appeal to the Supreme Court and if they don't do it in that time-frame then we're done; we don't know if they will … but we don't see that there's a constitutional issue involved there, and the Supreme Court takes up a very small percentage of cases that are made to it on appeal, so we think there's a low probability that that will go any further," Bosley said.

That IP litigation outcome in the US would remove the threat of limiting Editas' freedom to operate and develop CRISPR-based products.

Editas says it currently has more than 70 issued patents for CRISPR/Cas9 and CRISPR/Cpf1, and aims to continue expanding that "on a regular basis".

Published online 13 November 2018

Sobi Taps AstraZeneca's RSV Therapies, Both Current And Future, For US Expansion

JOHN DAVIS john.davis@informa.com

Swedish Orphan Biovitrum AB's agreements to acquire US rights to **AstraZeneca PLC**'s RSV prophylactic, *Synagis* (palivizumab), and to participate in future earnings from a candidate RSV prophylactic therapy, MEDI8897, may keep the Swedish company active in the pediatrics/immunology sector for a much longer time than a more straightforward licensing agreement, and allow Sobi's to pursue further in-licensing deals.

For AstraZeneca, the deal continues a series of product divestments as the big pharma focuses increasingly on oncology and a small number of other therapeutic categories.

In the proposed agreements, announced on Nov. 13 and valued at $1.5bn, Sobi will extend its commercial activities in the US by acquiring perpetual rights to Synagis in the US, and will participate in 50% of future earnings in the US from MEDI8897, a Phase IIb long-acting MAb being co-developed by AstraZeneca and **Sanofi Pasteur** under a deal between the two companies struck in 2017.

Under the proposed transaction, AstraZeneca will acquire an 8.1% share of Sobi – the upfront payment from the Sobi consists of $1bn in cash and $500m in newly issued Sobi shares. Sobi will also pay $20m in cash every year for the three years 2019 to 2021 as a consideration for MEDI8897. Synagis-related sales milestones of up to $470m could be paid by Sobi from 2026 onwards, plus a milestone of $175m following submission of the US BLA for MEDI8897. Potential payments to AstraZeneca of approximately $110m on achievement of other milestones are expected from 2023 onwards.

The Sobi/AstraZeneca deal is broader than most, as it includes the transfer of 130 AstraZeneca employees to Sobi, a move which will help build the Swedish company's US commercial platform and its activities in pediatrics, immunology and orphan products.

It comes at a time when Sobi's business is in a growth phase from the relatively recent launches of the long-acting Factor VIII product, *Elocta* (efmoroctocog alfa) and the long-acting Factor IX product, *Alprolix* (eftrenonacog alfa). In the 2018 third quarter, Sobi's revenues grew by 45% to SEK2.32bn ($256m), with sales for Elocta and Alprolix growing by 110% and 161% respectively. As a consequence the company has attracted interest as a takeover target for big pharma.

The agreements will "transform our US footprint" and this is a "super-exciting" day at Sobi, said CEO Guido Oelkers in a briefing for analysts on Nov. 13. The US accounts for around 14% of Sobi's business, "clearly not an ideal situation for us, and one we wanted to correct quickly," he added.

Analysts were not entirely convinced, questioning whether Synagis was a "declining asset", and pointing to the potential of **Roche**'s recently launched hemophilia product, *Hemlibra* (emicizumab) to impact Sobi's business. In reply, Oelkers said Sobi was not spending its money lightly on Synagis. "We are comfortable the product will perform well under our ownership," and there is "quite a bit of headroom to further increase penetration of the product," he remarked.

Oelkers also noted the rather different approach Sanofi was taking to the development of MEDI8897, which involves the product's development by the vaccines division, Sanofi Pasteur. A vaccines-type approach could provide utility of the product in all babies, so may be a larger opportunity, albeit at a different price point, than Synagis. MEDI8897 also brings with it the potential of a "longitudinal earnings stream," he added.

With regard to competition to its marketed hemophilia products, Oelkers noted that Roche was a formidable competitor, but that Sobi had built up its activities in the area, and he was convinced Sobi would continue to take share in the market. "We have real world evidence with our products, patients can personalize therapy, and there are few complications, and we will remain one of the driving forces in hemophilia," Oelkers commented.

SYNAGIS US MARKETING

Under the agreements between AstraZeneca and Sobi, due to be completed by the end of 2018 or early in 2019, Sobi will be responsible for the commercialization of Synagis in the US. In ex-US markets, including the EU, AstraZeneca has a partnership agreement with **AbbVie Inc.** for Synagis, which is not affected by the proposed transaction.

Synagis is indicated in the US for the prophylaxis of RSV in high-risk infants and is expected to double Sobi's US revenues and the size of its US organization; the product is expected to raise the US's contribution to Sobi's total revenues to approximately one third. Synagis sales in the 12 months to June 30, 2018 were $269m, and Sobi expects the product to have an EBITA margin of above 60%.

The second product, MEDI8897, is a single-dose, extended half-life anti-RSV F MAb for the entire RSV season, and is being developed for a larger patient population than Synagis, the prevention of lower respiratory tract infections caused by RSV in all infants entering their first RSV season, and children with chronic lung disease or congenital heart disease entering their first and second RSV season.

Under the March 2017 agreement, AstraZeneca is responsible for the development of MEDI8897 through to initial approvals and manufacturing, while Sanofi Pasteur will be leading commercialization activities, with the two companies sharing costs and profits equally.

Sobi indicated that the agreements with AstraZeneca may not be the end to its acquisitive ambitions. "Significant top-line additions will give Sobi substantial recurring earnings to further advance the US expansion and enable future strategic acquisitions over the mid-term," the company said in a same-day statement. "We see the acquisition as a stepping stone to drive sustainable growth in the US and to make Sobi more attractive for partnering."

The growth of Sobi's last-stage product pipeline that would complement the company's own research was an aim of CEO Guido Oelkers when he joined the company in the middle of 2017.

One of the first examples of this outward-looking strategy occurred in August this year, when Sobi acquired global rights to **NovImmune SA**'s emapalumab, an interferon gamma antagonist for the rare immune condition primary hemophagocytic lymphohistiocytosis in a deal valued at CHF450m; the compound has been submitted for US and EU approval.

Published online 13 November 2018

Pfizer's Epogen Biosimilar Retacrit Launches At 33% Off In A US Market Where Amgen's Already Competitive

MANDY JACKSON mandy.jackson@informausa.com

Pfizer Inc. said on Nov. 14 that it launched the anemia drug *Retacrit* – the first US biosimilar for **Amgen Inc.**'s *Epogen* and **Johnson & Johnson**'s *Procrit* – at 33.5% and 57.1% discounts, respectively, to the reference products as it gears up to win share in a market where competition already is fierce.

Epogen (epoetin alfa) sales have been in decline for the past few years due to biosimilars outside the US and following the launch of novel anemia therapies, including Amgen's own long-acting erythropoietin stimulating agent (ESA) *Aranesp* (darbepoetin alfa), which also is facing competitive pressures.

Pfizer's Retacrit (epoetin alfa-epbx) could gain market share with its significant list price discount, but it will be going to battle against originator products that already have in-roads with cost-sensitive health care providers and payers.

Retacrit was approved in May for all of the indications listed on the Epogen and Procrit (epoetin alfa) labels – anemia in chronic kidney disease (CKD) patients on dialysis, in HIV patients taking zidovudine and due to chemotherapy. The biosimilar was not able to launch immediately due to ongoing patent litigation at the time of approval.

Though Epogen and Procrit have similar labels, Johnson & Johnson's licensing agreement with Amgen for epoetin alfa does not allow J&J to market Procrit for anemia in CKD patients on dialysis – the area where Epogen has lost market share to Aranesp and **Roche**'s *Mircera* (methoxy polyethylene glycol-epoetin beta). Amgen has explained in the past that Epogen suffered from Roche's contracting with Fresenius dialysis centers.

SALES STRUGGLE IN US ESA MARKET

In addition to Amgen's Epogen sales at dialysis centers in the US, the company earns epoetin alfa royalties from J&J for Procrit sales (excluding the dialysis market) in the US and in all indications in ex-US markets. Epogen sales declined 5% year-over-year to $252m in the

third quarter – all at dialysis centers in the US – and Aranesp sales in the nephrology and oncology markets fell 8% to $477m globally.

"Epogen declined 5% year-over-year due to lower net selling price in a category that is becoming increasingly competitive," Amgen Executive Vice President-Global Commercial Operations Murdo Gordon said during the company's Oct. 30 earnings call.

"With the potential launch of a biosimilar in the US, we would expect a further decline in net selling price. Aranesp declined 8% year over year, primarily driven by increased competition from a long-acting product in the independent and mid-size dialysis organizations. … Assuming that the approved epoetin biosimilar will launch in all segments, we're prepared to compete," Gordon said.

J&J Chief Financial Officer Joseph Wolk also noted during a third quarter earnings call on Oct. 18 that the company anticipated a Procrit biosimilar launch still this year. The product's third quarter sales grew 7.1% year-over-year to $255m in the third quarter.

Pfizer's Retacrit pricing shows that the big pharma, which began shipping the biosimilar to wholesalers in the US on Nov. 12, and its partner **Vifor Pharma Group** also are playing to win in dialysis and other markets. Vifor will commercialize Retacrit in certain channels, having licensed the biosimilar for the US dialysis market.

Retacrit's wholesale acquisition cost (WAC) is $11.03 per 1,000 units/mL, which Pfizer said is 57.1% below the Procrit WAC of $25.72 per 1,000 units/mL and 33.5% below the Epogen WAC of $16.58 per 1,000 units/mL. The WAC, or list price, does not include discounts and rebates negotiated with payers, providers, distributors and other purchasing organizations. Retacrit has been assigned two unique Q-codes by the Centers for Medicare and Medicaid Services (CMS): Q5105 for use in patients with end-stage renal disease (ESRD) on dialysis and Q5106 for non-ESRD uses. The biosimilar also qualifies for pass-through status under the hospital outpatient prospective payment system (OPPS).

But as Amgen's Gordon indicated in October, the company will make every effort to retain what remains of its Epogen market share. It appears that Amgen already has been in negotiations with payers and others for contracts that favor its product – or at least that the list price reductions mentioned by Gordon are paying off.

UnitedHealthcare said last month that it will institute step therapy – requiring patients to try and fail less expensive treatments before providing reimbursement for more costly medicines – for Medicare Part B drugs in its Medicare Advantage plans, including anti-inflammatory drugs and ESAs. Procrit, Aranesp and Retacrit will be subject to step therapy requirements, but Epogen and Mircera will not.

But Retacrit has made inroads in ex-US markets, according to Pfizer's third quarter earnings report. The company's biosimilars revenue totaled $197m worldwide in the third quarter and $558m for the first nine months of 2018, which were up 40% and 45%, respectively, year-over-year. The biosimilars total included Retacrit sales in certain European and Africa/Middle Eastern markets.

The product is Pfizer's third biosimilar launch in the US after *Inflectra* (infliximab-dyyb), a copy of J&J's TNF inhibitor *Remicade* (infliximab) partnered with **Coherus BioSciences Inc.**, and *Nivestym* (filgrastim-aafi), a biosimilar of Amgen's *Neupogen* (filgrastim).

Nivestym was launched Oct. 1 at a WAC that is 30.3% lower than Neupogen's list price and below the pre-discount prices for competing biosimilars *Zarxio* (filgrastim-sndz) from the **Novartis AG** generics subsidiary Sandoz and **Teva Pharmaceutical Industries Ltd.**'s *Granix* (tbo-filgrastim). However, the first biosimilar for Amgen's longer-acting neutropenia treatment *Neulasta* (pegfilgrastim) – **Mylan NV**'s *Fulphila* (pegfilgrastim-jmbd) – launched in July and could steal market share from Neupogen as well as the Neupogen biosimilars. Fulphila will be followed by a second Neulasta biosimilar from Coherus in January, *Udenyca* (pegfilgrastim-cbqv).

Pfizer's Retacrit could gain market share with its significant list price discount

Pfizer seems to have learned a valuable lesson about biosimilar pricing from its launch of Inflectra two years ago at a 15% discount to Remicade's WAC. J&J has held on to 94% of the US infliximab market as of the third quarter of this year through substantial rebating. Pfizer has sued J&J alleging anti-competitive activity. Aggressive commercial tactics have kept biosimilars from gaining major traction and significantly cutting pharmaceutical costs to date. The FDA is looking at ways to make the biosimilars market more competitive. Pfizer also has taken its beef with J&J to the FDA, asking the regulator to smack down marketing materials that suggest biosimilars are inferior products.

DOUBLING DOWN DESPITE BIOSIMILAR CHALLENGES

Regardless of the competitive pressures, the company has doubled down on its biosimilars investments, deciding recently to pull those products out of Pfizer's Essential Health business segment and include them in its Innovative Health group.

Pfizer Essential Health President Angela Hwang said during the company's third quarter earnings call that progress has been made in the biosimilars portfolio with many US payers, but negotiations with commercial payers still are difficult, because of "J&J's exclusionary contracting" around Remicade.

"However, our portfolio is changing in that we are now venturing from just Inflectra alone to entering the oncology biosimilar space, where we see very different dynamics here and are also excited about this growth," Hwang continued. "This is a market that has already seen the entrance of biosimilars in the form of filgrastim, and there has already been really good uptake of filgrastim in the US."

She described "different dynamics" in the oncology setting, such as shorter duration of treatment that means patients cycle through anemia or neutropenia therapy faster than arthritis therapy.

"That is going to enable payers and customers to transition patients from the originator molecule to biosimilars much more quickly, thereby allowing them to benefit from the savings," Hwang said.

Published online 14 November 2018

ICER On Asthma Biologics: 50%-79% Price Discounts Needed To Meet Value Assessment Metrics

JESSICA MERRILL jessica.merrill@informa.com

Net prices for biologic drugs to treat asthma need to be discounted by 50% to 79% to meet Institute for Clinical and Economic Review (ICER) thresholds for cost effectiveness, the independent value assessment organization concluded in a draft assessment released Nov. 13.

Rind said in a statement. "However, the treatments' net prices appear to be far out of alignment with these incremental clinical benefits, and the entire therapy class would need to see price discounts of at least 50% to reach commonly cited thresholds for cost-effectiveness."

ICER's economic assessment of long-term cost-effectiveness found that all five marketed biologics for severe asthma exceed the commonly cited threshold of $50,000 to $150,000 per quality-adjusted life year (QALY).

The outcome of the value assessment is a disappointment to the makers of the five drugs, though not unexpected, since ICER released a draft evidence report in September indicating the drugs appeared to be priced higher than the long-term modeled benefits, based on ICER's cost effectiveness thresholds.

The updated assessment is the first time ICER has incorporated information highlighting how much the drug prices would need to be lowered to meet the $150,000 per QALY metric. To meet that benchmark, prices for the asthma biologics would have to be discounted to a range of $10,400-$13,400 annually from their current wholesale acquisition costs of $30,000-$40,000 annually, ICER found.

"All five biologics modestly reduce asthma exacerbations and improve daily quality of life," ICER Chief Medical Officer David

ICER's QALY Estimates For Asthma Biologics

Cinqair $391,000 per QALY
Dupixent $374,000 per QALY
Fasenra $371,000 per QALY
Nucala $344,0000 per QALY
Xolair $325,000 per QALY

A DYNAMIC CATEGORY DRAWS ICER'S ATTENTION

The drug category is one that has seen a lot of commercial activity in the last two years, as drug makers have sought to bring better targeted therapies to the most severely afflicted patients. Even though biologics are targeted to a small portion of asthma patients, just about 10% of them, the high prices of the new drugs have worried payers. Drug makers have countered that the ability for new biologics to reduce high costs associated with severe asthma present a value to the health care system. *(Also see "Severe Asthma Market Snapshot: A Competitive Therapy Area That Will Test Payers' Influence" - Scrip, 23 May, 2018.)*

Patients with severe asthma represent fewer than 10% of all asthma patients, but account for around 50% of the costs, including hospitalizations and emergency room visits.

For many years, **Roche**'s *Xolair* (omalizumab) was the only biologic on the market for asthma. The IgE antibody was approved for allergic asthma in 2003. But a wave of new biologics has hit the market, including a trio of IL-5 inhibitors, **GlaxoSmithKline PLC**'s *Nucala* (mepolizumab) in 2015, **Teva Pharmaceutical Industries Ltd.**'s *Cinqair* (reslizumab) in 2016, and **AstraZeneca PLC**s *Fasenra* (benralizumab) in 2017, as well as **Regeneron Pharmaceuticals Inc./Sanofi**'s IL-4/IL-13 blocker *Dupixent* (dupilumab) in 2018.

Nucala, Cinqair and Fasenra are all approved for eosinophilic asthma, while Dupixent was approved by the FDA in October with a slightly broader label in patients with an eosinophilic phenotype or with oral corticosteroid-dependent asthma. *(Also see "Dupixent Approved For Severe Asthma With Broader Label Than Other Biologics" - Scrip, 21 Oct, 2018.)*

ICER has been gaining influence with its $150,000 QALY benchmark to gauge cost effectiveness. Earlier this year the pharmacy benefit manager **CVS Health Corp.** said it would introduce a new cost management program that would exclude certain new treatments from coverage if they did not meet ICER's benchmark. *(Also see "CVS Launching Program To Exclude New Drugs Deemed Not Cost Effective " - Pink Sheet, 9 Aug, 2018.)*

In the case of the new asthma meds, the discrepancy between the WAC prices of the drugs and the prices ICER would deem cost-effective is a chasm.

DRUG MAKERS TAKE ISSUE

Drug makers say that they have concerns with ICER's methodology for calculating long-term value and some argued the safety and efficacy of their products are misrepresented in the evidence report. ICER's clinical

evidence rating for their products should be raised, several drug makers argued.

"We continue to have concerns with how ICER evaluates products from both a clinical and economic perspective," AstraZeneca said in a statement. "Our concerns include the level of transparency provided regarding ICER's analysis and assumptions as well as the subjective nature of its calculations. We are also concerned with the lack of recognition of the benefits of personalized medicine."

"The model defines value without taking into consideration the unique needs of individual patients," AstraZeneca added.

GlaxoSmithKline, in comments submitted to ICER on the draft assessment, argued that ICER should incorporate more information on the indirect burden of severe asthma in its economic analysis, including the impact of missed work days. The company pointed to data from an Asthma and Allergy Foundation of America (AAFA) survey that could be used, showing 41% of patients with severe asthma report missing more than 10 work days due to asthma symptoms.

"We reiterate the need for ICER to evaluate the clinical and economic value of severe asthma medicines using a societal perspective as the base case," GSK said in comments. "We recommend that ICER use more recent patient-centric estimates of lost productivity, missed work/school days due to severe asthma from AAFA7 and fully account for the difference in indirect costs by disease severity, patient age and care-giver impacts."

But ICER responded that the burden of evidence in isolation is not helpful to the cost-effectiveness estimates, because it does not show how the burden changes with biologic treatment. In cases where there was evidence of changes on treatment, ICER said it did incorporate that information.

And, in line with its value assessment framework, ICER said that while it presents an analysis from both a health sector and societal perspective, its economic evaluations are presented only from a health sector perspective except for diseases/disorders that fall under the definition of ultra-rare diseases.

Notably, Sanofi and Regeneron worked closely with ICER on the cost analysis for Dupixent when it was first approved for atopic dermatitis in 2017 and landed on a price that both parties agreed was reasonable. The price tag is the same in asthma.

ICER's evidence report will be the subject of a public meeting of the Midwest Comparative Effectiveness Public Advisory Council on Nov. 29 in St. Louis, MO.

Published online 15 November 2018

New Year Present For Takeda As Shire Close Nears?

IAN HAYDOCK ian.haydock@informa.com

Assuming the satisfactory resolution of European antitrust concerns, and a smooth shareholder approval process at both companies, **Takeda Pharmaceutical Co. Ltd.** says its much-touted acquisition of **Shire PLC** could now formally be completed as early as January 8.

A number of key dates in relation to the closing of the $62.4bn deal – the biggest-ever overseas M&A transaction by any Japanese company, and fifth biggest historically in the biopharma sector – are now crystallizing.

Takeda said it has set December 5 as the date for an Extraordinary General Meeting in Osaka for a vote by its shareholders on the acquisition. Meanwhile, the European Commission is due to issue its regulatory decision on the planned transaction on or before November 20.

Shire has just published its Scheme Document in relation to the deal, and will also hold shareholder meetings to discuss this on December 5, after the Takeda EGM given the time difference.

All going well, January 8 has now emerged as the date for completion, "or as soon as practicable thereafter" if EC antimonopoly concerns remain to be resolved after the November ruling, Takeda said.

STAGE IS SET

While there are pockets of lingering opposition from some Takeda shareholders – including a group linked to the company's founding family – securing investor approval of the deal at this stage looks highly unlikely to present a last-stage hurdle.

Given previous general expectations around timing, the new dates also provided little surprise to investors, with Takeda's share price stable in morning trading in Tokyo on November 13, closing the session around 1% down.

Takeda Closing In On Global Competitiveness

The EC concerns relate to a potentially dominant position for the merged company in inflammatory bowel disease, given Takeda's existing strength in the sector through *Entyvio* (vedolizumab) for ulcerative colitis and Crohn's disease.

The Japanese firm has already acted quickly to address this hurdle, offering to divest Shire's Phase III stage drug SHP647, which is being developed for the same indications and certain related rights. *(Also see "Takeda Offers Shire Asset Disposal To Assuage EC Merger Concerns" - Scrip, 28 Oct, 2018.)*

As part of a sustained effort to win over any skeptical shareholders, Takeda president and CEO Christophe Weber again highlighted in a statement the "compelling strategic and financial benefits of this transaction".

In an ongoing initiative to build momentum ahead of the shareholder meetings, Weber and Takeda external board chair Masahiro Sakane have also released new public video messages on the strategic rationale and process behind the deal, and the longer-term financial outlook for the combined group.

Adding weight to this, Deutsche Bank stated in a recent pro forma analysis of the deal that "we continue to see a strong case for the acquisition, with strong accretion to Core EPS [earnings per share] into the medium term (+30-40%)."

FUNDING STRUCTURE

The Takeda investor concerns have largely centered around the funding of the transaction, although Takeda executives have stressed repeatedly that they will pay down new debt as much and as quickly as possible, divest non-core assets, and maintain shareholder returns.

In Deutsche Bank's view, "the combined company has the cash flow to de-lever while maintaining shareholder returns…we are comfortable with Takeda's capacity to manage its debts and bring down its leverage to a net debt EBITDA [earnings before interest, taxes, depreciation and amortization] of less than 2x within three years, thereby maintaining its investment grade status."

Moody's Investors Service was also generally positive, stating in a recent Issuer Comment that progress so far supports its expectations that its ratings review will ultimately lead to ratings in the "mid to high Baa [moderate credit risk] range."

In a breakdown of the deal's funding arrangements, Credit Analyst Bryce Trinka at *Informa's Financial Intelligence* noted that financing arrangements with a total cash value of around $30.85bn have been made, comprising a $7.5bn five-year term loan, an approximately $4.39bn (JPY500bn) short-term loan, and the remaining $18.96bn coming via a bridge loan. In a recent net roadshow presentation, the company indicated it was aiming to raise around $14.05bn equivalent in US dollar and Euro senior bonds, leaving around $4.8bn equivalent to be funded by other means, including expected divestitures, she noted.

While the final amount is not yet clear, Trinka said a minimum Euro deal size of €5-6bn, but more probably €8bn, is likely, leaving around $5bn to be raised in US dollars.

Deutsche Bank expects the combined entity will have the equivalent of around $51bn in outstanding debt at closing. Moody's sees pro forma net debt of $48bn at this time, including $13.7bn in Shire net debt and acquisition debt of $29.8bn to find the cash component of the deal. The transaction is also set to bring a massive pay day for those involved, with a total of $963m in financing and other fees going out to advisers and brokers to both companies, new disclosures revealed.

POSSIBLE DIVESTMENTS

Any major divestments to pay down the debt are expected only after the formal completion of the deal, as Takeda looks to rapidly deleverage its balance sheet by paying down the debt and honing its strategic focus, Trinka noted.

Takeda itself has illustrated its intention to do this with an assumption, for illustrative purposes only, of up to $10bn in non-core business divestments.

However, the extent and speed of post-closing de-leveraging cannot be ascertained until concrete moves are made, and also given the earnings that will be lost, Moody's observed.

Speculation continues over the likely candidates for asset-shedding after the deal is sealed. In its analysis, Deutsche Bank models various scenarios, including the potential sell-off of Shire's ophthalmology unit, which had already been posited by some investors at the time the M&A plan first emerged earlier this year.

This comprises the marketed dry eye drug *Xiidra* (lifitegrast), which has around $600m in annual sales, and the Phase III conjunctivitis candidate SHP640. Together the business could potentially sell for about $6bn, the bank estimates.

In addition to gastrointestinal asset SHP647, which might raise around $2bn assuming four to five times peak projected sales, another possible candidate for a sell-off is Takeda's consumer healthcare unit, which could raise $4-4.5bn, Deutsche Bank states.

However, "there is a certain brand association with some of the long-standing consumer products in Japan that Takeda might wish to keep" given the strong consumer and brand image these have, it adds.

Published online 12 November 2018
From the editors of PharmAsia News.

Bayer Eyes More Link-Ups Like Loxo After Pipeline Blips

KEVIN GROGAN kevin.grogan@informa.com

While **Bayer AG**'s third-quarter press call was dominated by discussions on Monsanto legal battles, the German group has also been stressing the importance of pharma and the need to add to its pipeline.

Among the results, which showed that sales rose 1.9% to €9.90bn, while core earnings before interest, tax, depreciation and amortisation (EBITDA) were flat at €2.20bn, Bayer's pipeline update revealed a few discontinued projects. After the failure of a Phase II trial of its antibody-drug conjugate anetumab ravtansine as second-line monotherapy for malignant mesothelioma, Bayer confirmed that it would not pursue any further studies in this indication, but the **MorphoSys AG**-partnered drug will continue to be investigated in other Phase I studies for solid tumors. *(Also see "Bayer And Morphosys Brush Off ADC Mesothelioma Failure" - Scrip, 24 Jul, 2017.)*

The development of neladenoson bialanate, an oral partial adenosine A1 receptor agonist, has also been discontinued after two Phase II studies involving heart failure patients did not reach their primary endpoints, while last month ,"following an interim analysis of available clinical data to date," Bayer decided to not pursue further development of its prostate cancer drug *Xofigo* (radium-223) as a treatment for breast cancer.

Also last month, the Leverkusen-headquartered company presented results from a failed Phase II study of its pulmonary hypertension drug *Adempas* (riociguat) in patients with diffuse cutaneous systemic sclerosis and Bayer and partner **Merck & Co. Inc.** have pulled the plug on that indication.

Speaking to *Scrip*, chairman Werner Baumann said that these setbacks were part and parcel of research, particularly in the extremely

risky areas of early-mid-stages of drug development. He said that on balance, the quarter was a beneficial one for the company on the clinical side and cited recently presented positive Phase III data on darolutamide, as well as progressing products already on the market. *(Also see "Positive Phase III For Darolutamide In Prostate Cancer Could Improve Options For Orion" - Scrip, 24 Oct, 2018.)*

Bayer and partner **Johnson & Johnson** recently got marketing authorization for the blockbuster *Xarelto* (rivaroxaban) in the US in another indication, the treatment of coronary and peripheral artery disease, making it the only oral anticoagulant approved for this indication, thus "offering substantial therapeutic benefit for patients and high sales potential," Baumann noted.

> Baumann said that Bayer was always looking at possibilities and cited the Loxo alliance as the type of deal the company is interested in

He was also enthusiastic about the company's closely watched tropomyosin receptor kinase inhibitor larotrectinib. The tissue-agnostic drug, partnered with **Loxo Oncology Inc.** and filed in Europe in August, is getting a priority review from the FDA for locally advanced or metastatic solid tumors with a neurotrophic tyrosine receptor kinase (NTRK) gene fusion and has a target action date of Nov. 26.

When asked about adding to the pipeline, Baumann said that Bayer was always looking at possibilities and cited the Loxo alliance as the type of deal the company is interested in. The firms linked up almost exactly a year ago with Bayer paying $400m upfront, while Loxo stands to receive an additional $1.15bn in milestone fees. Baumann said deals of this "order of magnitude" would be pursued. *(Also see "Loxo's Tissue-Agnostic Approach Brings $400m Upfront From Bayer" - Scrip, 14 Nov, 2017.)*

Back to the third quarter results and Bayer's pharma division fared pretty well, with sales increasing 2.4% to €4.16bn, driven by healthy rises for Xarelto, up 16.8% to €933m and eye disorders drug *Eylea* (aflibercept), which rose 15.4% to €541m. Xofigo sales fell 12.7% to €102m and Baumann told *Scrip* the decline was due in part to a decline in demand in the aftermath of a Phase III trial looking at a combination of Xofigo with J&J's *Zytiga* (abiraterone) which was halted over a high rate of deaths in the treatment arm.

(Also see "EU-Wide Restrictions In Store For Bayer's Prostate Cancer Drug" - Pink Sheet, 26 Jul, 2018.)

The initial investment community response to the results was not particularly enthusiastic. Jean-Jacques Le Fur, an analyst at Bryan Garnier, said the pharma division performance was disappointing despite sales slightly above expectations as EBITDA was boosted by a one-time payment of €190m payment from J&J for the aforementioned new indication for Xarelto. He also pointed out negative effects relating to temporary supply disruptions related to quality issues at the company's Leverkusen plant which has resulted in five R&D projects being stopped. Regarding those problems, Baumann said that the company's response to a warning letter issued by the FDA was going to plan and he expected a re-inspection from the agency at the beginning of 2019. *(Also see "Bayer In FDA's Bad Books Over Facility Failures" - Scrip, 14 Feb, 2018.)*

Tim Race at Deutsche Bank described the results as "no disaster, just a low quality beat." He pointed out that while Bayer beat consensus, stripping out the €190m payment from J&J, "the beat turned into a slight miss" and "this was not the quarter to provide the required confidence that Bayer was on track post-acquisition."

The acquisition in question is that of Monsanto which dominated the press call. The seeds giant accounted for €2.2bn out of €3.7bn of sales in Bayer's crop science division, and made a significant contribution to profits but Baumann had to spend much of the call dealing with questions concerning ongoing litigation in the US regarding the safety of Monsanto's herbicide glyphosate.

Last month, a US judge slashed a $289m damages bill to $78.6m in a closely watched case involving a man – Dewayne Johnson – who claimed that glyphosate, which is contained in Monsanto's weedkiller *Roundup*, had caused his cancer. Baumann, who noted that the number of plaintiffs has risen by 600 to 9,300 since the second quarter, reiterated Bayer's stance that the jury's verdict in the Johnson case was "an incorrect one in our eyes" and the firm would appeal.

Baumann was also asked about the structure of Bayer, especially following comments that full-year forecasts for its consumer health and animal health divisions "look increasingly ambitious." He responded by saying that any strategical moves would not and should not be made on the basis of a third quarter performance.

As for the importance of pharma to the group, something which has been occasionally questioned since the Monsanto deal, Baumann stressed that it is "an integral component" that has significantly outgrown the market in recent years. He concluded by saying Bayer would continue to invest heavily in its pharma pipeline.

Published online 13 November 2018

Celltrion Hit By Truxima Price Cut, Temporary Utilization Rate Drop

JUNG WON SHIN jungwon.shin@informa.com

Celltrion Inc. surprised the market with worse than expected third quarter earnings, as the company lowered the unit supply price of *Truxima* (biosimilar rituximab) in Europe to brace for intensifying competition, and the utilization rate dropped temporarily at its main production facility.

Third quarter sales, on a consolidated basis, were marginally down 0.4% from a year earlier to KRW231.1bn ($203.8m), as increased unit sales offset lower selling prices. Meanwhile, operating profit plunged 44% to KRW73.6bn and net income declined 49% to KRW54.7bn.

As well as the lower price of Truxima and factory utilization rate, increased litigation costs related to the early market entry of CT-P10 (biosimilar rituximab) and CT-P06 (biosimilar trastuzumab) were other reasons for the poor earnings. Celltrion's stock price in South Korea's second-tier Kosdaq market fell 12% on Nov. 11 on the new figures.

SUCCESSFUL EUROPE LAUNCHES OF REMSIMA, TRUXIMA

Celltrion has been enjoying the successful launches of *Remsima* (biosimilar infliximab) and Truxima in Europe. In about a year after its launch there, Truxima's market share had risen to 32% of the rituximab market in the second quarter. So far, Truxima has been launched in 22 European countries and there are plans to expand to the entire region by the first half of next year.

Meanwhile, the European market share of Remsima - which launched in the region in 2016 - reached 54% in the second quarter, even exceeding that of the original drug (*Remicade*).

Celltrion's *Herzuma* (biosimilar trastuzumab), which kicked off sales in the region from the second quarter, is also settling in comfortably, with its market share reaching 7% just one month after launch; Celltrion plans to expand the launches across all of Europe by the first half of next year.

However, as multinational firms begin to speed up their development of biosimilars, competition in the sector in general is becoming fierce, and this impact is starting to be reflected in pricing.

According to its recent disclosure to the stock market, Celltrion has slashed the unit supply price of Truxima by 15% to aggressively deal with a change in the biosimilar market environment, and to step up the price competitiveness of the product to support rapid market penetration and obtain prescriptions. The company said the price cut rate could vary by country.

Another factor that dampened Celltrion's earnings was a lower factory capacity utilization ratio as it gears up for a capacity increase at its No. 1 plant of 50,000 liters. The company is also aiming to build a third plant, but details haven't been finalized yet.

"Celltrion has established the unrivaled trust of the market through its first antibody biosimilar Remsima in the global market. Based on this, its follow-up products Truxima and Herzuma are also rapidly increasing sales in Europe. Truxima and Herzuma are expected to receive approvals in the US this year, so we are aiming to grow in the longer term with these products," said the company in a statement on the results.

The company has also adopted new accounting guidelines issued by the financial authorities in South Korea on the treatment of R&D spending of pharma/biotech companies. *(Also see "Biosimilar Firms Main Beneficiaries Of Korea R&D Cost Accounting Changes?" - Scrip, 25 Sep, 2018.)*

ANALYSTS ROSY ON OUTLOOK

Despite the lower than expected earnings, analysts still pictured a brighter outlook for the company in 2019, as it is poised to receive approvals from the US FDA this year on Herzuma and Truxima, and a possible approval in Europe next year for its subcutaneous version of Remsima, the first biosimilar with a changed formulation.

In October this year, the FDA's Oncologic Drugs Advisory Committee unanimously endorsed the approval of Celltrion's CT-P10 (rituximab biosimilar), concluding it to be highly similar to original drug *Rituxan* and that small analytical differences between the products were not clinically meaningful. *(Also see "Celltrion's Rituximab Biosimilar Has Easy US FDA Panel Ride Despite Questions About Narrow Label" - Pink Sheet, 10 Oct, 2018.)*

In August, Celltrion said it was preparing to file for the regulatory approval in the EU of a subcutaneous version of its infliximab biosimilar Remsima in the second half of this year, to diversify its portfolio and boost the product's market competitiveness. *(Also see "Celltrion Plans EU Filing For Remsima SC As Phase III Completed" - Scrip, 30 Aug, 2018.)*

The FDA accepted for review the BLA for Celltrion's CT-P6 (trastuzumab) in August last year.

Mirae Asset Daewoo said despite the poor earnings, there are still many positive factors to count on. On the US approvals, it will be worth watching Truxima's performance there given the Advisory Committee's unanimous endorsement. In addition, Sandoz has recently given up on getting US approval of *Rixathon* (rituximab), so Truxima is expected to benefit from first mover status, it noted. *(Also see "Novartis Gives Up On Rituxan Biosimilar For US Market" - Scrip, 5 Nov, 2018.)*

Secondly, on the expected submission for Remsima SC in Europe this year, the company has already proven this is comparable in terms of efficacy and safety with the IV formulation through studies presented at international conferences. The Remsima franchise is poised to shore up its market position, Mirae said.

Finally, the company's planned third plant will have a capacity of 360,000 liters, although details such as timing and location have not been finalized. However, once these deals are decided, the company's corporate value is expected to rise further, said the brokerage in a research note.

Celltrion is also set to begin a Phase III global clinical trial of CT-P16, its biosimilar bevacizumab product.

Published online 13 November 2018
From the editors of PharmAsia News.

AbbVie Explores Uncharted Territory With DUB Inhibitor Neuroscience Deal

JO SHORTHOUSE joanne.shorthouse@informa.com

AbbVie Inc. is looking to carve a wider path into the neurology space, and is hoping a new collaboration with UK biotech **Mission Therapeutics Ltd.** will help it to steal a march on the development of deubiquitylating enzymes (DUB) inhibitors for use in Alzheimer's and Parkinson's disease.

The two companies will collaborate during the research stage to identify specific DUBs using Mission's proprietary DUB platform, and discover suitable compounds. AbbVie will then have the option to gain exclusive rights to develop and commercialize DUB inhibitors against up to four selected targets.

While no specific financial details have been disclosed, AbbVie will pay Mission an upfront license fee, with the UK biotech eligible to receive success-based milestone payments and royalty payments for each commercialized product.

Speaking on the sidelines of the Jefferies 2018 Healthcare meeting in London, Anker Lundemose, Mission Therapeutics' CEO, told *Scrip* that he would have been happy to share the size of Abbvie's financial commitment to the collaboration. "This deal will be transformative for Mission. It will give us the latitude to support our proprietary pipeline and will enable us to get at least two of our own programs into Phase I development," he added.

As Abbvie has declined to disclose the size of the upfront it is unlikely to be running into the three figures of other deals it has structured as that would have been material. Nevertheless, delegates at the Jefferies meeting canvassed by *Scrip* speculated that the upfront to Mission probably runs into the tens of millions and that the milestones are, owing to how hot the DUB space is, likely to be at the top end of other platform deals, which could give the collaboration a biodollar valuation somewhere in the $2bn range.

While the industry's knowledge of the physiological role of DUBs has evolved over the last few years, a way to develop DUB inhibitors in clinical development has not been forthcoming.

> 'There is an urgent need for new treatments that will make a positive impact on the lives of patients with Alzheimer's and Parkinson's disease' – James B Summers, AbbVie

Key to piquing AbbVie's interest in the DUB platform, was "the application of a small-molecule approach to the protein degradation issue and its application in the CNS arena", added Lundemose.

Alzheimer's and Parkinson's diseases are associated with the accumulation of misfolded, toxic proteins, which are believed to cause impaired function and death of nerve cells in the brain.

DUBs play an important role in keeping a cell healthy by regulating the degradation of these proteins. There are over 100 different DUBs in humans. By modulating specific DUBs within the brain, AbbVie and Mission are aiming to develop potential therapeutics that enable the degradation of these toxic proteins and prevent their accumulation.

Lundemose added that there were many other market opportunities for DUB inhibitors such as oncology, inflammation, rare disease, fibrosis, and mitochondrial disease.

James B Summers, vice president of neuroscience discovery research at AbbVie, said: "There is an urgent need for new treatments that will make a positive impact on the lives of patients with Alzheimer's and Parkinson's disease. Mission's scientists have developed impressive early research toward the understanding of these diseases. Together, we will work to advance this early science and develop meaningful therapies."

In 2017, an estimated 50 million people were living with dementia and Alzheimer's disease; this number is expected to double every 20 years, reaching 75 million by 2030. More than 10 million people worldwide are living with Parkinson's disease.

This is the first major collaborator for Mission, which has two in-house lead programs, USP30 and USP10. These are not part of the collaboration, and Mission confirmed to *Scrip* that it was not actively seeking partners for these programs.

Mission has received $130m in funding from a syndicate that includes Touchstone Innovations, Woodford Patient Capital Trust, Sofinnova Partners, SR One, Roche Venture Fund and Pfizer Venture Investments.

Scrip Awards Finalists 2018

www.scripawards.com

Scrip Awards
Pharma intelligence | informa

Syneos Health's Best New Drug Award

Launching innovative new products is the most important function of the industry and this Award recognizes excellence in pharmaceutical development.

TiGenix's Alofisel (darvadstrocel)

In March, Alofisel became the first allogeneic stem cell therapy to receive central marketing authorization approval in the EU. Alofisel was approved for the treatment of complex perianal fistulas in adult patients with non-active/mildly active luminal Crohn's disease. It offers a novel, minimally invasive and well tolerated alternative treatment option for patients who do not respond to currently available therapies, and until now had limited treatment options.

Roche's Hemlibra (emicizumab)

Hemlibra is the first new medicine approved in over 20 years for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children with hemophilia A with Factor VIII inhibitors. The subcutaneous product was designed to help overcome current clinical challenges in hemophilia A: the short-lasting effects of existing treatments, the development of Factor VIII inhibitors and the need for frequent venous access.

Novartis's Kymriah (tisagenlecleucel)

With this innovative therapy, Novartis was at the forefront of investigational immunocellular therapy as the first pharmaceutical company to initiate global CAR-T trials and to receive FDA approval for this novel drug class. Kymriah was approved for pediatric acute lymphoblastic leukemia, a rapidly progressing disease and becomes fatal within a few months if left untreated, and for which previous options were suboptimal.

Spark Therapeutics' Luxturna (voretigene neparvovec-rzyl)

Spark Therapeutics' Luxturna is the first directly administered gene therapy approved in the US and the first and only pharmacologic treatment for an inherited retinal disease. It was approved under a priority review by the FDA for the treatment of biallelic RPE65 mutation-associated retinal dystrophy which nearly always progresses to complete blindness. The approval represents a paradigm shift for patients, who up until now have had no pharmacologic treatment options.

Kite Pharma/Gilead Sciences' Yescarta (axicabtagene ciloleucel)

Yescarta (axicabtagene ciloleucel) – developed by Kite Pharma (a Gilead company) – was the first chimeric antigen receptor T-cell (CAR T) therapy approved for the treatment of adult patients with relapsed or refractory large B-cell lymphoma. CAR T therapy is a breakthrough in hematologic cancer treatment in which a patient's own T-cells are engineered to seek and destroy cancer cells, and has been touted as the new frontier of cancer therapy.

Pharma Company of the Year
(Sponsored by CMIC)

Scrip's Pharma Company of the Year Award honors outstanding achievement by pharmaceutical companies over the qualifying 12 months.

The winner of the Pharma Company of the Year Award is chosen by Scrip's senior editorial team, which looks for excellent performance across the full range of business activities between Jun. 1, 2017 and May 31, 2018.

The decision is based on a variety of key metrics, including:

- Financial performance in 2017 compared with the previous year.
- Strategic advances, looking at its most significant achievements over the year.
- Progress in the emerging markets.
- New product launches including line-extensions and formulations.
- Advances in the drug pipeline, including major clinical trial reports.

Scrip's Lifetime Achievement Award
(Sponsored by ICON)

The winner of this special Award is an exceptional individual with a consistent history of service, above and beyond the call of duty, throughout their career.

This prestigious international Award will be presented to someone who has enjoyed a distinguished career in the biotech or pharmaceutical arena, primarily within industry. They may be retired or semi-retired but will still be active in the industry in some capacity.

Previous recipients have come from a variety of backgrounds within pharma and biotech, and their allied industries.

To find out more about attending the Scrip Awards, visit www.scripawards.com

ONE SMALL STEP

AbbVie has been exploring different options in age-related disease such as Alzheimer's with its recently extended **Calico** collaboration, and its partnership with **Voyager Therapeutics** to create a single-administration gene therapy for the neurological condition. These collaborations have yet to bear any fruit that has made it to the clinic. *(Also see "AbbVie, Calico Extend Their Collaboration On Aging" - Scrip, 26 Jun, 2018.)(Also see "AbbVie's Alzheimer's Efforts Voyage Into AAV-Targeted Tau Antibodies" - Scrip, 20 Feb, 2018.)*

It only has one asset in Phase II for Alzheimer's disease, ABV-8E12, a humanized antibody targeting the tau protein which is part of its 2015 license agreement with C_2N Diagnostics. It is also indicated in progressive supranuclear palsy. At the time of the deal, AbbVie said the global licensing agreement would pair its neuroscience acumen with C_2N's expertise in Alzheimer's, which includes a suite of biomarker assays and drug-discovery tools.

The large pharma has one product approved for Parkinson's disease. *Duopa*, an enteral suspension formulation of levodopa and carbidopa, was approved in the US in 2015, making sales of $106m in Q3 2018. *(Also see "AbbVie's Parkinson's drug Duopa OK'd in US" - Scrip, 13 Jan, 2015.)*. In Phase I, AbbVie is developing ABBV-951, a subcutaneous product delivering levodopa and carbidopa.

WE ARE NOT ALONE

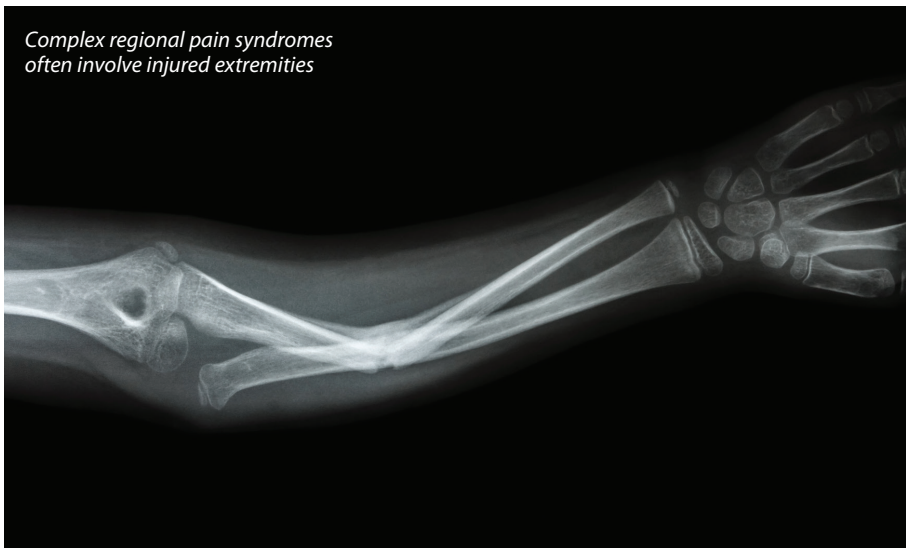
Mission is not alone in its development of DUB inhibitors. **Forma Therapeutics Holdings LLC** recently entered into a collaborative partnership with the University of Oxford to develop (DUB) inhibitors for treating neurodegenerative diseases. Swedish biotech **Medivir AB** developed a DUB platform in 2016, but it is unclear whether this remains a priority for the newly streamlined company. *(Also see "Medivir Clears The Decks For Clinical Focus, Cuts All Preclinical Projects" - Scrip, 18 Oct, 2018.)*

Carmot Therapeutics Inc. is using its Chemotype Evolution technology platform to develop DUB-targeted libraries of covalent inhibitors that are being applied broadly to identify chemical scaffolds selective for specific DUBs. It signed a partnership with **Amgen Inc.** in 2017, for drug discovery in Parkinson's disease, but it is unclear if this is targeting DUBs, or using another of Chemotype Evolution's targeting capabilities.

Published online 16 November 2018

Grunenthal Establishing US Presence With Tailored Marketing Strategy

JOHN DAVIS john.davis@informa.com



Complex regional pain syndromes often involve injured extremities

By acquiring the small New York-based company, **Averitas Pharma**, the family-owned European-based specialty company, **Grunenthal GMBH**, is aiming to use Averitas's experience in a specialty pharmacy and hub services model to commercialize, for the first time, its own portfolio of niche pain-related therapies in the US.

The acquisition confirms that US market opportunities are as much a draw for privately held companies as they are for publicly quoted companies. Another mid-sized European pharmaceutical company, the Nasdaq Stockholm-listed **Swedish Orphan Biovitrum AB**, has also just announced an expansion of its US commercial infrastructure.

Aachen, Germany-based Grunenthal started 2018 by entering into a commercial partnership for China with **Mundipharma International Corp. Ltd.**, and the purchase of Averitas, announced on Nov. 14, 2018, for an undisclosed amount, continues the theme of geographic expansion. "I am proud to say that we are now establishing our own commercial presence in the world's biggest pharma market, the US, for the first time," said its CEO, Gabriel Baertschi, in a same-day statement.

"The acquisition is another important milestone in executing our growth strategy and expanding our business across multiple pain-related therapeutic categories and geographies," Baertschi continued. He told *Scrip* last year that Grunenthal wanted to expand its activities into the US and other markets from its core business in Europe and Latin America, while consolidating its position as a leader in pain therapeutics. Read the full article here

In a Nov. 14 interview with *Scrip*, Baertschi pointed out that Grunenthal was holding firm to that therapeutic leadership strategy. It has acquired European rights to *Nexium* (esomeprazole), the global (ex-US and Japan) rights to *Vimovo* (naproxen/esomeprazole), and in 2017 acquired global (ex-Japan) rights to the migraine therapy, *Zomig* (zolmitriptan), all from **AstraZeneca PLC**.

"In the past 18 months we have spent around $1.8bn in growing the company, and that's going to be transformative for Grunenthal, doubling our EBITDA next year," Baertschi remarked. In 2017, Grunenthal achieved revenues of approximately €1.3bn, and has a goal of becoming a €2bn company by 2022.

Grunenthal has already earmarked the product that will lead its commercial push in the US, the analgesic patch, *Qutenza* (capsaicin 8%), additional rights to which it acquired earlier this month from **Acorda Therapeutics Inc.** for an undisclosed sum.

CONTINUED ON PAGE 20

Scrip Awards 2018

Pharma intelligence | informa

Book your table

The 14th Annual Scrip Awards

2018

www.scripawards.com

28 November 2018 | The Hilton on Park Lane, London, UK

Entry and General Enquiries:
Natalie Cornwell
Tel: +44 (0) 7827 993 776 | Email: natalie.cornwell@informa.com

Sponsorship and Table Booking Enquiries:
Christopher Keeling
Tel: +44 (0) 20 3377 3183 | Email: christopher.keeling@informa.com

Headline Sponsor

IMS Health & Quintiles are now IQVIA

Sponsored by

CMIC ICON Lachman Consultants Masters MC Services MSD Inventing for Life SKIPTA Syneos Health Worldwide Clinical Trials WuXi AppTec

Social Media Sponsor

medidata

CONTINUED FROM PAGE 18

Those rights mean that Grunenthal is now the sole owner of Qutenza in the US, Latin America, Asia and Australia, having acquired exclusive rights for Europe, the Middle East and Africa in Dec. 2016. A single one-hour application of the patch can provide at least three months of relief from, for example, post-shingles nerve pain, the company noted.

"Averitas Pharma brings infrastructure and specialty product marketing expertise to Grunenthal. Employees in that company have expertise and experience in the US with a commercial model that meets our needs," Baertschi said.

This experience was of particular interest with regard to Qutenza, a patch which is only applied to the skin for up to an hour in a process that many doctors in the US found burdensome. Averitas Pharma has experience in marketing to specialty pharmacy and health hub/clinics, where Qutenza can be accessed by patients more easily, and the company can support health care professionals in prescribing and applying it.

"This will help us in transitioning and ramping up the Qutenza business, bringing the product back onto a growth path in the US," Baertschi said.

Averitas Pharma will be the name under which Grunenthal will commercialize Qutenza in the US, and the business will also work towards gaining a broader neuropathic pain indication for the product from the US FDA – the patch is currently only approved in the US for the treatment of post-herpetic neuralgia, while in Europe it is approved for a broad peripheral neuropathic pain indication in adults, including post-surgical neuropathic pain, cancer-related neuropathic pain and painful diabetic peripheral neuropathy. It was first approved in the US in 2009.

The new US business will also be involved in marketing Grunenthal's pipeline of niche pain-related products, or in-licensed products, without the need for expensive marketing or sales forces. The European firm is one of the few research-based pharmaceutical companies involved in developing pain therapeutics even though there is a high unmet need for non-opioid and non-systemic treatments, like Qutenza.

COMPLEX REGIONAL PAIN SYNDROMES

"We also have a pipeline of products which will fit with the Averitas Pharma infrastructure, including neridronic acid, which is being evaluated in two Phase III studies in patients with complex regional pain syndrome (CRPS)," Baertschi said.

CRPS is a rare and debilitating continuous throbbing pain, often present after injury or surgery to an extremity, which can lead to loss of physical function and permanent disability. There are no FDA- or EMA-approved treatments for CRPS. Neridronic acid was discovered and developed by the Italian company, **Abiogen Pharma SPA**, and Grunenthal acquired the rights to the product for North, South and Central America and the Caribbean in 2013.

Another compound in Grunenthal's pain pipeline, GRT6010, is in Phase II for bladder pain syndrome, and there are a number of others in development including drug-device combinations and abuse deterrent formulations which may be of use in addressing the opioid abuse crisis.

Meanwhile in Europe, *Duzallo*, a fixed-dose combination of allopurinol and lesinurad, was approved for the treatment of gout, a very painful condition, in Europe at the end of August 2018, and is expected to be launched in 2019 by Grunenthal.

Published online 15 November 2018

Mystic Miss Not Make Or Break For Imfinzi

KEVIN GROGAN kevin.grogan@informa.com

AstraZeneca PLC' s confirmation that the closely-watched MYSTIC lung cancer trial of *Imfinzi* (durvalumab) has failed has disappointed investors but the company is keeping faith with the PD-L1 inhibitor and tremelimumab in other NSCLC trials.

Hopes have not been high for MYSTIC since the initial release of data back in July 2017 which showed that Imfinzi in combination with AstraZeneca's investigational anti-CTLA-4 antibody tremelimumab failed to improve progression-free survival (PFS) compared to platinum-based standard of care chemotherapy in previously untreated patients with stage IV (metastatic) non-small cell lung cancer. At the time, the company pointed out that the trial was designed to measure overall survival (OS) for the combo as well as for Imfinzi monotherapy, not PFS, but the data released Nov. 16 has confirmed the failure. *(Also see "MYSTIC Misses: Devastation For AstraZeneca As Imfinzi Fails PFS Endpoint In NSCLC" - Scrip, 27 Jul, 2017.)*

STATISTICAL SIGNIFICANCE

In the primary analysis population of patients whose tumors express PD-L1 on 25% or more of their cancer cells, Imfinzi monotherapy and the Imfinzi/tremelimumab combo did not meet the primary endpoints of improving OS compared to standard chemotherapy. The company tried to find some positives from the results, pointing to a 24% reduction, which was not statistically significant, in the risk of death for Imfinzi on its own compared to chemotherapy, but the future prospects for the Imfinzi/tremelimumab seem pretty grim as it performed worse than monotherapy, with a hazard ratio of 0.85 for the combo.

The final nail in the MYSTIC coffin comes after another high-profile Imfinzi/tremelimumab trial disappointed. Initial data from the ARCTIC study published in April showed that the combo failed to produce either a PFS or OS benefit when used in the late-stage treatment of advanced NSCLC patients, initial data show. *(Also see "ARCTIC Chill Descends On AstraZeneca's Imfinzi/Treme Combo In NSCLC" - Scrip, 24 Apr, 2018.)*

Sean Bohen, AstraZenenca's chief medical officer, said in a statement that "we are disappointed that these results missed statistical significance [but] we are encouraged to see that Imfinzi monotherapy activity is in-line with that of the anti-PD-1 class in previously-untreated patients with stage IV NSCLC. He insisted that "we remain confident in Imfinzi as the cornerstone of our

CONTINUED ON PAGE 23

Alnylam Offering Value-Based Deals In EU For Breakthrough RNAi Drug Onpattro

STEN STOVALL sten.stovall@informa.com

Mirroring its approach in the US, **Alnylam Pharmaceuticals Inc.** is offering outcomes-based contracts for its small interfering RNA (siRNA) therapeutic *Onpattro* (patisiran) in the rare disease of hereditary transthyretin-mediated amyloidosis, and has already launched the gene-silencing drug in Germany, the group's president Barry Greene told *Scrip*.

"We like to be as innovative on the commercial side as we have been on the R&D side. When we issued our patient access principles, we said that we would proactively offer value-based agreements – agreements that allowed payers to pay us when we achieved the kind of outcomes we saw in clinical trials and, on the other hand, pay less if the patient performs less well," Greene said in an interview during a recent visit to London.

Onpattro became the first RNAi therapeutic approved in the US and in Europe in August and the first drug cleared for hereditary transthyretin-medicated amyloidosis (hATTR) patients, a rare, rapidly progressive, fatal illness thought to affect some 50,000 people worldwide.

The drug's US and EU approvals were based on the pivotal APOLLO trial that showed nearly all patisiran-treated patients having the disease halted or slowed, with more than half seeing their neuropathy reversed.

'UNIQUE' VALUE-BASED APPROACH

"In the US we've proactively offered value-based agreements. This to our knowledge has never been done proactively before. We're taking that same attitude and perspective across the world," Greene said.

But a value-based approach to drug reimbursement wouldn't work for ever country, he added. "There are some countries that are open for discussions like that. Others have different processes that they like to follow which do not lend themselves to such discussion. But Alnylam is very willing anywhere in the world to engage in value-based agreement discussions," Greene said.

Barry Greene

'In the US we've proactively offered value-based agreements. This to our knowledge has never been done proactively before. We're taking that same attitude and perspective across the world'

Onpattro has now been launched in the US, where it has a list price of $450,000 per patient per year, and in Germany, its first European launch market, where it will cost around €362,500 ($410,200) per patient per year.

The drug's indication means that 10,000-15,000 patients could be eligible for treatment in the US, but many are undiagnosed, so the current target population there is 3,000 patients.

The company has not made public any peak sales projections for Onpattro. "In an orphan launch it's very difficult to predict, particularly when the disease is so mis-diagnosed and under-diagnosed," Greene told *Scrip*.

"What we are saying is that in Europe we think there's about 2,000 patients diagnosed with hATTR amyloidosis that are appropriate for treatment with Onpattro. It takes considerable time to finds them and make sure they are in the system. We think there's several hundred patients just in Germany."

MESSAGE TO TRUMP: 'PAY FOR INNOVATION'

Turning to the Trump Administration's mooted reforms in healthcare and drug prices, the Alnylam executive said he had sympathy with some of the arguments being set out by the White House, but stressed that it is in everyone's interests that real medical innovation is not choked off.

"We think some of the policies are helpful: stripping down bureaucracy, trying to drive down costs overall – but our view is that the focus should be on moving patients on to generic drugs where generic drugs are available, speeding up generic approvals, but certainly not targeting innovation," Greene said.

"Innovation should be paid for. Because the drugs that we're paying for today, if we follow our moral obligation and our generic laws, should be free to our children in the decades to come. So you've got to pay for innovation."

Published online 14 November 2018

Scrip's weekly **Pipeline Watch** tabulates the most recently reported late-stage clinical trial and regulatory developments from the more than 10,000 drug candidates currently under active research worldwide.

Click here for the entire pipeline with added commentary: http://bit.ly/2mx4jY3

Selected clinical trial developments for the week 9–15 November 2018

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
PHASE III INTERIM/TOP-LINE RESULTS			
AbbVie Inc.	*Mavyret* (glecaprevir/ pibrentasvir)	hepatitis C	M16-135; high virologic cure rates.
Merck & Co., Inc.	*Keytruda* (pembrolizumab)	esophageal cancer, second-line	KEYNOTE-181; improved overall survival.
UPDATED PHASE III RESULTS			
AbbVie Inc./ Neurocrine Biosciences, Inc.	*Orilissa* (elagolix)	uterine fibroids	ELARIS UF-I, UF-II; reduced menstrual bleeding.
Amarin Corp	*Vascepa* (icosapent ethyl)	cardiovascular disease	REDUCE-IT; improved CV outcomes.
Esperion Therapeutics, Inc.	ETC-1002	dyslipidemia	CLEAR-Serenity; efficacy confirmed.
AstraZeneca PLC	*Farxiga* (dapagliflozin)	diabetes type 2	DECLARE-TIMI58; CV outcomes improved.
PHASE III INITIATED			
Isofol Medical AB	Modufolin	colorectal cancer, first-line	ISO-CC-007; in US, Canada, Europe.
Biohaven Pharma	rimegepant	migraine prevention	An oral CGRP antagonist.
PHASE II INTERIM/TOP-LINE RESULTS			
Gilead Sciences, Inc./Phenex Inc.	GS-9674	primary sclerosing cholangitis	Improved liver markers.
MacroGenics, Inc.	enoblituzumab	prostate cancer	J1693; objective responses seen.
Eidos Therapeutics, Inc.	AG10	transthyretin amyloid cardiomyopathy	Positive clinical results.
Dr. Reddy's Laboratories	CA-170	cancer	Antitumor activity observed.
Quantum Genomics Corp.	firibastat	hypertension (systemic)	NEW-HOPE; met primary endpoint,
Ophthotech Corp	*Zimura* (avacincaptad pegol)	wet age-related macular degeneration	w/Lucentis; mixed results.
MYR GmbH	*Myrcludex B*	hepatitis D	w/PEG INF; strong synergism noted.
Factor Therapeutics Ltd	VF-001	diabetic foot and other ulcers	Missed endpoints.
Novan Therapeutics	SB206	molluscum contagiosum	Positive results.
Stemline Therapeutics, Inc.	tagraxofusp	blastic plasmacytoid dendritic cell neoplasm	High response rates.
Otsuka Holdings Co., Ltd.	VIS410	Influenza	Positive clinical activity.
DNAtrix, Inc.	tasadenoturev (DNX-2401)	brain cancer	CAPTIVE/KEYNOTE-192; promising results.
uniQure N.V.	AMT-061, gene therapy	hemophilia B	Achieved therapeutic levels.
UPDATED PHASE II RESULTS			
Novartis AG/Conatus Pharma	emricasan	hepatitis C	Signs of efficacy.
Concert Pharmaceuticals	CTP-543	hair loss	Symptoms reduced.
Innate Pharma	monalizumab	head and neck cancer	w/cetuximab; encouraging results.
PHASE II INITIATED			
Oryzon Genomics S.A.	iadademstat (ORY-1001)	acute myelogenous leukemia	ALICE; combined with azacitidine.
Attenua, Inc.	bradanicline	chronic cough	In patients with refractory symptoms.
DCPrime B.V.	DCP-001	acute myelogenous leukemia	ADVANCE-II; in Europe.

Source: Biomedtracker | Informa, 2018

CONTINUED FROM PAGE 20

IO programme and continue to evaluate its potential in ongoing NSCLC trials." Stage IV first-line NSCLC trials include PEARL (just Imfinzi) and the tremelimumab combo studies NEPTUNE and POSEIDON, with initial readouts expected in the first and third quarters of 2019, respectively.

In an investor note, Alex Arfaei at BMO Capital Markets said that MYSTIC "barely missed OS, apparently because of statistical powering. The silver lining is that Imfinzi clearly seems active, and possibly comparable to **Merck & Co. Inc.**'s *Keytruda* (pembrolizumab), however, the incremental benefit of tremelimumab is now highly uncertain."

He claimed that the NEPTUNE and POSEIDON trials "seem to have a higher probability of success but second-line PD1 treatment is a concern for both." The analyst added that he cautiously estimates a 20% probability of success for the combo in first-line NSCLC, noting that "the key uncertainty is tolerability."

Arfaei went on to say that another important variable in these trials is second-line PD1 treatment of the chemo arm as PD1s are now increasingly available as standard of care. "Given that AstraZeneca is now further behind Merck, and that it will likely only compete with Imfinzi and tremelimumab in first-line-NSCLC (no Imfinzi monotherapy), we now forecast peak market share of 10%, down from 15%," he concluded.

Dustin Phan, an analyst at *Informa's Datamonitor Healthcare*, told *Scrip* that "this is a devastating outcome for Imfinzi plus tremelimumab in first-line NSCLC, and could have rippling effects for POSEIDON and NEPTUNE." He added that observers will likely be following these trials now "with some skepticism."

Phan added that even if MYSTIC had demonstrated statistically significant OS, "this would likely have had a minimal real-world impact with the availability of Keytruda plus chemotherapy," which showed both a PFS and OS benefit in all comers. He noted that Roche's PD-L1 inhibitor *Tecentriq* (atezolizumab) plus chemotherapy has also demonstrated PFS and OS improvements over chemotherapy "and these combinations will continue to serve as barriers to entry for the first-line setting." *(Also see "Roche's Tecentriq Positive But Not Perfect In IMpower130 First-line Lung Cancer Study" - Scrip, 22 Oct, 2018.)*

IMFINZI POTENTIAL

While the failure of MYSTIC in stage IV lung cancer is a blow, it is arguably not going to have much of an effect on the potential for Imfinzi. AstraZeneca has carved out a sizeable niche for the drug in stage III NSCLC, a space where the company has a monopoly and will continue to have for some time. That position of strength in stage III has been consolidated by recent updated data from AstraZeneca's PACIFIC study which showed a 32% overall survival benefit for Imfinzi. In the third quarter, the drug had sales of $187m. *(Also see "AstraZeneca's PACIFIC Update Bolsters Imfinzi's Lead In Stage III Lung Cancer" - Scrip, 25 Sep, 2018.)*

Nevertheless, investors were a bit spooked by the MYSTIC miss and AstraZeneca shares fell 3% before recovering to close down 1.7% to £62.04.

Published online 16 November 2018

APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
Michael Culler	Alize Pharma	Chief Scientific Officer	Ipsen	Vice President, Endocrinology	14-Nov-18
Mariola Sohngen	Convert Pharmaceuticals SA	Chief Executive Officer	Mologen	Chief Executive Officer	8-Nov-18
Todd Zavodnick	Dermavant Sciences	Chief Executive Officer	Revance	Chief Commercial Officer and President, Aesthetics and Therapeutics	15-Nov-18
Elliot Ehrich	Expansion Therapeutics	Chief Medical Officer	Alkermes plc	Executive Vice President, Research and Development and Chief Medical Officer	13-Nov-18
Wei Lin	Nektar Therapeutics	Senior Vice President, Clinical Development and Head, Oncology Programs	Genentech	Global Development Leader	14-Nov-18
Brad Mathis	Orchard Therapeutics	Vice President, US Commercial Operations	Sucampo Pharmaceuticals Inc	Vice President, Head, US Commercial Operations	8-Nov-18
Robin Kenselaar	Orchard Therapeutics	Senior Vice President and General Manager, EMEA Commercial Operations	Sanofi Genzyme	Head, Commercial, Europe	8-Nov-18

Click here for all appointments: https://bit.ly/2oHWRYn

Source: Medtrack | Informa, 2018

Brought to you by Citeline Pharma intelligence | informa

Sponsored by medidata

Clinical & Research Excellence Awards | 2019
Pharma intelligence

CLINICAL & RESEARCH EXCELLENCE AWARDS 2019

May 2, 2019
Hyatt Regency Boston, Boston, MA

NOMINATIONS ARE OPEN

Entry Deadline: January, 18

www.clinicalresearchexcellence.com

General Enquiries:

Jo Kirkpatrick | Tel: +44 (0) 20 7017 7180 | Email: jo.kirkpatrick@informa.com