Scrip
13 October 2017
No. 3875
scrip.pharmamedtechbi.com
Pharma intelligence | informa

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# Surprise! Mylan's Copaxone Generic Sets Teva Up For A Struggle

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**Mylan NV** has won the FDA's approval of the first generic version of a 40mg dose of **Teva Pharmaceutical Industries Ltd.**'s *Copaxone* (glatiramer) for multiple sclerosis, setting Mylan up for a potentially lucrative commercial opportunity while adding to Teva's mounting challenges.

The news, announced after market closed on Oct. 3, took investors from both companies by surprise since Mylan's management recently warned investors not to expect any of its complex generics pending at the US FDA to be approved until 2018, citing the challenging environment at the agency. *(Also see "Mylan Preparing Response To Generic Advair CRL, And It Needs A Win" Scrip, 9 Aug, 2017.)*

Mylan said it plans to launch the drug "imminently," but provided no details on the timeline. The product is the subject of an appeal in a patent infringement case filed by Teva. A district court judge already ruled that patents on the 40 mg product are invalid and the Patent and Trademark Office's Patent Trial and Appeal Board (PTAB) ruled that three patents covering the 40 mg dose are unpatentable. *(Also see "Copaxone 40mg Generic At-Risk Launch Anticipated As Soon As February" Pink Sheet, 31 Jan, 2017.)*

As a result, Mylan may feel confident about moving ahead with a launch, though Teva said in a statement that any launch ahead of a decision in the court case would be considered "at-risk," meaning Mylan could have to pay damages if the appeals court rules in Teva's favor. Oral arguments in the case are not expected to be heard before December or the first quarter 2018 at the earliest.

Mylan has sought to position itself as a leader in complex generics and biosimilars as the US generic drug market has come under pressure and as the company has sought to recover from its own challenges with the rescue allergy medication *EpiPen*. Thus, the FDA's approval of the company's glatiramer ANDA is an important feather in the cap for Mylan. The approval includes both the 40 mg version, dosed three times a week, and the original 20 mg version dosed daily.

The 40 mg version is considered the more lucrative commercial opportunity given the dosing advantage, and the fact that Teva has successfully switched most patients to the newer formula. **Novartis AG**'s **Sandoz Inc.** generic drug unit already sells a version of the 20 mg formula called *Glatopa*, which has not had an enormous impact on Teva's number-one-selling specialty brand. Copaxone generated sales of $4.22bn in 2016, most of which come from the US, and accounted for 19% of Teva's top line.

"We believe this milestone validates our investment thesis that Mylan's pipeline of complex generics was underappreciated," Barclay's analyst Douglas Tsao said in an Oct. 4 research note.

"Copaxone is a big win but we still see other potential key approvals over the next 15 months, including generic versions of *Advair*, *Restasis*, *Estrace* as well as biosimilars," he said. "We believe Copaxone approval will enhance investor confidence that Mylan will be able to monetize those other opportunities."

Securing the FDA's approval of the first generic version of **GlaxoSmithKline**

CONTINUED ON PAGE 7

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**Real World Data**
**Boehringer/Anthem Put Stiolto Duo To Test (p5)**

**Caterpillar To Butterfly?**
**Ablynx Says Caplacizumab Data Transformational (p16)**

**India CEO Pay**
**Local Firms Still Way Ahead Of Foreign Peers (p21)**

## from the editor

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Increasingly vilified by politicians and the press for charging too much for drugs, should pharma companies also be tackled for giving their drugs away too cheaply? When strings are attached they should, according to Shire, which has filed suit against rival Allergan (see p8).

Shire argues that Allergan is illegally squeezing it out of the dry eye market by offering deep discounts on Restasis and other drugs in Allergan portfolio if Medicare Part D payers agree to leave Shire's competing drug Xiidra off their formularies. Allergan's leverage is such that some payers wouldn't put Xiidra on their formulary even if it was free, Shire says.

It could be argued that Shire could team up with other companies to bundle Xiidra with non-Shire products, thus protecting itself from being squeezed out of the market while at the same time preserving the cost benefits for payers that Allergan is offering. This would have the merit of turning an allegedly anticompetitive scenario into a pro-competitive one, with the payer ultimately benefiting from keen pricing.

Variations on the theme of anticompetitive drug selling have been thrashed out in the courts repeatedly as far back as the 1970s when Lilly was found to have used bundling to acquire and maintain a monopoly position in cephalosporins in violation of antitrust law at the expense of SmithKline. The Shire/Allergan case itself follows rapidly on from that launched by Pfizer against Johnson & Johnson regarding the latter's bundling tactics to protect its blockbuster Remicade from Pfizer's biosimilar version. Drawing a definitive line between anticompetitive and pro-competitive practice is no simple matter.

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Scrip is published by Informa UK Limited.  ISSN 0143 7690.

 




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# inside:



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# Takeda Paves The Way For Myovant With Phase III Fibroid Success

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**Takeda Pharmaceutical Co. Ltd.** has reported the first Phase III data for the investigational uterine fibroid treatment relugolix in Japanese patients in a study that is seen as a bellwether for larger international studies being undertaken by licensee **Myovant Sciences Ltd.**

The US firm licensed rights to the product outside Japan and certain other Asian countries in June 2016 for use in endometriosis, uterine fibroids and hormone-sensitive prostate cancer. Success for Myovant would in turn take some pressure off its parent company, **Roivant Sciences GMBH**, after the recent failure of sister firm Axovant Sciences' Phase III Alzheimer's trial with intepirdine. *(Also see "Takeda Continues To Shed Pipeline Assets In Roivant Deal" Scrip, 7 Jun, 2016.)(Also see "Disappointed, Yes, But Roivant's Not Roiled By Axovant's Alzheimer's Failure" Scrip, 26 Sep, 2017.)*

Relugolix is competing with **AbbVie Inc.**'s elagolix to be the first oral gonadotropin-releasing hormone (GnRH) receptor antagonist on the market; these are expected to elbow out older injectable products such as leuprorelin and provide an alternative to surgery for patients.

The topline data reported by Takeda show relugolix is non-inferior to leuprorelin in decreasing menstrual bleeding in women with uterine fibroids. This is the first of two Phase III studies in Japanese women designed to support a Japanese approval filing. The second is in 70 women with pain associated with uterine fibroids, with results due by the end of the year.

Together, analysts say, they should boost confidence in the likely success of Myovant's two international pivotal clinical trials (LIBERTY 1 and LIBERTY 2) of relugolix in women with heavy menstrual bleeding associated with uterine fibroids. These began in January.

Takeda's non-inferiority study in about 280 women with heavy menstrual bleeding associated with uterine fibroids compared relugolix 40 mg orally once daily with subcutaneously injected leuprorelin, dosed at 1.88 mg or 3.75 mg every four weeks, for 24 weeks. Leuprorelin (leuprolide acetate) is an injectable GnRH agonist approved for pre-operative treatment of uterine fibroids in Japan.

The primary endpoint was the proportion of women who achieved a total score of less than 10 on the Pictorial Blood Loss Assessment Chart (PBAC), a patient-reported outcome measure for evaluation of menstrual blood loss in clinical trials, from week six to week 12. All participants had a PBAC ≥120 upon entry into the study.

> This is the first of two Phase III studies in Japanese women designed to support a Japanese approval filing

In the trial, relugolix successfully demonstrated non-inferiority to leuprorelin with 82.2% of patients treated with relugolix achieving a score of less than 10 on the PBAC, compared with 83.1% of patients treated with leuprorelin (p=0.0013). Adverse events were generally similar between treatment groups and consistent with the mechanism of action of the study medications.

The Takeda trial design and endpoints differ from those employed in Myovant's Phase III studies, but the data are expected to be used to support Myovant's NDA for relugolix in the US and beyond.

Myovant's identical LIBERTY 1 and 2 studies are testing a hormone add-back arm regimen to try to reduce the bone mineral adverse effects of GnRH inhibition, as well as using a more stringent blood loss test. Each will enrol 390 women with heavy menstrual bleeding associated with uterine fibroids to compare treatment with relugolix 40 mg once daily co-administered with commercially available low-dose hormonal add-back therapy (estradiol and norethindrone acetate) for 24 weeks, relugolix 40 mg once daily monotherapy for 12 weeks followed by relugolix 40 mg once daily co-administered with hormonal add-back therapy for an additional 12 weeks, or placebo once daily for a period of 24 weeks. To be enrolled, women must have a monthly menstrual blood loss of at least 80 mL.

The primary efficacy endpoint for LIBERTY 1 and LIBERTY 2 is the proportion of all women enrolled who achieve a menstrual blood loss volume of less than 80 mL and at least a 50% reduction in menstrual blood loss volume from baseline over the last month of treatment as measured by the alkaline hematin method, a quantitative measure of menstrual blood loss.

## COMPETITIVE ADVANTAGE?

Analysts at Baird note that this efficacy endpoint matches that used by AbbVie for its pivotal studies of elagolix. Phase III data for this product are expected by year end or early in 2018, as compared with a 2019 readout for the LIBERTY studies.

Analysts at JPM believe that relugolix should have advantages over its main competitor, elagolix, with potential to be best in class because of its high potency and extended half-life. "Both elagolix and relugolix are biologically (and we believe therapeutically) active GnRH antagonists. However, relugolix is a more potent antagonist with an IC50 of 0.12nM vs. elagolix's 1.5nM. Relugolix also has a relatively extended half-life of 37-42 hours, vs. 2-6 hours for elagolix. These pharmacologic properties result in a pharmacodynamics profile where relugolix (40mg QD) achieves near-complete suppression of estrogen," they said in a research note.

*Published online 3 October 2017*

View Products In Clinical Testing For Uterine Fibroids here:
**http://bit.ly/2fTX3Q2**

# Boehringer And Anthem Put Stiolto Duo To Real World Test In COPD

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**Boehringer Ingelheim GMBH** is putting its *Stiolto Respimat* LABA/LAMA combo to a real-world test in the US with the large AIRWISE study in chronic obstructive pulmonary disease, designed and run jointly with **HealthCore Inc.**, an outcomes research subsidiary of the insurer **Anthem Inc.**

Approved by the FDA in 2015 for COPD, including chronic bronchitis and emphysema, Stiolto is a fixed dose, once-daily combination of two products marketed as single agents – the long-acting muscarinic antagonist (LAMA) *Spiriva* (tiotropium bromide), and *Striverdi* (olodaterol), a long-acting beta-agonist (LABA) – for use with the company's Respimat inhaler.

In addition to Stiolto, three other LAMA/LABA combinations are commercially available in the US: **GlaxoSmithKline PLC**'s *Anoro* (umeclidinium/vilanterol), **Novartis AG**'s *Ultibro* (glycopyrronium/indacaterol) and **AstraZeneca PLC**'s *Genuair* (aclidinium/formoterol). *(Also see "GOLD Pushes LABA/LAMA Class In New COPD Treatment Update" Scrip, 28 Nov, 2016.)*

Boehringer, Anthem and its independent research arm HealthCore announced on Oct. 5 that the first patients have enrolled in the real-world, open-label study AIRWISE, which will randomize 3,200 participants not controlled on their COPD therapy to Stiolto or any commercially available triple combination therapy regimen – that is a LABA, LAMA and an inhaled corticosteroid (ICS).

"Whether or not an ICS provides a meaningful benefit in reducing COPD exacerbations, in addition to a LAMA and a LABA, is currently a topic of scientific debate," the companies explained.

The AIRWISE study is an outgrowth of a multi-year research collaboration forged by the partners in 2014 aimed at assessing appropriateness of care and measuring outcomes of commercially available therapies. *(Also see "Boehringer/WellPoint Outcomes Research To Inform Pradaxa Treatment" Pink Sheet, 2 Dec, 2014.)* Results are expected in 2020.

A real-world or "pragmatic" study aims to test drugs and other interventions in a natural environment, in contrast with randomized trials where inclusion and exclusion criteria are tightly controlled. They involve randomization but providers are left on their own to make treatment decisions. Real-world studies are becoming more common as pharmaceutical companies seek to differentiate their products in crowded markets and demonstrate the value of new follow-on therapies.

The results will be applicable to a range of clinical audiences including precribers, Anthem and other payers and policy makers, Vince Willey, HealthCore staff vice president, commented in an interview.

"We feel that this type of data collected in more of a real-world setting – different from randomized controlled trials – is really going to have utility across the healthcare system," Willey said.

**GlaxoSmithKline PLC** has been a leader in the area of real-world trials, having run the UK-based Salford Lung study of its once-daily LABA/ICS combination *Breo/Relvar* (fluticasone/furoate vilanterol) in 2,802 people with COPD and 4,000 with asthma. *(Also see "Real-World Evidence: Lessons From GSK's Salford Lung Study" Scrip, 9 Sep, 2016.)*

For Boehringer, AIRWISE represents an important step as the first pragmatic study sponsored directly by the company, added Thomas Seck, the pharma's vice president of clinical development and medical affairs for primary care.

"What we observed in the environment in general over the last decade, but it has really been gaining steam over the last few years or so, is that it is becoming more important to generate data in less selected populations in the real world to see how these treatment options perform in the real world and how they compare with each other," Seck told *Scrip*.

The latest guidelines from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) now favor fixed-dose LABA/LAMA combinations over ICS/LABA combinations in the treatment of COPD and advise reserving triple therapy for the most severe cases, people who are highly symptomatic. It's questionable whether real world practice is in accordance with this guidance, however. The study sponsors note that adding an ICS to LABA/LAMA may result in added side effects without better outcomes.

Some 15m Americans have been diagnosed with COPD, according to the companies. About one-third of COPD patients reportedly receive triple therapy through multiple inhalers.

## AIRWISE TRIAL DESIGN

The partners claim that this is the largest real-world study ever conducted in COPD. The nationwide study will include Anthem beneficiaries for the most part, but it will also include people covered by other providers. Results will be monitored over 52 weeks.

The study has few inclusion or exclusion criteria and treatment will be carried out by doctors in the community, as if in routine practice. However, data will quietly be collected in the background.

One of the challenges with this type of trial is that there is no push to get patients into the study, rather researchers rely on the normal flow of clinical practice – the market dynamic is not under your control, HealthCore vice president-research Mark Cziraky noted.

The primary endpoint of the AIRWISE study is the time to occurrence of moderate-to-severe exacerbations related to COPD.

In addition to the primary endpoint, the study will assess the annual rates of moderate or severe exacerbations and all-cause COPD-related healthcare resource utilization, including hospital admissions and emergency room visits.

The sponsors wanted to pick endpoints that would resonate and be most relevant to clinicians, payers and policy makers. The rate of exacerbations is a very important issue and the secondary endpoints look at things "you can't study well in a traditional clinical trial but you can in this type of trial," Willey said.

There could be a reduction in healthcare utilization, but that will need to be confirmed, Boehringer's Seck said.

*Published online 6 October 2017*

# ESUS Fails But Hurt Minimal For Bayer/Janssen's Xarelto

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**Bayer AG** and **Janssen Inc.** have put a stop to the Phase III NAVIGATE ESUS study of the novel oral anticoagulant *Xarelto* (rivaroxaban) in secondary stroke prevention after it looked unlikely to show any benefit over low-dose aspirin and showed an added bleeding risk.

The study is one of a number in the companies' wide-ranging EXPLORER program which aims to support as broad a label as possible for Xarelto to distinguish it from its rivals, namely **Pfizer Inc./Bristol-Myers Squibb Co.**'s *Eliquis* (apixaban) and **Boehringer Ingelheim GMBH**'s *Pradaxa* (dabigatran). But analysts say this particular market's potential is small fry compared with that for the much more successful COMPASS study, which was presented at the European Society of Cardiology meeting in August.

The 7,214-patient NAVIGATE ESUS trial was looking at the secondary prevention of stroke and systemic embolism in patients with a recent embolic stroke of undetermined source (ESUS). This does not include patients with atrial fibrillation or established atherosclerotic disease making the patient population in NAVIGATE ESUS different from the currently approved indications for rivaroxaban. The risk of stroke recurrence for ESUS patients remains substantial despite recommended treatments. "Patients with ESUS currently have limited treatment options and the role of anticoagulants in this area remains uncertain," said Dr. Joerg Moeller, Bayer's head of development.

Bayer has said it does not expect any impact from NAVIGATE ESUS' failure on its peak sales forecasts for the product, which it last year raised to more than €5bn. Bayer markets the product outside the US.

## DISAPPOINTING BUT MINOR

Analysts at Jefferies said: "While disappointing, this was a relatively minor opportunity for Xarelto. In the US, the ESUS indication only accounts for c.0.5m patients which pales into insignificance against the c.15m incremental US patients Xarelto is expected to gain access to via the successful COMPASS trial."

First approved in 2011, Xarelto's approved indications in the EU and US cover reduction of risk for stroke and embolism in patients with non-valvular atrial fibrillation (its biggest market), prevention or treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and recurrence of DVT and PE, and prevention of DVT in patients undergoing knee or hip replacement surgery.

In the EU it is additionally approved for the prevention of atherothrombotic events after an acute coronary syndrome in adult patients with elevated cardiac biomarkers and no prior stroke or transient ischemic attack when co-administered with aspirin alone or with aspirin plus clopidogrel or ticlopidine. However, attempts to obtain a similar indication in the US met with repeated rebuffs.

Filings based on the COMPASS study, which revealed its benefit in coronary artery and peripheral arterial disease patients, are due by the end of the year, while other studies in the EXPLORER program are looking at its use in heart failure patients, PCI valve replacement, cancer-associated thrombosis and medically ill patients. *(Also see "COMPASS Success Reinforces J&J/Bayer's Broad Labeling Strategy For Xarelto" Scrip, 10 Feb, 2017.)*

In the NAVIGATE ESUS study, patients were randomized to receive either rivaroxaban 15 mg once daily or aspirin 100 mg once daily alone. The primary efficacy endpoint was a composite of stroke (ischemic, hemorrhagic and undefined stroke, transient ischemic attack with positive neuroimaging) and systemic embolism. The full data will be presented at an upcoming medical meeting next year.

The trial's Independent Data Monitoring Committee recommended the halt following a planned interim analysis, as it showed comparable efficacy between the rivaroxaban and aspirin arms and had very little chance of showing overall benefit if completed. While bleeding rates were low overall, an increase in bleeding was seen in the rivaroxaban arm over the low-dose aspirin arm.

*Published online 6 October 2017*

# Europe Approves Glatiramer Generic Too

**Synthon BV** and **Alvogen**, collaborators on the development of a 40 mg/ml generic version of **Teva Pharmaceutical Industries Ltd.**'s multiple sclerosis therapy *Copaxone* (glatiramer acetate), announced on Oct. 5 that their product has been approved for marketing in Europe.

The development comes a day after another generics company, **Mylan Pharmaceuticals Inc.**, surprised the markets by saying it had won the US FDA's approval for its substitutable generic versions of Copaxone 20 mg/ml and 40 mg/ml in the US (see p1). Mylan had previously expected approval in 2018.

The European news piles further pressure on Teva, which is facing both increased pricing pressure in its generics business, and greater competition in its specialty business, principally from Copaxone generics. The Mylan generic was developed in collaboration with an Indian partner, **Natco Pharma Ltd.**

Alvogen already markets once-daily *Remurel* containing 20 mg/ml of glatiramer acetate as a generic version of Copaxone 20 mg/ml in European countries, and believes its three-times-weekly glatiramer acetate 40 mg/ml version will be the first generic equivalent of Copaxone 40 mg/ml to be made available in Europe. The generic is therapeutically equivalent to Copaxone, Synthon and Alvogen noted.

Remurel 40 mg/ml has completed the EU's decentralized procedure involving 27 EU/EEA countries, and the product is expected to be launched after national approvals are issued over the coming days and weeks.

The Iceland-headquartered Alvogen is expected to introduce its new 40 mg/ml generic at a lower cost compared with the branded product in Europe. The company said the approval was "excellent news for the multiple sclerosis community, providing a high-quality and affordable alternative."

john.davis@informa.com, 6 Oct 2017

CONTINUED FROM COVER

**PLC**'s blockbuster asthma drug *Advair Diskus* would also be a boon. The company was the first to file an ANDA with the FDA, but received a complete response letter earlier this year.

## PRESSURE ON INCOMING CEO

Mylan's stock opened on Oct. 4 up 19.5% at $38. Teva's stock, meanwhile, opened 13% lower at $16.33. For Teva, the news comes at a particularly challenging time with the company trying to regain its footing. The generic side of the business is experiencing unrelenting US pricing pressure, while the specialty side of the business now faces a substantial generic threat. A generic rival to its all-important Copaxone franchise will give incoming CEO Kare Schultz even more headaches as he attempts to turnaround the struggling generic drug giant when he joins the company later this year. *(Also see "Teva Lands A CEO: Can Schultz Replicate Lundbeck Success?" Scrip, 11 Sep, 2017.)*

If Mylan is granted 180-day exclusivity, that could limit the amount of generics that get to market and therefore the amount of price erosion – giving Teva some breathing room.

Teva said it is too early to say how the news could change the company's full-year business outlook, but an early assessment shows fourth quarter earnings could be $0.25 lower per share. While Copaxone accounts for 19% of Teva's 2016 revenues, Credit Suisse's Vamil Divan speculated the franchise could account for 40%-50% of the company's operating profit.

"We would expect this news to pressure Teva's shares and lead to further questions around Teva's financial outlook," Divan said. "However, on the bright side, some clarity on Copaxone could lessen the focus on an issue that has been an overhang on Teva's shares and allow for a cleaner start when the new CEO joins the company later this year."

Analysts are upgrading their expectations for Mylan given the early approval. "Given this, the launch (assuming no other player in FY18) could add 75% to FY18 EPS. FY19 EPS will see a moderate 12% boost led by one additional quarter of sales," Jefferies equity analysts Piyush Nahar and Sagar Sahu said in an Oct. 4 flash note.

Mylan could further benefit from 180-day exclusivity of the 40 mg product, as it was one of the first to submit a complete ANDA with a Paragraph IV certification, but the company said the FDA has not made a formal determination on exclusivity. Sandoz and partner **Momenta Pharmaceuticals Inc.** have filed a 40 mg version of Copaxone with the FDA, but the submission has been delayed by a manufacturing issue with its third-party supplier.

In terms of competition, the Jefferies analysts expect Mylan has a clear window for the next six months, as the Sandoz warning letter is likely to delay approval until next year. "**Dr. Reddy's Laboratories Ltd.** has a TAD [target action date] for end-CY17 but we believe that it can get further queries," they said.

The generic approval, coming after Mylan had pointed a finger at the FDA for administrative challenges, could also signal the agency's commitment to improving the speed to getting complex generics to market. The topic has been a pivotal talking point of new Commissioner Scott Gottlieb and his initiative to help reduce the cost of health care. Just one day before the approval was announced, the agency issued new guidance on the FDA review process for complex generics, with an accompanying blog post from Gottlieb highlighting the importance of speeding up the process of getting complex generics to market. *(Also see "Complex ANDAs: Early Meetings With FDA Can Generate Bonus Communication" Scrip, 2 Oct, 2017.)*

*Published online 6 October 2017*

*Additional reporting contributed by Anju Ghangurde (anju.ghangurde@informa.com)*



# Otezla Versions On Horizon But Celgene Cool?

At least half a dozen Indian firms including **Hetero Labs**, **Dr. Reddy's Laboratories Ltd.**, **Ajanta Pharma**, **Glenmark Pharmaceuticals Ltd.**, **MSN Laboratories Pvt. Ltd.** and **Synokem Pharmaceuticals Ltd** appear to be readying for the launch of generic versions of **Celgene Corp.**'s psoriasis drug, *Otezla*, (apremilast) on the domestic market.

The launch-related activity is significant given, among other factors, that Otzela is under patent in key international markets though Celgene doesn't appear to have pressed for IP rights in India, if some industry insiders are to be believed.

Many of the Indian players appear to be on course to complete relevant studies for apremilast having received requisite clearances from the Subject Expert Committee (SEC), an expert panel which advises the Indian drug regulator on trial-related approvals. The SEC (dermatology and allergy) has over the recent past recommended granting permission for Phase III clinical trials and bio-equivalence studies in the case of most of these firms including Dr Reddy's and Hetero.

Dr Reddy's declined to comment on plans to develop and launch apremilast, while Hetero did not immediately respond to an email request for comment on the issue.

Glenmark, on the other hand, recently presented its clinical study and bioequivalence study report to the expert panel. The SEC, at its meeting on Sept. 21, recommended that Glenmark's apremilast tablets 10/20/30 mg be granted manufacturing and marketing permission for treatment of patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy, setting the stage for an imminent launch of the generic version.

anju.ghangurde@informa.com, 6 Oct 2017

Read more about Otezla's potential here: **http://bit.ly/2z8U8et**

# Shire Vs Allergan Brings Exclusive Contracts Out Of The Shadows (Again)

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Growing questions over exclusive reimbursement contracts – and whether or not they are fair play when it comes to defending entrenched brands – are poised to be decided in court. The second lawsuit in just over a week charging anti-competitive practices related to exclusive contracting by drug makers was filed on Oct. 2 in New Jersey district court by **Shire PLC**.

Shutterstock: Lightspring

Shire alleges that **Allergan PLC** has coerced payers under Medicare Part D to exclude its new dry eye disease drug *Xiidra* (lifitegrast) or severely restrict access while favoring Allergan's older *Restasis* (cyclosporine). While Xiidra has picked up significant traction under the commercially-reimbursed market, Restasis has maintained a market share of nearly 90% in the Part D market, the suit alleges. Dry eye disease frequently affects elderly people, which makes the Part D market a critical one for both products. Some 40% of dry eye patients are covered under Medicare, according to the companies.

The lawsuit echoes one filed by **Pfizer Inc.** in late September against **Johnson & Johnson** related to exclusive contracting for *Remicade* (infliximab), which Pfizer claims has blocked access to its biosimilar *Inflectra* (infliximab-dyyb). There are important differences between the two lawsuits. Notably, the potentially precedent-setting Pfizer case centers around tactics impacting what is intended to be a cheaper biosimilar, not a rival brand, and the Pfizer suit also revolves around commercial reimbursement rather than government contracts.

But at the heart of the two cases are allegations of questionable rebating tactics, with the plaintiffs alleging that the defendants threatened to withhold vital cost-saving rebates and discounts for their products if the competitor product was reimbursed.

Allergan responded in a statement that there is no merit to the lawsuit. "In our negotiations with Medicare Part D sponsors, we are competing on value and price, and competition in the chronic dry eye therapeutic market has driven pricing down for patients and payers in Medicare Part D and commercial plans," Allergan said.

Restasis, which has been on the market for 15 years, is Allergan's top-selling drug behind *Botox,* with sales of $1.4bn in 2016. Xiidra only launched a year ago and generated sales of $96m in the first six months of 2017. Xiidra has a broader indication for treating dry eye disease, while Restasis is approved for increasing tear production in patients who have dry eye.

## BUNDLING RESTASIS WITH GLAUCOMA DRUGS

Allergan is offering steep rebates on Restasis and other drugs in its portfolio – a tactic known as bundling – to plans who agree to exclude Xiidra on formularies or significantly restrict access, according to Shire. Other products made by Allergan and reimbursed through Part D include the glaucoma drugs *Lumigan* (bimatoprost), *Combigan* (brimonidine/timolol) and *Alphagan* (brimonidine), according to the suit. In the last four quarters (Q3 2016 through Q2 2017), Allergan's sales of the three glaucoma drugs to Part D plans accounted for almost $750,000, while Restasis accounted for another $719,000, the suit says.

"The glaucoma drugs alone provide Allergan with more than enough financial wherewithal to give the plans discounts and rebates that far exceed anything that Shire could offer on Xiidra (including giving it to the plans for free)," Shire contends.

"The loss in value of Allergan's discounts and/or rebates to the Part D plans is so substantial that it is impossible for Shire to gain formulary access for Xiidra, no matter what financial terms it offers," the lawsuit states.

Shire says it has offered Part D plans discounts and rebates that exceed the discounts on Xiidra it has offered commercial plans, but the plans have rejected Shire's offers. One plan administrator apparently told Shire, "You could give [Xiidra] to us for free, and the numbers still wouldn't work."

The result has an impact on patients too, Shire points out. If a drug is excluded from a formulary, Part D beneficiaries either do not have coverage for that drug or will only get coverage if their physician appeals by filing for an exception, which usually requires failure of the preferred drug. And, if the appeal is granted, patients typically have to pay a significantly higher copay.

"In cases where Xiidra is 'not covered,' patients can expect to have a copayment that is two to five times higher than would be the case if Xiidra were on formulary as a 'preferred' drug," the lawsuit says.

Shire is requesting that Allergan's conduct be deemed anticompetitive and unlawful and is seeking financial relief for bringing the lawsuit forward.

The lawsuit is just the latest on Allergan's aggressive tactics for wringing revenue out of its maturing franchise. The company has also gotten some negative attention after announcing a deal with a Native American tribe that could help it protect patents related to Restasis from the inter partes review (IPR) process. Four Democratic Senators sent a letter to Senate Judiciary Committee Chairman Charles Grassley, R-IA, on Sept. 27 requesting an investigation into the controversial deal.

*Published online 2 October 2017*

# Spain's Oryzon Moves To Madrid From Barcelona As Catalan Crisis Deepens

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Days after the controversial independence referendum held in Catalonia, eyebrows have been raised over the decision by flagship Spanish biotech **Oryzon Genomics SA** to relocate its head office to Madrid from Barcelona.

The company says that the move to Madrid has been driven by a need to "optimize its operations and relationship with investors," as well as a desire to be closer to the country's medicines regulator. In a short statement to Spain's National Securities Market Commission, Oryzon, which also has an office in Cambridge, Mass., says its administration and management will be based in the capital but it should be noted that the firm's laboratories and 40-strong R&D staff will continue to operate out of Barcelona.

The timing of the move is particularly pertinent given the chaos that has ensued in Catalonia following the vote led by a section of the autonomous Catalan government which had been declared illegal by the Spanish state and its courts. The company did not comment specifically on whether the move is linked to the upheaval in the north-eastern region and it is highly unlikely that the decision is a knee-jerk reaction to Sunday's vote.

However, according to a report in the Spanish business newspaper *Cinco Dias*, Oryzon chief executive Carlos Buesa was quoted as saying that "everything is weighed up. Let everyone value it as you see fit." He also noted that regarding the sovereignty debate and the tension between Catalonia and the central government, he believes that it is not appropriate for companies to position themselves publicly on the matter and that is the role of politicians.

Buesa also stressed the wish to be closer to investors as he feels Oryzon had been excessively punished by the market following Roche's decision to pull out of a potentially lucrative cancer partnership in July "due to a portfolio prioritization." The drug in question is the investigational lysine specific demethylase-1 (LSD1) inhibitor code-named ORY-1001 and the pact, signed in April 2014 and heralded as the biggest licensing deal

Oryzon

*Moving to Madrid: Carlos Buesa*

in the history of the Spanish biotech sector at the time, would have been worth more than $500m.

Oryzon still has very high hopes for ORY-1001, which is initially being developed for acute myeloid leukemia (AML) as well as solid tumors. In July, Buesa told *Scrip* that he was confident a new partner for the compound.

As for the bigger picture, a number of sources within the Spanish pharmaceutical sector have expressed their alarm to *Scrip* over the escalation of the Catalan crisis. In a rare televised speech to the nation on Oct. 3, King Felipe VI accused the Catalan authorities of attempting to break "the unity of Spain" saying their behavior had "eroded the harmony and co-existence within Catalan society itself, managing, unfortunately, to divide it".

The tension is continuing to rise with Catalonia president Carles Puigdemont declaring the region will declare unilateral independence within days. The Spanish Prime Minister Mariano Rajoy has yet to respond to the threat but his position of defending Spanish sovereignty is not going to change.

Rajoy has the support of world leaders and crucially the European Commission which issued a statement that the vote in Catalonia was not legal and the problem is "an internal matter for Spain that has to be dealt with in line with the constitutional order of Spain." It added that "if a referendum were to be organised in line with the Spanish Constitution it would mean that the territory leaving would find itself outside of the European Union."

In response to the news, the Spanish Association of Biotech Companies (ASEBIO) sent a statement to *Scrip* saying that it is not appropriate to comment on the business decisions of its individual members, adding that for its part, "we do not know if other biotech companies are considering changing their headquarters."

However, ASEBIO stated that the biotechnology sector requires an environment to help R&D investment "which must necessarily be based on the existence of legal security and stability for companies to develop their projects and their business." It added that, "Catalonia has stood out for being able to generate an environment that has allowed the development of a thriving biotechnology industry and we hope that this environment will continue."

In Catalonia, ASEBIO has 70 members, 26% of its total across the country. It is the autonomous community (there are 17 of them in Spain) with the highest number of user biotechnology companies (515) and strictly biotech firms (181). It leads the way in terms of R&D investment and only last week, ASEBIO held an event in Barcelona with presentations of 30 Spanish projects for 50 international investors, including the likes of Ysios Capital, Edmond de Rothschild, Merck Ventures, Omnix Health and Sofinnova.

The Catalonian problem is not only an issue for domestic drugmakers as a large number of multinational pharmaceutical companies have their headquarters and facilities in the region. How committed they will continue to be to the area given the political turmoil (a matter which could be fatally damaging to Barcelona's bid to host the European Medicines Agency) remains to be seen.

As for investors, they seemed impressed by Oryzon's Madrid move and the company's shares shot up over 30% during the day before slipping back to close up 13% to €2.02. *Published online 6 October 2017*

# Cell And Gene Therapies: Where Few Standard Rules Apply

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The main rule of the cell and gene therapy market is there are few hard and fast rules when it comes to how to manufacture, distribute, administer and price these potentially curative treatments for cancer and rare diseases.

Without a standard set of rules agreed to by the therapies' developers, the first companies with approved products – along with their vendors, treating physicians and payers – will dictate the complex path forward. Biopharmaceutical companies and reimbursement experts discussed the challenges associated with commercialization of cell and gene therapies during the Alliance for Regenerative Medicine's (ARM's) Cell and Gene Meeting on the Mesa on Oct. 5 in San Diego.

The first of these products is **Novartis AG**'s chimeric antigen receptor T cell (CAR-T) therapy *Kymriah* (tisagenlecleucel), which the US FDA approved at the end of August for relapsed or refractory pediatric and young adult patients with B-cell precursor acute lymphoblastic leukemia (ALL), and Novartis Senior Vice President and Global Head of Oncology Strategy and Business Development Pascal Touchon spoke about the company's experience during a panel on commercialization challenges.

"When it came to Kymriah, we thought from the beginning that we had to be innovative, not only in bringing this transformative therapy to patients, which includes a lot of challenges in general, but also [in trying to ensure] patient access," Touchon said.

That is why Novartis is negotiating with payers to receive reimbursement for the CAR-T therapy's cost via outcomes-based and indication-based pricing agreements, he noted, like the company's contract with the Centers for Medicare and Medicaid Services (CMS). Novartis – betting on its high early response rate of 83% at three months in the pivotal trial – will supply the therapy at no charge if patients do not respond to treatment within one month. *(Also see "Novartis Begins CAR-T Payment Experiments With Outcomes-Based Contract With CMS" Scrip, 30 Aug, 2017.)*

*Complexity Drives Way Forward*

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"The key in the case of Kymriah is … we have an outcome that has been accepted and cleared by the different stakeholders around remission," Touchon said. "That's very specific to Kymriah, that's very specific to pediatric ALL, and every therapy, every disease, every indication will lead to a different type of approach."

The challenge, he added, is that the US health care system is not set up to negotiate and manage such agreements, so payers are hesitant when approached about outcomes-based and indication-specific pricing arrangements.

## EUROPE HAS ITS OWN CHALLENGES

**bluebird bio Inc.** chief financial and strategy officer Jeffrey Walsh noted during the panel on commercialization challenges that biopharmaceutical companies will have to spend a lot of time educating payers in Europe about pricing and reimbursement that reflects the value their cell and gene therapies may provide, such as outcomes-based agreements. Each payer in the various EU countries, however, will have a different view on what those agreements should look like and how they should be managed.

"I think we've learned through a lot of conversations with [health technology assessment (HTA)] bodies and payers, particularly in Europe, that it has to be not only indication-specific, but almost payer-specific and certainly country-specific," Walsh said. "We're not as deep into the US conversations [as Novartis], but we are probably deeper into understanding the different fail points in the [EU] system for these types of therapies."

Bluebird expects to take the first of its gene therapies to market in Europe, with plans to seek conditional approval later this year for its *LentiGlobin* product in the treatment of transfusion-dependent beta thalassemia (TDT).

Keith Tolley, director of Tolley Health Economics, noted during a separate panel discussion about technology assessment and reimbursement in the US and Europe that the UK already has a value framework in place to determine the clinical and cost effectiveness of new prescription medicines, and he thinks various HTAs' assessments of value for cell and gene therapies would be no different.

However, Tolley – a consultant to Scotland's HTA, the Scottish Medicines Consortium – said authorities reviewing HTA reports to determine whether to reimburse the costs of gene and cell therapies may still decide not to cover those products, because of the high cost.

The National Health Service in the UK, like payers in other European countries, has a limited pool of public funds to spend on pharmaceutical products and may not be able to afford the high price tag of cell and gene therapies – especially as more products hit the market in more indications.

## SO MANY PAYERS, TOO MANY OPTIONS

Pricing pressure may not be as great in the US where most patients are covered by private health insurance plans, but reimbursement negotiations are complicated by the fact that biopharma companies must negotiate agreements with dozens of payers. Even so, as more cell and gene therapies hit the US market, payers will struggle to cover the cumulative costs of treatments that are expected to cost as much as $1m for curative therapies.

Novartis priced Kymriah at $475,000 for the one-time treatment in a small indication, but when **Gilead Sciences Inc.** – the recent acquirer of Novartis' closest competitor **Kite Pharma Inc.** for $11.9bn – wins FDA approval for axicabtagene ciloleucel in non-Hodgkin lymphoma and as additional CAR-T therapies come to market, there will be thousands of patients eligible for treatment rather than hundreds. *(Also see "Gilead Makes Cell Therapy The Base Of Its Oncology Platform With Kite Buy" Scrip, 29 Aug, 2017.)*

Quoting a US congressman who once said "a billion dollars here, a billion there, pretty soon we're talking real money," **Anthem Inc.**'s medical director for care management John Goldenring likened the cumulative wave of cell and gene therapies to the hit US payers took when Gilead launched its instant blockbuster *Sovaldi* (sofosbuvir) for hepatitis C.

The drug generated big demand because of its high cure rates, but at $84,000 for 12 weeks of therapy and billions of dollars in sales each quarter, many payers – especially those managing Medicaid claims – went bankrupt. Payers authorized treatment only for patients already diagnosed with advanced liver disease, because of the tremendous cost.

"For the first time in my career we rationed care. We made up all kinds of creative ways to limit spending," Goldenring said during the panel on reimbursement challenges. "Just because something's curative, it doesn't solve our problem. In hemophilia, if we had something that could cure hemophilia, we would save enough money in three years that we could pay for it. For a lot of these therapies, that ain't gonna happen, and the more prevalent the condition the less we're really getting anything back in offsetting costs."

Payers will want more evidence from drug makers that cell and gene therapies have long-lasting effects or significantly reduce the costs associated with a disease over time. That will contribute to the difficulty of negotiating outcomes-based and indication-specific reimbursement agreements, because the data to answer payers' questions is not available for a lot of these treatments. It also will mean a different contract with every payer based on each one's appetite for risk. *(Also see "Trial And Trial: Bracing For Commercialization Of Cell & Gene Therapies" Scrip, 25 Aug, 2017.)*

"It's going to be product by product and it's going to be a mess," said consultant Jim Cross, former vice president of national medical policy and operations at **Aetna Inc.**

Cross and others suggested during the reimbursement panel that there may need to be a special government-supported fund to help pay for cell and gene therapies, because the combined demand across many small indications will be high based on the chance that the therapies will cure patients or transform the treatment of their disease.

## APPROVED, REIMBURSED, NOW WHAT?

Once cell and gene therapy developers make it over the hurdles of approval and reimbursement, they face perhaps their biggest obstacle yet – manufacturing their products and getting them safely to patients. Companies typically begin to worry about how they'll manufacture cell and gene therapies at commercial scale at the same time as they begin worrying about testing their treatments in patients, because of the complex process of making the products and delivering them to health care providers. *(Also see "Regulators Promote Early Process Understanding As Key To Success In Cell Therapy Manufacturing" Scrip, 3 Aug, 2017.)*

Autologous therapies – like Kymriah, which requires removing T-cells from patients, engineering them to target cancer cells expressing CD19 and then injecting the cells back into patients – are particularly challenging. Novartis uses cryopreservation to stabilize the cells as they're shipped to and from the company's manufacturing site in New Jersey and has systems in place to track the products closely as they're shipped across borders. Treating physicians at academic centers and large cancer clinics are specially trained to withdraw and ship the cells, administer the CAR-T therapies and treat the side effects, which come on quickly and can be severe, even deadly.

"As we learn more about these products, we're going to have to understand more about the cells that go into the product and how they impact the patient," **Juno Therapeutics Inc.**'s executive vice president and chief commercial officer Bob Azelby said during the commercialization panel. "How do we improve on the safety profile so you can democratize access to these products, because 80% of these patients reside outside of these centers of excellence? I think the science will continue to evolve as we go forward."

Standardization of procedures for withdrawing cells, administering engineered cells and treating the side effects of CAR-T therapies may be necessary as more products come to market, Azelby said. Otherwise, treatment will be limited to only certain academic centers and cancer clinics with doctors unwilling to try later market entrants, because they don't want to learn a new set of procedures, he noted.

Bluebird's Walsh pointed out that the cross-border challenges – especially in Europe – can't be ignored, since some patients may have their cells withdrawn in one country and receive treatment or follow-up care in another country. It's important, because the payers will change as patients move and patients could become more difficult to track in terms of assessing outcomes-based value.

Touchon said Novartis has good market access for Kymriah in the US, "but ex-US – that's what keeps me awake at night, because I know there are kids out there and we need to find a way to treat them."

Regardless of the market, Juno's Azelby said the biggest challenge for CAR-T therapies will be making sure patients have access, because of the "enormous" efficacy seen in clinical trials to date.

"That's not only figuring out how to take the product to the patient, but it also requires how you scale from a manufacturing perspective and a capacity perspective to impact as many folks as you can in not only the US and Europe, but around the world," Azelby said. "I think that will be a monumental task."

*Published online 6 October 2017*

# Praluent Lives On As US Court Vacates Amgen's PCSK9 Patent Win

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**Sanofi** and **Regeneron Pharmaceuticals Inc.** scored a big legal victory over *Repatha* (evolocumab) marketer **Amgen Inc.** Oct. 5 with a US federal appeals court ruling that indefinitely keeps their PCSK9 inhibitor *Praluent* (alirocumab) on the market.

However, the decision effectively maintains the status quo in the US, where sales of the two LDL-cholesterol-lowering agents remain modest and significant market expansion is likely to come only with the FDA's approval in a broader patient population.

In a 24-page opinion, a three-judge panel of the US Court of Appeals for the Federal Circuit unanimously reversed a patent infringement verdict for Amgen and vacated a permanent injunction against Sanofi and Regeneron's marketing of Praluent.

The panel concluded the trial judge erred by excluding Sanofi/Regeneron's evidence supporting their written description and enablement defenses and improperly instructing the jury on written description. The case was remanded for a new trial on these defenses to Amgen's patent infringement claims.

The court also vacated US District Judge Sue Robinson's January order preventing the marketing, selling or manufacturing of Praluent in the US during the term of two Amgen patents, both of which expire in August 2028. That injunction was stayed pending Sanofi and Regeneron's appeal to the Federal Circuit and has never taken effect.

In a statement, Sanofi and Regeneron said the schedule for a new trial has not yet been determined, but the companies "do not anticipate any new trial proceedings to start in 2017."

"We are pleased with the Federal Circuit's decision to remand for a new trial that allows us to present our complete evidence to the jury," said Karen Linehan, Sanofi's executive vice president and general counsel. "It is our longstanding position that Amgen's asserted patent claims are invalid, and we remain confident in the long-term availability of Praluent for patients."

"We continue to believe that the law and facts support our position, and we look forward to presenting our complete evidence at trial to a new jury," said Joseph LaRosa, Regeneron's senior vice president, general counsel and secretary.

Amgen could seek a rehearing of the panel's decision by the full appellate court, or petition the Supreme Court for review.

"We are disappointed by the court's action in reversing and remanding the district court's decision with respect to validity of our patents based on select pre-trial rulings," Amgen said in a statement. "We firmly believe in the validity of our patents and we look forward to reasserting our rights in court."

## PRALUENT OVERHANG REMOVED

For now, Praluent and Repatha will continue to compete in the US market. Although Repatha, which gained the FDA's approval one month after Praluent, has grabbed the larger share of the PCSK9 market, both drugs thus far have posted disappointing sales due to limited indications, lack of outcomes data, high price (annual wholesale acquisition costs of about $14,500 each) and payer restrictions.

US sales of Repatha in the first half of 2017 totaled $93m, while US sales of Praluent were approximately $57m in the same time period.

However, cardiovascular outcomes trials for the two drugs could lead to labeling changes that would significantly broaden the PCSK9 inhibitors' use beyond their currently limited indications as an adjunct to diet and maximally tolerated statin therapy for adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease who require additional LDL-C lowering. Repatha also is approved for treatment of homozygous familial hypercholesterolemia.

Amgen's supplemental biologics license application to expand Repatha's labeling based on results from the FOURIER CV outcomes study has a Dec. 2 user fee goal date at FDA. Data from Sanofi/Regeneron's ODYSSEY Outcomes trial are expected in 2018.

Some analysts saw limited commercial upside in the appeals court's decision for Sanofi/Regeneron, believing it removes an overhang for Praluent that could help to even out the market share between the two drugs.

The decision "should help shift the market share trend back from the current state of Repatha dominance to a more equal market split long-term," Leerink analyst Geoffrey Porges said in an Oct. 5 note.

"For now this takes the worst case (injunction) off the table" for Praluent, Credit Suisse analyst Alethia Young said.

However, the court's decision "doesn't change our thesis on either [Regeneron] or [Amgen]; we think PCSK9 therapies as a growth driver has been an uphill battle," Young said. "Currently Amgen's Repatha has the lead market share, but we think this could have been due to the thought of a potential impending injunction for Repatha. We currently model ~$2bil in 2025 US Repatha and Praluent sales each, but the drugs are trending far below that currently."

The appeals court's decision to send the case back for a new trial also could spur settlement talks between Amgen and Sanofi/Regeneron.

"Today's opinion supports our belief that the two parties will reach some sort of licensing agreement to resolve the matter (likely now a smaller royalty or ~10% on US sales)," Barclays analyst Geoff Meacham said. "We do not believe that the parties will opt to re-litigate at the district court level, nor do we believe that Amgen will appeal to the US Supreme Court."

## EVIDENTIARY RULINGS CHALLENGED

Amgen sued Sanofi and Regeneron in US District Court for the District of Delaware alleging that Praluent infringed two patents, Nos. 8,829,165 and 8,859,741, which claim monoclonal antibodies that bind to specific amino acid residues on PCSK9 or block PCSK9 from binding to LDL receptors. After Sanofi/Regeneron stipulated to infringement of Amgen's patents, a jury found the Praluent marketers failed to prove the pat-

ents invalid for lack of written description and enablement.

Judge Robinson issued the permanent injunction in January but delayed its effective date to give Sanofi and Regeneron an opportunity to appeal.

On appeal, Sanofi/Regeneron challenged Robinson's pretrial rulings that excluded evidence they described as central to their written description and enablement defenses.

The companies asserted they were prevented from introducing into evidence alirocumab and other structurally dissimilar PCSK9 antibodies developed after the priority date of Amgen's patents to demonstrate the claims lacked sufficient written description and enablement. Sanofi/Regeneron also argued the district court erroneously instructed the jury that the written description requirement was satisfied if Amgen disclosed a "newly characterized antigen," and they challenged the permanent injunction.

The injunction was not raised during oral arguments to the Federal Circuit panel in June. Rather, the appellate judges focused their attention on the lower court's evidentiary rulings and the validity of Amgen's patents. The panel's written opinion centered on the evidentiary rulings and did not reach the issue of patent validity. *(For more analysis of the written opinion, see Pink Sheet story.)*

While the Federal Circuit determined that the erroneous evidentiary rulings and jury instructions necessitated a new trial, it also took aim at the district court's permanent injunction analysis.

Although the district court concluded that the public interest is best served by having a choice of drugs on the market, "eliminating a choice of drugs is not, by itself, sufficient to disserve the public interest," the appeals court said. "Under such an approach, courts could never enjoin a drug because doing so would always reduce a choice of drugs. That, of course, is not the law."

"Just as a patent owner does not automatically receive an injunction merely by proving infringement … an accused infringer cannot escape an injunction merely by producing infringing drugs," the panel said.

Joshua Whitehill, an associate at Goodwin Procter, said the Federal Circuit's ruling suggests that if the case gets retried and Amgen prevails, when the injunction is relitigated "there will have to be a much greater focus on the elements of Praluent that make it unique." *Published online 6 October 2017*

# Harmony Biosciences Raises $270m; Acquires Narcolepsy Drug

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**Harmony Biosciences**, founded in 2017, has raised $270m via equity investment to pursue novel therapies for sleep and central nervous system disorders; to kick off its portfolio plans the company has acquired US rights to pitolisant from French company, **Bioprojet SCR**.

Pitolisant, which has recently been approved in Europe under the tradename *Wakix* for the treatment of narcolepsy in adult patients, is a selective histamine H3-receptor antagonist/inverse agonist that enhances the activity of histaminergic neurons. Harmony expects to file a new drug application for the drug with the US FDA in the first half of 2018.

There is a gap in the US market for a novel approach to treating narcolepsy and its symptoms as all approved therapies are facing generic competition. However, there are a few products in late-stage trials targeting the condition from **Jazz Pharmaceuticals PLC**, **Avadel Pharmaceuticals PLC** and **NLS Pharma Group**.

## FIRST MARKETED DRUG

If approved in the US, pitolisant will be Harmony's first marketed drug and the company's recent financing will help it become a commercial-stage business.

The company is led by CEO Bob Repella, a veteran of the industry "with significant experience bringing drugs to market," the company's spokesperson told *Scrip*.

Repella joined Harmony from **CSL Behring** where he was executive vice president of global commercial operations. Prior to joining CSL, he held senior management roles at several pharmaceutical companies including **Cephalon** and **Wyeth**.

"Given the unmet medical need for patients suffering from narcolepsy who have been unable to find suitable treatments, we are excited to pursue the development and registration of pitolisant in the US," Harmony's spokesperson added.

Narcolepsy is a rare neurological condition that affects the brain's ability to regulate the normal sleep-wake cycle; it can lead to symptoms such as disturbed nighttime sleep, excessive daytime sleepiness and cataplexy (the term given to sudden muscular weakness triggered by emotion). Pitolisant, which has orphan designation in Europe and the US for the treatment of narcolepsy, targets cataplexy specifically. According to charity Narcolepsy UK, around 75% of patients with narcolepsy experience cataplexy.

We are excited to pursue the development and registration of pitolisant in the US

Biomedtracker analysts have given pitolisant a likelihood of approval rating of 53% in the US, 1% above the average rating for similar products at the same stage of development. Analysts also said in January this year, when Phase III data were published in the Lancet, that pitolisant was well tolerated and efficacious in late-stage trials.

"If confirmed in long-term studies, pitolisant might constitute a useful first-line therapy for cataplexy in patients with narcolepsy, for whom there are currently few therapeutic options," they noted.

## OTHER INDICATIONS

Additional indications for pitolisant will be pursued collaboratively by Harmony and Bioprojet through a joint development committee, the Harmony said. The drug is already in Phase III for excessive sleepiness associated with medical conditions and Phase II for schizophrenia.

Harmony, a **Paragon Biosciences** company, will also use its recent cash influx to pursue other assets for the treatment of sleep disorders and orphan diseases effecting the central nervous system. Currently though, the company has no other preclinical or clinical assets in its pipeline. *Published online 6 October 2017*

# Confidence Builds For Theratechnologies' Game-Changing HIV Monoclonal

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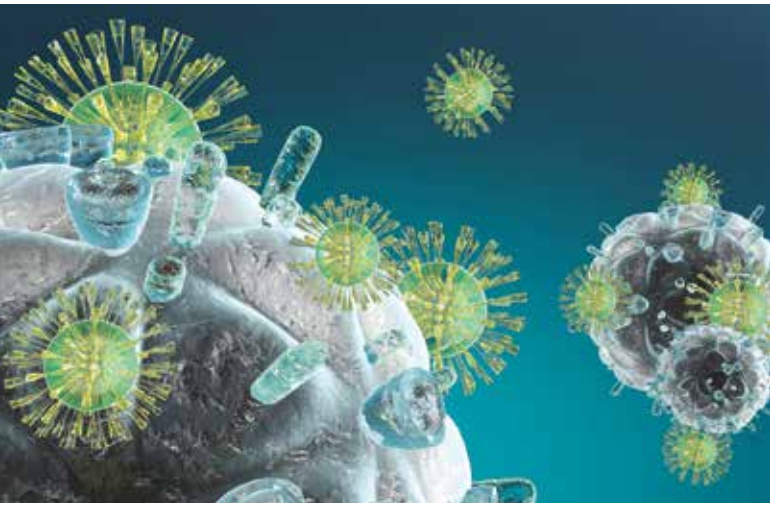
Updated pivotal data for **Theratechnologies Inc.**'s novel monoclonal antibody ibalizumab for advanced HIV support its efficacy over 48 weeks, boosting hopes that it might gain approval ahead of time.

Ibalizumab was filed for US approval in May on the back of 24-week efficacy data from the TMB-301 study for the product in 27 patients with multidrug resistant (MDR) HIV-1 infection. *(Also see "Theratechnologies' Novel AIDS Drug Filed In US" Scrip, 4 May, 2017.)*



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The updated data, due to be presented at the IDWeek conference in San Diego on Oct. 6 and released already online, are "impressive and approvable", said analysts at Echelon Wealth Partners. The strong efficacy out to 48 weeks "should support FDA regard when rendered by PDUFA date in Jan. 2018, if not sooner". The actual PDUFA date is Jan. 3.

The arrival of highly active antiretroviral therapy altered the disease course in HIV, but more and more patients are beginning to run through the current treatment options, increasing the demand for novel treatment strategies for resistant patients.

No other approved therapy is effective at reducing HIV burden in patients for whom existing small molecule nucleoside analog drugs, protease inhibitor drugs or integrase inhibitor drugs are no longer effective, and ibalizumab is the lead in a number of new therapies aiming to fill this gap. The product is expected to bring in peak revenues in the order of C$300m, outstripping those for the Canadian firm's only marketed product to date, *Egrifta* (tesamorelin acetate). The lipodystrophy therapy brought in just over C$37m in 2016, but sales are forecast to reach around C$75m in 2023.

All 27 patients who completed the 24-week treatment period in TMB-301 entered TMB-311, the ibalizumab Expanded Access Program, where patients continued to receive ibalizumab at 800 mg every two weeks for up to 48 weeks. 59% and 33% of the patients in the study had exhausted at least three or four antiretroviral (ARV) classes, respectively, and 15% had HIV-1 resistant to all approved ARVs.

The virologic suppression observed at week 24 was sustained through week 48; median viral load reduction from baseline was 2.5log$_{10}$ at weeks 24 and 48. In TMB-311, all 15 patients with an undetectable viral load at week 24 maintained suppression to week 48. Another patient in TMB-311 reached less than 50 copies/mL at week 48 after having a detectable viral load at week 24. A total of 17 patients (63%) achieved a viral load of less than 200 copies/mL.

In TMB-311, ibalizumab plus optimized background regimen was well tolerated; of the 27 patients in the study, 24 (89%) continued to receive treatment until week 48 and three patients discontinued early due to non-ibalizumab-related reasons. No new or unexpected safety concerns emerged between weeks 24 and 48. The most common adverse reactions were diarrhea, dizziness, nausea and rash.

The analysts at Echelon Wealth Partners said that the median HIV-1 viral load reduction of 2.5log was "clearly strong in comparison to viral load reductions that MDR patients were able to achieve with previous therapies to which by definition they were no longer responsive".

> The strong efficacy out to 48 weeks 'should support FDA regard when rendered by PDUFA date in Jan. 2018, if not sooner'

"If anything, patients were even more multidrug-resistant than study protocol required them to be," they said, noting: "We believe that ibalizumab's clinical performance within the context of disease severity in the overall study population, if anything, enhances the possibility of eventually positive FDA regard."

## COMPETITIVE PRESSURE

Analysts at the National Bank of Canada pointed out that a viral load of >200 mL while adhering to treatment is technically a treatment failure, but noted that the patients enrolled had a high viral load at the beginning (about 100,000 copies/mL) and about half were resistant to drugs from at least three classes. "Overall, we view the results positively in the context of multi-drug resistant patients."

They added that the greatest threat to ibalizumab comes not from the regulators, but from competitive pressure from other late-stage development products for this patient population, including **ViiV Healthcare**'s fostemsavir and **CytoDyn Inc.**'s anti-CCR5 monoclonal antibody product PRO 140, both in Phase III.

*Published online 5 October 2017*

# Scrip Awards Finalists 2017

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## Community Partnership of the Year
**(Sponsored by Medidata)**

This Award is designed to acknowledge the numerous ways in which pharma and biotech companies give back to the wider community.

### Antidote and Juvenile Diabetes Research Foundation's Clinical Trials Connection

The aim of this partnership was to match type 1 diabetes patients to trials to accelerate research using Antidote's Antidote Match patient-matching technology. Within the first month, more people had searched for trials on the JDRF website than in the previous 10 years, and the partnership is now being expanded.

### AstraZeneca's Active Science program

As part of its commitment to promote science, AstraZeneca sponsors a new health and science education element, "Active Science", in the local Cambridge United Community Trust's school sports program. It aims to deliver a fun and interactive program that combines science education with sport to increase children's enjoyment of and enthusiasm for science.

### Glenmark Foundation's Project mMitra

Glenmark's CSR arm is actively working towards improving child health and reducing infant and maternal mortality in Mumbai, India. Together with an NGO and a local government hospital, it uses mMitra, a voice messaging service to provide more than 19,000 underprivileged pregnant women with relevant information appropriate to their gestational age.

### QuintilesIMS India's Race for 7

For the second year running, QuintilesIMS partnered with the Organization for Rare Diseases India to host the Race for 7, a seven km walk/race to raise awareness of the 7,000 known rare diseases and the estimated 70 million rare disease patients in India. The race drew more than 3,500 participants, including patients and their caregivers.

### Sandoz' Sandoz HACk – Healthcare Access Challenge

With its healthcare access challenge, Sandoz threw down the gauntlet to innovators and social change agents to solve local access to healthcare issues using mobile technologies. In just three months, Sandoz far exceeded its target to secure nearly 150 ideas from 30 countries, and three winners were chosen to receive €20K each.

### Shire's Rare Count campaign

Shire's Rare Count campaign aimed to raise awareness of the one in 20 people worldwide living with rare diseases. It applied the 1-in-20 statistic to a users' social network to highlight the number of people they know who could be living with an orphan disease, and pledged $1 to patient advocacy organizations for each person who participated.

## Business Development Team of the Year

This Award will honor the achievements of business development teams whether they are from a single firm or a cross-company team responsible for a specific deal or collaborative project.

### AstraZeneca's Scientific Partnering & Alliances Team

During the year, this team concluded over 30 major deals and hundreds of smaller collaborations and several key out-licensing deals. The small team of fewer than 20 people, which works closely with legal and IP colleagues, has had a significant impact on early research at AstraZeneca, advancing it in new and evolving research areas.

### BioNTech's Business Development Team

This team, led by BioNTech COO Sean Marett, was able to convince Genentech to close a deal in which the two firms will share equally all development costs and profits for BioNTech's individualized mRNA cancer vaccines. Genentech will pay $310m in upfront and near-term milestone payments, while BioNTech retains certain decision-making rights.

### Clinigen's Multidisciplinary Team for lifting Cardioxane's Article 31

Clinigen brought together an international group of KOLs to successfully challenge the EMA's Article 31 contraindication for pediatric use of the cardioprotectant Cardioxane – the first time such a restriction has been lifted. The team was able to compile new data for the regulator to support the move and revitalize the drug for the company.

### EUSA Pharma Business Development Team

This team had dramatically increased the company's future revenue stream by acquiring global commercialization and development rights to the orphan immune-oncology drug dinutuximab beta. The team delivered a rapid, detailed and comprehensive process to enable a successful global transaction to be negotiated and agreed in just 76 days.

### F-star and Denali Therapeutics' Transaction Team

Despite its potential complexity, the joint team behind F-star's agreement with Denali to discover and develop antibodies for delivery of medicines across the blood-brain barrier managed to conceive and seal the deal within nine months of first contact between the two companies – a testament to the mutual benefit of the deal.

### Ipsen Group's Merrimack Transaction Team

This BD team led the strategic transaction with Merrimack – the largest in Ipsen's history – to gain exclusive commercialization rights for current and future indications for Merrimack's key oncology asset, Onivyde. The deal expanded Ipsen's growing oncology portfolio and accelerated its long-term growth trajectory and profitability.

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

# Caterpillar To Butterfly? Ablynx Says Caplacizumab Data Transformational

**STEN STOVALL** sten.stovall@informa.com

**Ablynx NV** expects to take off on its own soon as a proprietary brand biotech, propelled by positive pivotal trial data for its lead investigational therapy, caplacizumab, in patients with the rare blood disorder, acquired thrombotic thrombocytopenic purpura (aTTP).

## HERCULES HEADLINES

Ablynx saw its shares jump 25.8% to €15.50 on Oct. 2 on news that caplacizumab, its anti-von Willebrand factor Nanobody medicine, met the primary goal and two of the four key secondary endpoints in the late-stage HERCULES trial in patients with aTTP.

"These were generally positive results for caplacizumab, meeting its primary and a number of secondary endpoints, though all patients started out receiving plasma exchange and there could be questions about which patients benefit most. On the other hand, the benefit on recurrences was pronounced, perhaps better illustrating the drug's effects," commented analysts at Informa Pharma Intelligence's Biomedtracker. Recurrences are a particular concern since they lead to thromboembolic events and morbidity and mortality. The analysts noted that "all in all the data appear supportive, though more details are needed;" they raised their likelihood of approval rating by two percentage points to 65%, which is five points above the average provability of FDA approval for Phase III hematology drugs.

> 'This trial data represents a huge kick up the ladder for Ablynx, sending us exactly where we want to go, to have a proprietary product'

The double-blind, placebo-controlled Phase III study evaluated caplacizumab in 145 patients with an acute episode of the rare blood-clotting disorder TTP. The primary endpoint, reduction in time to platelet normalization, was met as patients on treatment were 1.5 times more likely to achieve response at any point in time ($p<0.01$).

The study also reached statistical significance on two key secondary endpoints: caplacizumab treatment resulted in a 67% fall ($p<0.001$) in total recurrences/relapses over the entire study period. Caplacizumab treatment also resulted in a 74% relative reduction in the percentage of patients with aTTP-related death, a recurrence of aTTP, or at least one major thromboembolic event during the study drug treatment period.

Analysis of the third key secondary endpoint showed that no patients treated with caplacizumab were refractory to treatment compared to three patients treated with placebo ($p=0.057$). The analysis of the fourth key secondary endpoint showed a trend to faster normalization of the organ damage markers (lactate dehydrogenase, cardiac troponin I and serum creatinine) in patients treated with caplacizumab.

The data confirms Ablynx's earlier Phase II TITAN study using caplacizumab and will be used to drive the therapy's registration process in Europe and the US. Caplacizumab is wholly owned by Ablynx, so sales should be highly profitable once the medicine is launched, analysts say.

TTP is a rare disorder of the blood coagulation system that causes micro thrombi to form, which can block small blood vessels throughout the body.

## 'TRANSFORMATIONAL'

Ablynx's management says the Phase III data will have a transformational effect on the company, founded in 2001 to focus on the discovery and development of Nanobodies.

"These results are as good as they could have been, so we couldn't be more delighted," Ablynx CEO Edwin Moses told *Scrip*. "It was a small number of patients who took part, so we couldn't be more delighted with the outcome."

According to Biomedtracker's database, there are currently no approved therapies for the treatment of TTP and Ablynx's offering is the most advanced candidate.

Moses concurred. "We don't think anybody has conducted clinical trials in acquired TTP. The trial that we've done is by far the biggest, so we can see nothing else in development targeting acquired TTP," he added.

Ablynx won orphan drug designation status for caplacizumab in 2009 from both FDA and the EMA. The company in June 2014 announced positive proof-of-concept data of the Phase II TITAN study, allowing it to file for conditional approval in February this year for caplacizumab and, following recent fast track designation won in July, it has been able to start a rolling BLA with the FDA.

"In a perfect world, if we won approval, we could see launch in mid-2018 in Europe and the first half of 2019 in the US," Moses told *Scrip* in an interview.

The first EU launch would be in Germany, the region's largest market, then France, the UK and other European countries. Medical Science Liaisons are in place to facilitate market adoption and will be expanded together with the sales force upon market launch.

In the US, with FDA fast track designation won in July 2017 a BLA submission based on the HERCULES data could be anticipated for 2018, with subsequent entry in the US and Canadian markets likely in 2019.

Ablynx has so far largely earned its revenues through research-based collaborations with pharma partners, generating upfront payments and milestones. It has raised more than $450m in collaborative income.

"This trial data represents a huge kick up the ladder for Ablynx, sending us exactly where we want to go, to have a proprietary product. And it demonstrates how powerful our Nanobody-based therapeutic platform really is," said Moses.

"We've been very grateful for those collaborations with our pharma partners because of their disease expertise. For example, in immune-oncology, where we're partners

with **Merck & Co. Inc.** in the US, they bring an enormous amount of clinical data and expertise and we combine that with our platform capability. But we will increasingly identify niche orphan areas where we can build up an expertise ourselves and with our network of key opinion leaders so we can drive more proprietary through to the market."

Ablynx has around 45 programs at various stages of development – both proprietary ones and partnered programs. Caplacizumab is the most advanced, and it's fully owned by Ablynx, therefore key for the company's development.

"When the company started some 17 years ago, the idea of using this Nanobody platform and very small antibodies to create therapies was met with widespread skepticism, both with regards to efficacy and safety… The more I talked with people over the last week or so, however, getting complementary Phase III pivotal data like this which should lead to approval is a huge step forward for not only this molecule but also the company's entire Nanobody-based therapeutic platform," Moses said.

"We've made clear that we want to sell this product ourselves in Europe and the United States. Now we're creating a commercial infrastructure to do that and so it gives us the opportunity to become a fully integrated biopharma company."

Moses hopes Ablynx will be allowed to remain independent to develop its own portfolio of drugs, but acknowledged that being a listed company makes promising companies like his potentially vulnerable.

"We're very confident in our future as an independent company. We've found ways of working with big pharma in a collaborative way and that has worked very well for them and for us. We are focused on the independent future of the company," he concluded.

## GLOBAL OFFERING

Just hours after announcing the results, Ablynx filed a registration statement with the US SEC to launch a global offering of shares including American Depositary Shares (ADSs) in the US and ordinary shares offered via a private placement in Europe and elsewhere. It has applied to list its ADSs on Nasdaq. The maximum total of its offering was noted as $150m, and all shares will be offered by Ablynx. The Brussels-listed firm's market capitalization stands at around €952m.

*Published online 3 October 2017*

# Will Intas' Cut-Price Avastin Biosimilar Disrupt The Market?

**ANJU GHANGURDE** anju.ghangurde@informa.com

**Intas Pharmaceuticals Ltd.** has launched its cut-price biosimilar *Avastin* (bevacizumab) in India, raising questions on whether competitors will need to deploy sharper trade "bonuses and discounts" that are typically seen in such products to blunt the new entrant's pricing edge.

Intas said it had introduced its bevacizumab (marketed as *Bevatas*) at an maximum retail price (MRP) of INR39,995 for the 400 mg variant, which "makes it 60% less than the currently available options". Intas has underscored that the price plank is aimed at making the drug accessible to cancer patients in India, providing them with a "beacon of hope" in their fight against the disease.

The comparable price of **Roche**'s Avastin is said to be about INR107,065 ($1,647) while the **Hetero** group's *Cizumab* 400 mg was, at the time of launch, believed to be available at approximately INR102,600 (without trade discounts) as against INR105,010 for the same strength of **Reliance Life Sciences**'s *BevaciRel*.

## THE BLUE TREE

Innovator Roche isn't saying much currently though on how it views the new entrant's pricing plan.

Asked whether it expects to counter price competition for Avastin with probably a second brand approach or offer equated monthly instalment [EMI]-based options for its product, Roche told *Scrip* that Avastin was covered under its unique patient support program, The Blue Tree, which is designed to address multiple barriers in the patient journey.

"Patients are supported through a range of services through this program," Roche said.

The Blue Tree program through a single platform enables patients to overcome certain access hurdles primarily – diagnosis, reimbursement, affordability and adherence – by providing services such as biomarker test support, guidance on sources of funding, and reimbursement documentation assistance.

Roche has previously questioned the approval process for biosimilar bevacizumab in India in the Delhi High Court; the next hearing in slated later this month, though the ongoing case does not cover the Intas product.

## HOSPITALS CAN'T OVERCHARGE?

Significantly, industry experts told *Scrip* that while exorbitant pricing for medicines in India is "not in keeping with the DNA of the land", significant trade bonuses and discount offers that are commonplace in the industry could mean that the price differential of the Intas bevacizumab product and its competition may potentially be less dramatic.

"Intas probably has just been above board with the trade practice," one expert told *Scrip*.

Nevertheless, healthcare activists and other experts suggest that Intas' move could disrupt the market, especially if the price provided is the "MRP".

"Typically, bonus/discounts for anticancer drugs are not available to all patients. If Intas has stated the MRP upfront, it ensures that hospitals don't overcharge and all patients can access the product at the price," Leena Menghaney, representing "The Campaign for Affordable Trastuzumab", told *Scrip*.

With Intas' pricing strategy, bevacizumab competitors will now need to up their discounts or ensure these are available to all patients, she reckons.

"Competition is definitely welcome," Menghaney said, referring to how prices of trastuzumab have fallen sharply – by over 70% as per estimates – since the arrival of competition (**Biocon Ltd./Mylan NV**) in India.

An official with a life sciences advisory firm told *Scrip* that if Intas could do a "good job" at marketing Bevatas, volumes should, over time, build up and force the competition to "think differently".

"As long as quality is assured, physicians should be comfortable with the Intas brand," the official added.

*Published online 5 October 2017*

# Mooncakes Under The Sun: Can China's 'Name And Shame' Rule Create Level Playing Field?

**BRIAN YANG** brian.yang@informa.com

China's regulators have issued several rules to rein in sales representatives' commercial activities starting just days before the celebration of the Mid-Autumn Festival, traditionally a prime time for kickbacks.

China is a market with complexities, underscored by multiple layers of sales agents, the lack of hospital funding, and physicians relying on kickbacks to make up their meager incomes. The Mid-Autumn Festival coming on Oct. 4, China's Thanksgiving Day and biggest cultural holiday, traditionally has provided an opportunity for sales reps to use gift money and high-end mooncakes to gain access to physicians.

Now, the country's regulators hope to put an end to the practice of giving kickbacks to physicians. China FDA has issued a draft regulation proposing a nationwide registry covering all medical sales reps. The registry will include each rep's name, identification information and records of misconduct and violations, in a bid to name and shame violators. *(Also see "China Imposes Tough New Curbs On Rep Sales Activities" Scrip, 2 Mar, 2017.)*

Following the proposal, Shanghai regulators went one step further, requiring all sales reps operating in the city to get registered in two months after the issuance of its regulation. Shanghai also requires the employers of the sales reps to be held responsible for their conduct. In case of a violation for one sales rep, the employers need to make corrective measures; if there are violations for two or more sales reps, the registration of the whole company will be revoked.

The tightened grips over sales reps is a direct response to recent scandals of so-called "cash sales" in which medical sales reps reportedly give doctors cash kickbacks in exchange for drug prescriptions.

The registry, coupled with the harsh punishment for any violations, will have a profound impact on pharma compliance in China, noted experts attending China Healthcare Summit of Entrepreneurs, Scientists and Investors, held Sept. 23-24 in Beijing.

"We are regulating the not-yet-regulated area, and correcting the misconduct," said Dong Qian of the Industry Compliance Office, Healthcare Policy and Management Bureau at the China National Health and Family Planning Commission.

Others echo the view. "The registry is a step in the right direction," said Huang Donglin, a researcher with China Pharmaceutical Promotion and Clinical Unit (CPPCU), a consortium of trade associations, researchers and manufacturers.

However, the industry response to the Shanghai proposal has been fierce. Many say that the rule could violate medical sales reps' rights to conduct activities designated by China's labor laws.

"Our biggest challenge so far is how to deal with strong response from the industry," Dong acknowledged, adding that the regulatory agency also plays close attention to feedback to the Shanghai proposal. *(Also see "Shanghai's Tough Proposals For Medical Sales Reps Draw Ire" Pink Sheet, 4 Sep, 2017.)*

## SHORT PAINS, LONG GAINS

The new rules, aimed to increase transparency, could help create a level playing field in which those in compliance with the code of conduct won't lose ground to those that don't follow the rules, according to the experts.

"The frontrunners in compliance shouldn't have to face the loss of their market shares [to those who are not compliant]," Wang Lili, head of CCPCU, said.

One such example is **GlaxoSmithKline PLC**. The UK drug maker was at the epicenter of a national compliance crackdown that has changed the industry since 2013.

For the next two years following the scandal, GSK essentially halted commercial activities and there were no sales, recalled Zhang Yingwei, head of government affairs and corporate communications for **GlaxoSmithKline (China) Investment Co. Ltd.**

During that time, how to rebound and whether the company could afford such a hiatus in commercial activities were questions hovering in the executive's mind, he added.

Thus, GSK China management made two drastic decisions: no more sales quotas for medical sales reps and no bonus for sales-related activities, and GSK won't provide any fees to physicians for promotional activities.

The changes were intended to shift the focus to patients and science-based academic promotions, Zhang said.

So far, the results show that the changes have started to bear fruit. Zhang pointed to IMS data showing that GSK's major revenue generator in the local market, respiratory product sales, started growing in the past four quarters.

"Crisis also means opportunities. We built up our confidence by doing it step-by-step, and believing it is a right thing to do," Zhang stressed.

## COMPLIANCE CULTURE

For China's 600,000 or so medical sales reps, the future hinges on more transparent commercial conduct and a culture of compliance, the experts stressed.

"Compliance should not just follow the rules, but a behavior out of consciousness," GSK's Zhang noted.

A good market environment requires rules and guidance from the government's regulatory agencies; it also requires industry's code of conducts and strict compliance. Unlike multinational drug makers spending roughly 20% of their budgets on marketing and sales, domestic Chinese companies generally devote more than 50% to sales, the experts said.

It is thus important to provide medical sales reps compliance training and routine audits, enhance the role of medical affairs, and emphasize products' clinical value, they concluded.

*Published online 6 October 2017*

*From the editors of PharmAsia News*

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# FDA Orphan Disease Clinical Trial Grants Aim To Reduce Financial Risk

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FDA's latest round of funding of clinical trials for rare disease treatments will provide $22m over four years to 15 grant recipients. The studies include a Phase II trial of oxytocin, dubbed the "love hormone," for treatment of hyperphagia in Prader-Willi syndrome and a study of **Novartis AG**'s leukemia drug *Gleevec* (imatinib) in combination with **Array BioPharma Inc.**'s binimetinib (MEK162) for the treatment of gastrointestinal stromal tumors.

The FDA announced on Oct. 6 that it is awarding the research grants through its Orphan Products Clinical Trials Grants Program, which has provided more than $390m to fund more than 600 new clinical studies since its creation in 1983. At least 60 grants have supported the marketing approval of more than 55 orphan products. This year's funding sums are similar to those of previous years. In 2016, the agency awarded 21 research grants totaling $23m and in 2015 it awarded 18 research grants totaling more than $19m.

"By helping to support the cost of development of these potential new drugs, and reduce some of the financial risk, we also hope that these grants will lower the cost of the capital needed to develop these products, boost competition and translate into lower prices for successful medicines," the FDA Commissioner Scott Gottlieb said in a release.

Approximately 33% of the new grant awards fund studies to accelerate cancer research by enrolling patients with rare forms of cancer. The FDA noted that one study is recruiting children as young as one year old with a particularly aggressive form of neuroblastoma.

Albert Einstein College of Medicine received two grants, one to study oxytocin for treatment of hyperphagia in Prader-Willi syndrome and the other to study topical sodium nitrate for treatment of patients with sickle cell disease and leg ulcers. Oxytocin is released in large amounts during labor and has also been studied for its role in orgasm, bonding and maternal behaviors. The hormone has gained so much attention it was even featured in a recent episode of the TV show Grey's Anatomy, when a doctor suggested a pregnant patient be given an orgasm to produce oxytocin to help her give birth.

Other trials being funded include a study of **Eli Lilly & Co.**'s *Forteo* (teriparatide), approved for osteoporosis in postmenopausal women, for treatment of idiopathic osteoporosis in premenopausal women, and a trial of a new combination of existing antibiotics to treat pulmonary tuberculosis, including multidrug-resistant TB (*see table below*).

The FDA also announced the award of six grants for natural history studies.

*Published online 6 October 2017*

## FDA Research Grants For Rare Disease Clinical Trials

| GRANT RECIPIENT | STUDY |
|---|---|
| AADi LLC<br>*Approximately $2m* | Phase II study of ABI-009 for the treatment of advanced perivascular epithelioid cell tumors |
| Albert Einstein College of Medicine<br>*Approximately $2m* | Phase II study of topical sodium nitrite for the treatment of patients with sickle cell disease and leg ulcers |
| Albert Einstein College of Medicine<br>*Approximately $1.5m* | Phase II study of oxytocin for the treatment of hyperphagia in Prader-Willi syndrome |
| Alkeus Pharmaceuticals Inc.<br>*Approximately $250,000* | Phase II study of ALK-001 for the treatment of Stargardt disease |
| CereNova LLC<br>*Approximately $1m* | Phase IIA study of CN-105 for the treatment of intracerebral hemorrhage |
| Columbia University Medical Center<br>*Approximately $1.9m* | Phase II study of Lilly's Forteo (teriparatide) for the treatment of idiopathic osteoporosis in premenopausal women |
| Columbia University Medical Center<br>*Approximately $2m* | Phase II study of Daiichi-Sankyo's PLX3397 (pexidartinib) and Pfizer's *Rapamune* (sirolimus) for the treatment of malignant peripheral nerve sheath tumors |
| Dana-Farber Cancer Institute<br>*Approximately $750,000* | Phase I study of SignalRx Pharmaceuticals' dual P13K/BRD4 inhibitor SF1126 for the treatment of neuroblastoma |
| Duke University<br>*Approximately $1m* | Phase II study of Bristol-Myers Squibb's *Nulojix* (belatacept), Sanofi/Genzyme's *Lemtrada* (alemtuzumab) and Pfizer's Rapamune in renal transplant |
| Johns Hopkins University<br>*Approximately $2m* | Phase IIA study of Sanofi's *Rifadin* (rifampin), Pfizer's Merrem (meropenem) and Dr. Reddy's *Augmentin* (amoxicillin/clavulanic acid) for the treatment of pulmonary tuberculosis |
| New York Medical College<br>*Approximately $1.75m* | Phase II study of Jazz Pharmaceuticals' *Defitelio* (defibrotide) for the prevention of complications in high-risk sickle cell disease patients following allogeneic stem cell transplantation |
| Protalex Inc.<br>*Approximately $500,000* | Phase I/II study of PRTX-100 for the treatment of immune thrombocytopenia |
| Sloan-Kettering Institute for Cancer Research<br>*Approximately $2m* | Phase II study of Array Biopharma's MEK162 (binimetinib) and Novartis' Gleevec (imatinib) for the treatment of gastrointestinal stromal tumors |
| Tocagen Inc.<br>*Approximately $2m* | Phase II/III study of Toca 511 + Toca FC versus SOC in recurrent glioblastoma and anaplastic astrocytoma |
| University of California, San Francisco<br>*Approximately $2m* | Phase II study of lipoic acid for the treatment of cystine nephrolithiasis |

# India CEO Pay: Local Firms Still Way Ahead Of Foreign Peers

**ANJU GHANGURDE** anju.ghangurde@informa.com

The corner office job at foreign firms may seem fancier but heads of Indian companies, many part of the firm's founding family, are the ones who continue to make the real big bucks.

While a comparison of remuneration of CEOs from India's entrepreneurial founding family groups with that of MNC bosses in the country may not be completely rational - after all many of the former group are known to have invested their life's savings in building their firms from scratch - a review by *Scrip* of the latest available data on CEO remuneration at some firms reveals interesting trends.

While CEOs/managing directors at the Indian firms reviewed, in general, earned more than the heads of foreign firms in India (as seen in *Scrip*'s previous analysis as well), **Sun Pharmaceutical Industries Ltd.**'s founder and managing director Dilip Shanghvi is the only exception. *(Also see "Scrip 100: Indian CEO pay league table – Local heads beat big pharma bosses" Scrip, 16 Jul, 2014.)* The Sun boss took home about INR28.4m (about $434k at current rates), similar to the earnings of **Pfizer Ltd.** India's boss S Sridhar at INR27m, but higher than that of Sanofi India managing director Shailesh Ayyangar at INR16.1m.

The Sanofi India head's remuneration, though, excludes provision for leave encashment, gratuity, long service award and pension which are determined on the basis of actuarial valuation done on an overall basis for the company. The MD is also entitled to stock options/performance shares of the ultimate holding company, Sanofi SA.

Abbott India's managing director Ambati Venu took home INR26.4m in the Sept. 29, 2016-March 2017 period, which if extrapolated for 12 months makes him the top-earning MNC CEO in the list of companies drawn up by *Scrip*. Abbott India does not have any stock option plan for its employees; however, the managing director is entitled to restricted stock units of Abbott Laboratories US under its 'Long-Term Incentive Program', the perquisite value of which is included the remuneration figure, details in the Indian arm's 2016-17 annual report said.

It should be noted that *Scrip*'s review does not include the major – unlisted – players Merck & Co, Eli Lilly, Johnson & Johnson and Roche.

## INDIAN FIRMS

Among the CEOs at Indian firms, **Cadila Healthcare Ltd.** chairman and managing director Pankaj Patel, who recently handed over day-to-day running of the company to his son, Dr Sharvil Patel, tops the earnings chart drawing INR180m, while **Cipla Ltd.** MD and global CEO, Umang Vohra earned a cool INR136.6m. Vohra, a former head of **Dr. Reddy's Laboratories Ltd.** North America business, is the only CEO who is not part of the founding family of the India firm in the list covered by *Scrip*.

Vohra's remuneration for the full financial year 2016-17 comprises emoluments for serving the organization at various positions – as global chief operating officer and global chief financial officer up to July 2016; global chief operating officer from August 1- 31, 2016 and managing director and global chief executive officer effective Sept. 1, 2016.

Meanwhile, the ratio of the remuneration of the top management to the median remuneration of the employees of their respective companies was rather varied and in some instances significant. In the case of Pfizer India's managing director it stands at 36.88, while in the case of Abbott India's boss it is 47. In the case of Cadila Healthcare's chief the ratio was 507.04.

An industry expert told *Scrip* that while CEOs must receive remuneration according to the role, responsibility and status of the positions they hold, huge differentials are "definitely not acceptable."

"One may rationalize that CEO salaries are influenced by global levels while salaries in lower ranks are influenced more by local conditions, but reports show that British and American CEOs earn 331 times that of median salaries in their organizations. At the other extreme are public sector companies in India where CEO salaries are three-four times that of median salaries," an expert noted.

While it isn't clear if the public-sector CEO salaries includes all the perks that come with such positions, the idea is to "strike a balance" between adequate CEO remuneration and glaring inequalities, the expert added.

Dr Ajit Dangi, president and CEO of Dansen Consulting, noted that the ratio of CEO remuneration to the median is an important factor.

"While the CEO does provide leadership, the executive alone cannot produce results and team efforts are also equally important. This is particularly important

CONTINUED ON PAGE 23

### CEO Salary League Table

| COMPANY | MD/CEO | 2016-17 REMUNERATION (INR MILL.) |
|---|---|---|
| Cadila Healthcare | Pankaj Patel | ~180 |
| Cipla | Umang Vohra | ~136.6 |
| Dr Reddy's | GV Prasad | ~97.7 |
| Lupin | Nilesh Gupta | ~81.7 |
| Abbott India | Ambati Venu | ~26.4 (Sept. 29, 2016 to March 2017) |
| GSK India | A Vaidheesh | ~39.2 |
| Novartis India | Ranjit Shahani | ~37.6 |
| Sun Pharma | Dilip Shanghvi | ~28.4 |
| Pfizer India | S Sridhar | ~27 |
| Sanofi India | Dr S Ayyangar | ~16.1 (year ended Dec. 2016) |

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.

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## Selected clinical trial developments for the week 29 September – 5 October 2017

| LEAD COMPANY/PARTNER | COMPOUND | INDICATION | COMMENTS |
|---|---|---|---|
| **Phase III Results Published** | | | |
| bluebird bio Inc. | Lenti-D gene therapy | cerebral adrenoleuko-dystrophy | STARBEAM; *NEJM*, Oct. 4, 2017. |
| **Updated Phase III Results** | | | |
| Gilead Sciences Inc. | bictegravir | HIV/AIDS | Study 1878; efficacy shown when given in combination. |
| Achaogen Inc. | plazomicin | septicaemia, urinary tract infections | CARE and EPIC; improved survival vs colistin in carbapenem resistant pathogens. |
| Biogen Inc. | *Spinraza* (nusinersen) | spinal muscular atrophy | ENDEAR, EMBRACE; earlier initiation better in infants. |
| Theratechnologies Inc. | ibalizumab plus optimized background anti-HIV regimen | HIV/AIDS, multidrug resistant | TMB-301, 311; suppressed virus long term. |
| Zavante Therapeutics Inc. | *Zolyd* (fosfomycin) iv | complicated urinary tract infections | ZEUS; effective and well tolerated. |
| **Phase III Interim/Top-line Results** | | | |
| Ablynx NV | caplacizumab | thrombotic thrombocyto-penic purpura | HERCULES; met primary and key secondary endpoints. |
| Roivant Sciences GMBH/Takeda Pharmaceutical Co. Ltd. | relugolix | uterine fibroids | SPIRIT 2; safe and effective in Japanese patients. |
| Motif Bio PLC | iclaprim | skin and skin structure infections | REVIVE-2; safe and effective in second Phase III study. |
| The Medicines Co. | *Vabomere* (meropenem/ vaborbactam) | UTI infections, in the immune compromised, and against carbapenem-resistant microbes. | TANGO 2; higher overall cure rate vs. best available care. |
| Zogenix Inc. | ZX008 (low-dose fenflu-ramine) | Dravet syndrome | Study 1; reduced seizure frequency. |
| Vantia Therapeutics Ltd. | fedovapagon | nocturia in men with benign prostate hyperplasia | EQUINOC; reduced nocturnal voids, well tolerated. |
| Allergan PLC | *Kybella* (deoxycholic acid) | fat removal | REFINE; 3-year follow-up, shape maintained. |
| **Phase III Initiated** | | | |
| Acadia Pharmaceuticals Inc. | *Nuplazid* (pimavanserin) | dementia associated psychosis | HARMONY; to treat hallucinations and delusions. |
| Zai Lab Ltd./Tesaro Inc. | niraparib | ovarian cancer | China study as second-line maintenance. |
| **Phase III Announced** | | | |
| Catabasis Pharmaceuticals Inc. | edasalonexent | Duchenne muscular dystrophy | In children aged four to seven years. |
| AstraZeneca PLC | durvalumab and tremelimumab | liver cancer | HIMALAYA; as first-line therapy. |
| GlaxoSmithKline PLC | cabotegravir plus rilpivirine | HIV/AIDS | Study of long-acting agents. |
| Horizon Pharma PLC | teprotumumab | Grave's ophthalmopathy | ORBIT. |

*Source: Biomedtracker*

CONTINUED FROM PAGE 21

in a country like India where social inequality between haves and have-nots is significant," Dangi, a former president and executive director of Johnson & Johnson India, told *Scrip*.

## FOREIGN CEO PAY STAYS STATIC?

While MNC pharma CEO pay levels in the country, in general, appear quite modest despite the complexities in emerging markets like India and the fact that quite a few executives tend to go on to take larger regional positions in their companies, experts don't anticipate a major change in CEO remuneration at foreign firms in India at least in the short term.

Salil Kallianpur, an industry expert, previously with a frontline multinational, notes that it is unlikely that MNC pharma companies in India will see a spurt of growth in business in the short to medium term. And nor are policy headwinds expected to ease out until in 2019.

"With business growing organically, fewer global products being introduced and no major private sector investment expected in pharma, it is unlikely that a case for change of CEO salaries will happen in the short to medium term," Kallianpur told *Scrip*.

On how MNC pharma CEO salaries in India compare with peers in other regional markets like China, Kallianpur referred to research by the global advisory firm Willis Towers Watson that shows annual base salaries in India are the lowest in the Asia Pacific region and significantly lower than China.

> 'One may rationalize that CEO salaries are influenced by global levels while salaries in lower ranks are influenced more by local conditions'

"While this is not specific to India, it shows that at senior management levels, India offers the lowest average annual base salary across the region, which is almost half that of China," he said.

Danssen's Dangi said that most multinational firms have a structured approach towards CEO compensation. This is a complex matrix of industry norms, cost of living, inflation rate, purchasing power parity, the country's income tax rates, perquisites offered, size of the market and size of the portfolio the CEO is handling, and of course the performance vis-a-vis the KRAs [key result areas]. Hence comparing CEO pay packages in various countries "may not be proper", he avers.

"There was a time when most MNCs in India offered liberal perquisites to the CEOs. As the tax rates have come down over the years, the perquisites have been significantly reduced and now most companies work on C to C [cost to company] basis," Dangi said.

Some companies, he adds, also offer company stocks/options, and in some cases a joining bonus is offered; terminal benefits like pension, gratuity, provident fund etc. have also become part of the total compensation.

"Since the remuneration model in most MNCs is based on these factors, there is unlikely to be major change in the compensation structure. However, increasingly importance is being given to variable pay linked to the profitability," Dangi noted.

Typically, the variable component is tied to KRAs and incentivizes the executive to perform better.

"Beyond a point it becomes counter-productive. As long as the variable part is reasonable, say below 25-30% of the total package, it has a positive effect," Dangi said.

*Published online 3 October 2017*



**CRISPR Therapeutics AG** has promoted ***Samarth Kulkarni*** to CEO – effective Dec. 1, 2017. Kulkarni joined the company as chief business officer and most recently he was president of CRISPR Therapeutics Inc. Co-founder and current CEO Rodger Novak will be stepping down and continuing as a member of CRISPR's board of directors and an officer of its Swiss parent company, CRISPR AG.

***David Meeker*** has been appointed **KSQ Therapeutics**' CEO. Most recently he was head of Sanofi-Genzyme Corp.'s specialty care business unit and before this, he was CEO and president of Genzyme. ***Frank Stegmeier*** has also been named KSQ's chief scientific officer. Stegmeier led oncology target discovery at Novartis before joining KSQ, where he has led its platform development and R&D since its formation in 2015.

**Oncorus Inc.** has named ***Christophe Quéva*** chief scientific officer and senior vice president, research. Quéva joins Oncorus fromiTeos Therapeutics, where he was chief scientific officer and previously held senior positions at AstraZeneca PLC, Amgen Inc. and Gilead Sciences Inc.

***Andrew Hotchkiss*** has joined **Immunocore Ltd.** as chief commercial officer. He was previously at Eli Lilly & Co., where he held leadership positions, including vice president international business unit leader oncology and president biomedicines business units, Australia, Canada and Europe.

**Cellectis SA** has appointed ***Mathieu Simon*** interim chief medical officer – effective immediately. Simon will be succeeding ***Loan Hoang-Sayag***, who is leaving Cellectis to pursue other opportunities. Simon has been Cellectis' executive vice-president since 2012 and has previously been chief operating officer.

**biOasis Technologies Inc.**, a company focused on neurological diseases, has named ***Christopher P. Lowe*** chief financial officer (CFO) and board advisor. Lowe is a partner at FLG Partners and before this, he was strategy, financial and management consultant to various public and private companies. He has been CEO, CFO and president of Inspyr Therapeutics Inc., since 2016.

**Avillion LLP** has appointed ***Kathryn J. Gregory*** chief business officer. With more than 25 years of executive leadership experience in the biotech and pharma industry, Gregory joins Avillion from Seneb BioSciences. She has held roles at various companies, including Purdue Pharma LP and Shire PLC, where she was responsible for business development transactions.