

**Teva's 'Key Ingredient'
For Growth: Biosimilars**

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Indication-Based Pricing Could Be Windfall For Interleukin Inhibitors

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Express Scripts' plan to reimburse at levels according to value of specific indications in inflammatory diseases will create more space for new entrants with proven value.

Express Scripts Holding Co.'s implementation of indication-based pricing in inflammatory diseases could spur a big market shift toward anti-interleukin-17 drugs for psoriasis – Novartis AG's *Cosentyx* in particular – at the expense of TNF-inhibitors. It also signals an important shift in reimbursement strategy with implications across other markets.

The pharmacy benefit manager announced plans on Sept. 8 to implement indication-specific pricing as part of its Inflammatory Conditions Care Value Plan, with rollout set for 2017. The plan also includes a broad rebate program for patients who drop out of therapy.

Indication-based pricing is a new approach to reimbursement that involves contracting for drugs for specific uses, rather than across all indications.

In the anti-inflammatory category, anti-tumor necrosis factor (TNF) drugs like AbbVie Inc.'s *Humira* (adalimumab), Amgen Inc.'s *Enbrel* (etanercept) and Johnson &

Johnson's *Remicade* (infliximab) are approved for a broad range of indications and have benefited from broad contracts, at the expense of new entrants, such as interleukin inhibitors, approved for a smaller number of conditions.

With TNF inhibitors in such a dominant position, in the past it has been very difficult for payers, PBMs and employers to convince physicians to switch stabilized patients from these drugs, commented Roger Longman, CEO of the reimbursement intelligence company Real Endpoints. Manufacturers have maintained this domination through rebate dollars and PBMs have found it difficult to ease themselves off the rebates to allow use of newer drugs, even where there are proven benefits over TNF biologics.

J&J's IL-12/IL-23 inhibitor *Stelara* (ustekinumab) has managed to pry its way in to the psoriasis/psoriatic arthritis market and produced worldwide sales of \$2.5bn in 2015, but its market share could be a lot higher if the field was wide open.

During an American Academy of Dermatology meeting where data were presented showing superiority of new interleukin inhibitors over the standard of care, experts said that it was still unclear how the results would affect prescribing patterns, because decisions were often dictated by insurance coverage.

Novartis' IL-17 inhibitor *Cosentyx* (secukinumab) launched last year and is off to a strong start. Eli Lilly & Co.'s *Taltz* (ixekizumab) was approved in March. AbbVie Inc., UCB Group and J&J have IL-17 inhibitors in Phase II for inflammatory diseases.

Starting in 2017, Express Scripts will be breaking up the inflammatory disease category in negotiations with drug manu-

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from the editor

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The market for inflammatory disease therapies has been a bustling one for several years, and it is only going to get more varied.

As Emily Hayes explores in our cover story, the arrival of challengers to the old mainstay TNF inhibitors is prompting a diversification of offering and more sophistication among payers. Instead of selling a drug at “one-price-treats-all”, pricing will increasingly be tailored per indication to reflect the product’s varying levels of value.

Alongside this fine-tuning of the value proposition, biosimilar manufacturers are preparing to set out their stalls and drum up business by undercutting the brands, potentially also on an indication-specific basis. Pfizer/Celltrion’s *Inflectra*, biosimilar to J&J’s *Remicade* (infliximab), will be a bellwether launch in the US, but it’s not clear if it will happen on Oct. 3 (when the 180-day hold ends) or if it will continue to be held up by ongoing litigation.

Meanwhile, Teva wants to be among the biosimilar bigshots shaking things up in the US – but it needs a partner (see p3).

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Teva's 'Key Ingredient' For Growth: Biosimilars

Teva has conducted due diligence on 36 biosimilar companies with the aim of signing a partner soon to fill a critical gap in its generics pipeline.

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Teva Pharmaceutical Industries Ltd. is looking to close a deal with a biosimilar partner soon, according to Global Generic Medicines CEO Sigurdur Olafsson. The head of the generics business said biosimilars will be a “key ingredient” to the future of Teva, but acknowledged the recipe for success will require the help of a partner – and quickly.

Closing a deal in the biosimilar space is an important business priority for Teva in the near-term; the company's generic drug unit is otherwise focused on integrating Allergan PLC's generic drug business, a \$40.5bn acquisition that closed in July.

The combination of the two businesses was the impetus for the investor briefing held in New York Sept. 9, where Teva laid out its generic growth strategy, including big ambitions in biosimilars. The acquisition of the Allergan generics business did nothing to improve Teva's position in biosimilars, an emerging commercial opportunity Teva thus far has failed to take advantage of.

‘You need to have the infrastructure of a brand company, but you need to have the nimbleness and the cost structure of a generic company’

Teva has been aiming to build up its biosimilars pipeline after falling behind rivals like Sandoz (owned by Novartis AG) and Hospira (now owned by Pfizer Inc.). CEO Erez Vigodman made a commitment to complex generics and biosimilars a pillar of his turnaround strategy for the company in 2014, shortly after taking over as CEO.

Still, no big biosimilar deal has emerged yet. Olafsson insisted Teva is tackling the challenge, having screened about 120 biosimilar companies and completed due diligence on around 36.

“It's a little bit like when my mother was asking me, ‘when are you going to find a girlfriend,’” Olafsson said of the timeline for completing a deal. “I really don't know.”

The executive did offer some details about what kind of partner the firm is looking for: most importantly, one with biosimilars in late-stage development.

“We really think [the] key to be successful is to be in the first wave,” Olafsson said. “You don't have to be the first, but you do have to be in the first wave to introduce to the market.” He indicated that being among the first three players to market with a biosimilar will be important to having a strong competitive position in a given category.

“Companies that are a few years behind in development, we would probably not take that opportunity,” Olafsson added.

Teva is specifically looking to fill a gap it sees in its pipeline for biosimilars that could launch from now until 2021, he said. The firm believes it will have the capability to develop biosimilars in-

ternally that would be ready to launch post 2021.

Manufacturing capacity is another factor in Teva's search. The company currently doesn't have significant biologics manufacturing capacity, though it is investing in a new biologics plant in Ulm, Germany, dedicated primarily to manufacturing innovative biologics. In the near-term, Teva hopes it will be able to find a partner with excess manufacturing capacity to fill that gap.

RECIPE FOR SUCCESS: BRAND CAPABILITIES AND GENERIC COST INFRASTRUCTURE

Teva is optimistic about the opportunity for biosimilars in the US, despite challenges getting the products to market and what is expected to be hurdles getting them prescribed by physicians.

“I think it is going to be better than people expect,” Olafsson said of the opportunity. “Overall, the price erosion that people are talking about – some people are putting 50% to 60% price erosion for biosimilars – I think it's going to be less in the beginning because of the non-interchangeability, which will be a hurdle.”

He predicted that brand drugs will retain at least half of the market share initially, though biosimilar penetration could be more significant for products administered in a hospital setting.

“Hospital products, where the decision is made by a clinical committee in the hospital ... [and] the whole clinic is changed to a biosimilar, that is an easier part to penetrate versus where you have to influence the pen of the prescriber, like for some of the psoriasis drugs,” Olafsson said.

As for why Teva is positioned to compete in the space despite not being among the first companies to get a biosimilar approved in the US, Olafsson said it's because the company is ideally straddled between specialty drugs and generics.

“You need to have the infrastructure of a brand company, but you need to have the nimbleness and the cost structure of a generic company,” he said. “I think we have that.” The rivals, he said, that also bridge the divide are Novartis and Pfizer. “There's not many more companies that really have that infrastructure,” he said.

Teva was a biosimilar pioneer in the US, developing *Granix*, a version of Amgen Inc.'s *Neupogen* (filgrastim), which FDA approved in 2012. But Teva opted to file the application through the conventional BLA pathway rather than what at the time was the newly established 351(k) pathway for biosimilars. As a result, the title holder for first official biosimilar approved in the US is Sandoz for its version of filgrastim, approved as *Zarxio* three years later in 2015.

Teva so far has missed out on what is viewed as one of the biggest commercial opportunities in the field, biosimilar versions of the blockbuster anti-TNFs, approved for various inflammatory conditions including rheumatoid arthritis. Sandoz' *Erelzi* was recently approved as the first biosimilar version of Amgen's *Enbrel* (etanercept) and Celltrion Inc.'s *Inflextra* was approved as the first biosimilar of Johnson & Johnson's *Remicade* (infliximab), and others are pending. ▶

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Japan Issues Strong Warning Over Brexit

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Uncertainty is bad for business and can deter investment, warns Japan in relation to eventual talks on the UK's exit from the EU. Japan's preferred Brexit outcome? For the UK to keep both EU law and the European Medicines Agency.

Japanese companies, including some in the pharmaceutical sector, could move their European headquarters out of the UK if EU law ceases to apply there after the country leaves the union, Tokyo has warned.

Japan has also added its voice to those warning that London and more broadly the UK might become less appealing as a location for drug development if the European Medicines Agency relocates following Brexit.

Japan wants to see full transparency around any Brexit talks and sufficient transition time allowed for any major policy and regulation changes. "What Japanese businesses in Europe most wish to avoid is the situation in which they are unable to discern clearly the way the Brexit negotiations are going," the Ministry of Foreign Affairs said in a statement issued around the time of the recent G20 Summit in Hangzhou, China.

The UK is seen as a gateway to Europe by many Japanese businesses and nearly half of all Japanese direct investment intended for the EU has gone to the UK. Any uncertainty risks triggering a reconsideration of investments, the government cautions.

Much of the statement focuses on broad concerns, but it also covers areas of specific relevance to the pharmaceutical sector. It mentions the need to ensure the continuation of joint R&D projects and the unified protection of intellectual property rights, to maintain UK access to EU R&D budgets and the harmonization of regulations (and mutual recognition) between the UK and EU, and to ensure ongoing consistency in UK/EU regulations.

EMA RELOCATION WORRIES

Perhaps the biggest single worry voiced by Tokyo relates to the potential relocation of the European Medicines Agency away from London and the impact this could have on drug regulation in both the UK and Europe. "Japanese companies are concerned about the relocation of EU agencies currently located within the UK. Many Japanese phar-

maceutical companies are operating in London, due to the EMA's location," the ministry statement says.

It says the EMA should remain in the UK and that the current medicines certification system between the UK and EU should continue. The assumption following the June 23 referendum in which the UK voted the leave the EU has been that the agency will have to move to another EU member state when Brexit eventually happens.

Formal exit negotiations have yet to start but it would be no surprise were the UK to negotiate for the EMA to stay in London.

The UK is an important base for European drug research and commercial activities by Japanese pharma companies, several of which have their main regional development and sales offices there. The ministry says the appeal of London for drug development activities might be lost if the EMA moves following Brexit.

"[This] could possibly lead to a shift in the flow of R&D funds and personnel to Continental Europe. This could force Japanese companies to reconsider their business activities," the ministry warns.

If EU laws cease to apply in the UK after EU withdrawal, the statement says "Japanese businesses [of all types] with their European headquarters in the UK may decide to transfer their head office" elsewhere in Europe.

REDUCING PRESENCE?

Regardless of Brexit worries however, there have been moves by several Japanese pharma majors over the past few months to scale back their UK presence, driven more by global cost control initiatives than political concerns.

Daiichi Sankyo Co. Ltd. said in February it was planning to close its European drug development subsidiary near London. Takeda Pharmaceutical Co. Ltd., meanwhile, is looking to spin off its site and research programs in Cambridge into a new biotech company, as part of a larger worldwide R&D overhaul.

Eisai Co. Ltd. has also pointed to the market access troubles it is having in the UK with its cancer drug lenvatinib, saying that these may be a possible trigger for reduced UK investment. The company is responsible for the largest Japanese UK pharma investment so far, of more than £150m (\$200m) in its EMEA

Knowledge Centre, a major research and production site in Hatfield near London that opened in 2014.

On the positive side - although it was not referred to in the statement - the significant weakening of sterling against the yen following Brexit may yet open up some relatively cheap investment and M&A opportunities for Japanese pharma and other firms.

OTHER VIEWS

Scrip asked a number of major pharma companies in Japan for their views on Brexit but received few replies. There is still a lack of clarity and it is too early to comment, one firm said.

Hideo Norikoshi and Chia-Feng Lu from the Tokyo office of international law firm Baker & McKenzie replied to a number of questions on the matter.

The lawyers said it was natural to assume that in the short run uncertainties caused by the referendum result and the lack of reliable indications on what is to come would negatively impact new investment from Japan into the UK. The long-term implications for the pharmaceutical industry, however, would only really become apparent once the final model governing the UK's new relationship with the EU were determined.

In making investment decisions, the lawyers said, Japanese pharma companies would no doubt take numerous factors into account, such as access to talent, political stability, language, centralized marketing authorizations, access to public funding, and tax.

Many of these factors will depend on what the UK and the EU decide their future relationship should be, they said, adding, however, that the exchange rate would not be a decisive factor in the long run. In addition to covering concerns around the UK's exit from the EU, the ministry statement touched on general worries over the continuation of free trade and investment involving Japan and the EU. The government said it intended to send a "strong message" about its commitment to free trade by reaching an agreement in principle on the planned Japan-EU Economic Partnership Agreement "as early as possible this year." ▶

From the editors of PharmAsia News.

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Novavax's Phase III RSV Vaccine Failure Wipes Out Nearly \$2bn In Value

Novavax shocked investors with negative results for its RSV vaccine in a Phase III clinical trial immunizing older adults, but promised more data – and ideas for a potential second Phase III trial – in October.

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Novavax Inc.'s closely watched respiratory syncytial virus (RSV) vaccine – widely expected to show positive Phase III results after a successful Phase II program – not only fell short in its first Phase III clinical trial, but it was less effective than placebo in preventing moderate-to-severe RSV in older adults.

"It's clear that there will not be a [biologic license application (BLA)] filed in 2017," Novavax president and CEO Stanley Erck said during a Sept. 15 conference call to discuss a preliminary analysis of the Phase III Resolve trial results for the RSV F-protein recombinant nanoparticle vaccine candidate (RSV F Vaccine). The news sent the company's stock down 83.2% to \$1.40 per share in after-hours trading. The plunge wiped out roughly \$1.9bn in shareholder value based on Novavax's pre-Phase III data stock price of \$8.32 and \$2.3bn market cap.

Resolve enrolled 11,856 adults aged 60 or older and the primary endpoint was prevention of moderate-to-severe RSV-associated lower respiratory tract disease (RSV msLRTD) with a secondary endpoint of reducing the incidence of all symptomatic respiratory disease due to RSV (RSV ARD).

There were 26 individuals with RSV msLRTD in the placebo arm, or 0.44%, and 28 who received Novavax's RSV F Vaccine, or 0.47% ($p=0.78$). The vaccine performed better under the secondary measure – 117 people with RSV ARD (1.97%) in the placebo group versus 102 (1.72%) in the vaccine group – but the result was not significant ($p=0.32$).

"The failure of this pivotal trial is a blow to Novavax," a Sept. 15 Biomedtracker analysis said. "Company officials pointed to a mild RSV season as a possible cause for trial failure. Historically, annual seasonal RSV ARD attack rates between 3% and 7% have been observed in older adults. The Phase II trial conducted during the 2014/2015 season reported an RSV ARD attack rate of 4.9%, which is in line with historical rates (the RSV msLRTD attack rate was 1.8%). In contrast, this Phase III trial, conducted during the 2015/2016 season, reported an RSV ARD attack rate of 2% and an msLRTD attack rate of 0.4%."

Erck described the three most plausible explanations, in Novavax's view, for the Phase III Resolve trial's failure during the company's conference call: 1) the RSV F Vaccine approach doesn't work, despite a "preponderance" of animal and Phase II human data that suggest otherwise; 2) something may have changed from year to year in the vaccine produced for the Phase II and III studies, in conflict with batch comparisons conducted by the company; or 3) the attack rate, which appears to be the lowest rate of infection ever recorded for an RSV season, hindered the late-stage study.

Regardless, the Biomedtracker analysis noted that "we are struck by the finding that there was not even a trend in favor of the vaccine for the primary endpoint."

The lack of a trend towards positive efficacy was striking, according to Biomedtracker, because the rollover portion of the Phase II trial also was conducted during the 2015/2016 season and showed a

trend in favor of the vaccine for both RSV ARD (0.6% vs 2.4%) and RSV msLRTD (0% vs 0.3%). The rollover portion of the mid-stage study included older adults who re-enrolled for randomized treatment with a booster shot of Novavax's vaccine or a placebo a year after their first vaccine or placebo dose.

A SECOND PHASE III WITH A BOOSTER SHOT?

Biomedtracker said the trend toward efficacy spotted in the rollover results "may be an indication that a single course of treatment may not be sufficient. Accordingly, the company has indicated that they will continue developing this vaccine and that future work may incorporate a boosting strategy."

Novavax did not offer very much color on its plans for additional Phase III testing in older adults and data are not expected until 2018 from the company's separate ongoing Phase III clinical trial. That study is evaluating protection from RSV during the first three months of infants' lives after prenatal maternal vaccination.

"We see nothing that changes expectations for the maternal immunization study," Novavax president of research and development Gregory Glenn, said during the company's conference call. He noted that infants are RSV-naïve, and the vaccine used in the maternal study as well as its mechanism of action are different than in the older adult study, so Resolve's results shouldn't carry over to the other trial.

Novavax expects to share more of its Resolve data, a refined opinion of what caused the study's negative results, and potential plans for another Phase III trial in older adults during its R&D Day for analysts and investors on Oct. 11.

Novavax had \$366m in cash and investments at the end of the second quarter – thanks to the sale of \$315m in convertible debt early in 2016 – to put towards the costs of a new study. Chief financial officer Buck Phillips said the company still has more than \$300m on its balance sheet and it has seven years until it has to repay the debt underlying the recently sold convertible notes.

With a failed pivotal trial and a lack of significant efficacy in the Phase II study's rollover period, Biomedtracker lowered its likelihood of approval for the Novartis vaccine by 13% to 55%, which is 6% below average for late-stage vaccine programs.

Glenn said in Novavax's statement about the rollover data that: "We observed similar low [RSV] attack rates and absence of efficacy of a single immunization in [the rollover] trial as was observed in Phase III Resolve trial, although we did observe that a second season immunization [given one year after the initial Phase II dose] could provide efficacy. The event rate comparisons made to either placebo groups suggested that the second season immunization was protective, even in a year with a very low attack rate. Further understanding of these data may come forth with full evaluation of the immune responses." ▶

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Takeda Chooses PRA To Lead Its Revamped Clinical Development Ops

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Takeda has chosen US-based PRA Health Sciences to lead its clinical development as part of the Japanese drug maker's global R&D overhaul aimed at cutting costs and improving efficiency and innovation.

Having announced a major shakeup of its R&D operations in late July, Takeda Pharmaceutical Co. Ltd. has now chosen PRA Health Sciences Inc. to take control of the Japanese drug maker's pipeline of clinical studies and related product progression.

The pact, which the duo described as ground-breaking, will see around 300 Takeda employees offered the chance to "transition" to work with PRA in the US and Europe. Discussions regarding Japan employees are meanwhile "ongoing," the companies said in a statement Sept. 12. PRA Health has more than 12,000 employees working in more than 80 countries.

Heralding the transformation in July along with its first-quarter results, Takeda at the time said the planned revamp was needed to produce organizational and financial flexibility "to drive innovation, enhance partnerships, and improve R&D productivity for long-term, sustainable growth." Takeda has recently reduced the number of therapeutic areas it focuses on and now concentrates R&D on oncology, gastroenterology, and CNS, plus vaccines.

Takeda's chief medical and scientific officer Andy Plump said its partnership with PRA "is a fundamental part of Takeda's R&D transformation and represents a truly innovative approach to clinical development, unprecedented in our industry." He said PRA was chosen in part because of its reputation for providing tailored sourcing solutions. "We believe PRA will be an ideal partner as we focus, deliver and advance our current and future pipeline," he added.

Under the pact, PRA will manage an entire pipeline of human studies for Takeda across Phases I-IV and also provide regulatory, pharmacovigilance and other operational services for both development and marketed product portfolios.

"This is the first time that a pharmaceutical company and a clinical research organization (CRO) have come together to create such a comprehensive business and operational strategy," PRA's chief executive Colin Shannon said, adding that "this partnership model redefines collaboration and is the first of its kind in the CRO industry."

Observers note that externalizing R&D can help drug makers reduce their staff overheads and institutional inefficiencies while not seeming too ruthless. The approach has been tried before, notably by Merck Serono SA in 2013 and by GlaxoSmithKline PLC in 2014. ▶

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Takeda's Ninlaro Back In European Myeloma Race After CHMP Turnaround

A CHMP about turn on Takeda's Ninlaro (ixazomib) for multiple myeloma means the Japanese firm is back on track to compensate for lost revenues from the impending patent expiry of key product Velcade. However, the Japanese firm will have a tough time ensuring Ninlaro is not overshadowed by rivals.

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The European Medicines Agency's CHMP has reversed its initial negative opinion on Takeda Pharmaceutical Co. Ltd's *Ninlaro* (ixazomib) and has now green-lighted a conditional approval. The news will come as a relief for Takeda, which will now be better poised to offset a decline in sales from *Velcade* (bortezomib) following impending patent expiry. However, Takeda cannot afford to relax: it will have to work hard to establish *Ninlaro* in an increasingly crowded market while approval of a promising rival from Janssen looms.

On Sept. 15 the CHMP recommended conditional approval of *Ninlaro* in combination with lenalidomide (Celgene Corp's *Revlimid*) and dexamethasone for the treatment of adult patients with multiple myeloma who

have received at least one prior therapy.

The CHMP had initially issued a negative opinion because it did not think the data was sufficient to demonstrate a benefit.

The company had suggested limiting the medicine to patients whose disease was more difficult to treat and had returned after one previous treatment, and to patients whose disease had come back after two treatments. But the CHMP did not believe the data in these subgroups was compelling enough "and the rationale for assuming greater effectiveness in these patients was not clear." However, the CHMP agreed to re-examine the drug and consulted with oncology experts to consider the drug's safety profile, among other things.

The CHMP agreed with the expert group's

conclusion that the data indicated improvement in progression-free survival thanks to *Ninlaro*. But because of uncertainty surrounding the magnitude of improvement, Takeda will have to provide further confirmatory data to win full marketing authorization. The committee also noted *Ninlaro*'s favorable safety profile and the convenience of patients taking the capsules at home.

Despite the good news, Takeda cannot afford to relax as multiple myeloma is an increasingly crowded space. Recent trial results from Janssen Biotech Inc. for *Darzalex* (daratumumab) may cast a shadow over Takeda's good news. Read here how *Ninlaro* may compete on the market: <http://bit.ly/2cJlemr> ▶

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Continued from cover page

factors, for seven different indications: rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, ulcerative colitis and Crohn's disease.

Express Scripts says it will still be using a "blended" price at the drug level, regardless of indication, so a client still pays the same amount for each condition. But there are additional discounts and enhanced competition at the indication level. Medications will get formulary placement on the indication level, instead of the entire category of inflammatory conditions.

This will allow smaller drugs that have only one or two indications to better compete with a drug that has all seven indications – leveling the playing field and helping to drive more competition, Adam Kautzner, VP of Express Scripts Drug Trend and Formulary Solutions, explained in an interview.

Payment will be tied to value, with higher rebates for indications where drugs don't work as well.

Indication-based pricing is part of a move toward value-based pricing, Longman commented. The first big area is inflammatory disease, but the model could make sense for any drug approved for multiple indications – the industry has already seen experiments in oncology demonstrating proof-of-concept, Longman noted.

Express Scripts began contracting on an indication basis for cancer drugs earlier in 2016. Rival PBM CVS Health Corp. is also planning to introduce indication-specific pricing in oncology.

Datamonitor Healthcare analyst Astrid Kurniawan expects the model will be adopted by other commercial payers as well.

BIOSIMILARS WILL BOOST TREND

The emergence of biosimilars will give payers more leverage in a number of therapeutic areas, including inflammatory diseases, Longman noted.

The TNF inhibitors represent one of the major areas for biosimilar development. Sandoz Inc.'s *Erelzi* (etanercept-szss) still has some legal hurdles to clear, but the Enbrel biosimilar is expected to launch in October. Pfizer Inc./Celltrion Inc. also expect to launch *Inflextra* (infliximab-dyyb), a biosimilar version of Remicade, in October.

Kautzner said that indication-based pricing lays the groundwork for biosimilars, allowing Express Scripts to "slot them in at an indication level."

Inclusion as a preferred treatment will need to be in line with guidelines from the American College of Rheumatology and Express Scripts' Pharmacy and Therapeutics Committee will ensure that clinical value comes first, the exec said.

Manufacturers need to realize that the discounts may need to be very deep for biosimilars to compete, Kautzner said.

For new entrants, the new regime represents opportunity – at a price. Those with high-value products may be willing to deal more aggressively on pricing and rebates in order to win preferred status and gain market share, Longman said.

"Whereas before you could not break in, now you can," Longman predicted.

Kautzner notes that products need to be priced competitively and envisions that there will be broad access to a variety of preferred products, with a "large selection from the physician standpoint."

COSENTYX WELL-PLACED

Within the inflammatory category, there is likely to be a big shift in psoriasis in favor of interleukin inhibitors, with Cosentyx particularly well placed to benefit, Datamonitor's Kurniawan expects.

Interleukin inhibitors have proven superior to Enbrel in head-to-head studies. Payers appreciate this difference in efficacy but pricing is still an important factor.

Instead of competing under the entire umbrella of inflammation, new entrants will compete in a narrow spectrum, and "especially in psoriasis, this will really give interleukins a chance," Kurniawan said.

Cosentyx is likely to have the upper hand over Taltz and Stelara, because it proved superior to Stelara in a head-to-head study, whereas Lilly's Taltz met the less rigorous standard of superiority against Enbrel. However, the US market is very competitive on pricing and that upper hand could be diminished if Lilly offers a better price, the analyst explained.

As for Humira, the market implications are somewhat unclear. The drug is the market leader and is perceived as being more efficacious than Enbrel, but head-to-head data against Enbrel are not available, nor are head-to-head data for Humira against

the interleukin inhibitors.

J&J has tested its IL-23 inhibitor guselkumab, one of three drugs in the class in Phase III for inflammatory diseases, successfully against Humira in psoriasis in a mid-stage study.

Novartis recently unveiled comparative efficacy data for Cosentyx against Humira in ankylosing spondylitis and plans to run head-to-head studies of the two drugs in ankylosing spondylitis and psoriatic arthritis.

These smaller indications are now more in play, Kurniawan said, and head-to-head data will help sponsors make the value case.

HOW SPONSORS SHOULD RESPOND

Asked to comment on what manufacturers should be doing in response to the introduction of indication-based pricing, Express Scripts' Kautzner said that "they need to understand flexibility will be key."

Companies will need to have an understanding that other products with more competitive prices for a given indication may provide better care at a lower net cost and that just because a drug has multiple indications doesn't mean it has better overall value, Kautzner said.

Longman said that pharma need to spend more time on determining value for each indication. A number of models are now available for measuring value, including Real Endpoints' RxScorecard. The Institute for Clinical and Economic Review plans to issue a value report on anti-inflammatory drug classes in October.

Indication-specific pricing will also allow pricing for subpopulations within a particular disease. For example, in oncology, PD-1 inhibitors work better in lung cancer patients with higher levels of PD-1 expression.

"Pharmas should be focusing a lot more attention on proving value in specific subpopulations in which they are uniquely advantaged" against the competition, Longman said.

Kautzner said that indication-specific pricing for subpopulations is not part of the new program but that many possibilities are open for the future. There is always opportunity to enhance these programs and go to greater depths if the market warrants it, he said.

"This is the first great step," Kautzner said. ▶

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Meet The New Teva: 8% Global Generics Share, 300 ANDAs, 1,500 Launches

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The world's generic drug leader has cemented its leadership position for the foreseeable future with the acquisition of Allergan's generics business. Management outlined how it plans to grow the combined business by taking advantage of its size during an investor briefing.

Teva Pharmaceutical Industries Ltd. has gained a substantial lead in the global generic drug market with the \$40.5bn acquisition of Allergan PLC's generic drug business, and now is counting on the size to help sustain its lead and drive growth. The combined company will have a global generic market share of 8% and will be in a position to launch 1,500 products around the world in 2017.

CEO Erez Vigodman, Global Generic Medicines CEO Sigurdur Olafsson and the rest of the newly established management team unveiled the new generics unit to investors during a briefing in New York Sept. 9. The mega-deal was cleared by the Federal Trade Commission July 27 after Teva agreed to divest 79 products, paving the way for the merger of two of the world's largest generic drug units.

Allergan's generic drug business was formerly the generic drug company Actavis

before it bought Allergan and changed its name to the one with more consumer recognition in 2015. Teva also announced Aug. 3 that it will buy Allergan's Andia Inc., the fourth largest distributor of generic pharmaceuticals in the US, for \$500m. Now the integration of the two businesses is benefiting from the fact that Olafsson previously led the Actavis generics business and knows Actavis and Andia well.

The Allergan deal will cement Teva's leadership position in generic drugs for the foreseeable future. The company's 8% share of the global market, based on standard units from IMS Health's 2015 generic segment data, gives the company a significant lead over its rivals.

The second largest competitor by global market share will be Novartis AG's Sandoz

unit with a 4.8% market share, followed by Sanofi's Zentiva with a 3% share and Mylan NV with a 2.8% share.

The new Teva is among the top three generic drug companies in 40 markets around the world. It will generate annual revenues of \$14bn to \$15bn. It has 300 abbreviated new drug applications (ANDAs) pending at FDA, representing innovator sales value of \$110bn, and another almost 2,500 regulatory filings around the globe. In 2017, Teva expects to launch 1,500 products.

'To be top three in a market is so important. You have the opportunity of growing the market. You understand it'

SIZE EQUALS SUCCESS

Size is what management believes will help Teva compete in a changing generic drug environment, influenced by consolidation, pricing pressure and fewer blockbuster drugs going off patent.

"To be top three in a market is so important," Olafsson told investors. "You have the opportunity of growing the market. You understand it. You attract the best talent. You have the best employees on your team. You really have the opportunity of launching on time. The customers come to you for help. You are available. You have a flexible supply chain. So when we talk about top three position in more than 40

A Balanced Leadership Team

- **Global Generics Medicines CEO** – Sigurdur Olafsson (Legacy Teva With Prior Actavis Experience)
- **Head of Europe** – Dipankar Bhattacharjee (Legacy Teva)
- **Head of Growth Markets** – Erez Israeli (Legacy Teva)
- **Head of Biosimilars** – Edric Engert (Legacy Teva)
- **Head of North America** – Andy Boyer (Legacy Allergan)
- **Head of Generics R&D** – Hafrun Fridriksdottir (Legacy Allergan)
- **Head of Portfolio & Business Development** – Daniel Motto (legacy Allergan)

markets, this is one of the key ingredients.”

Size also counts when it comes to defending against price pressure.

“If there is price pressure on opioids, some of our competitors are badly hit and we have seen that. If there’s price pressure on dermatology, some of our competitors will show that in the numbers,” he said. “But, when we are close to 400 products on the market, any single price pressure that we see doesn’t affect Teva in the same way as our competitors.”

In North America, a market that accounts for about half of Teva’s global generics revenue, Teva is the market leader, with a 18% share of the generic drug market in the US. While the US will remain an important market for Teva going forward, Olafsson said Europe and “growth markets” will be the future growth driver of the business.

“This is where more and more opportunities are coming through,” he said, pointing to Eastern Europe, Russia, Japan and Asia.

ONE-THIRD OF 300 PENDING ANDAS ARE FIRST-TO-FILE

Teva’s focus in the US will remain on first-to-file opportunities. Of the 300 ANDAs Teva has pending at FDA currently about one-third are first-to-file opportunities with 180-day exclusivity, while more than one-third are considered “first wave,” where Teva expects to enter the market on day 181. In addition, of the 27 first-to-files posted by FDA on its website Sept. 7, Teva is the sponsor of 13, by far outpacing its rivals.

The head of North America Andy Boyer is new to Teva, having led generics sales and marketing for Allergan. He was groomed through the ranks at Actavis and the prior US-based legacy company Watson Pharma Inc., which acquired and merged with Actavis in 2012 and later changed its name to Actavis. Boyer, who joined Watson in 1998, was appointed to lead the US generics business of the combined company following the 2012 merger.

Half of Teva’s new generics leadership team are from Actavis, while the other half are from Teva (see box).

Fridriksdottir said the combined company will be an R&D powerhouse with the expertise to develop complex formulations like inhaled products, long-acting injectables (LAIs), transdermals and modified-release solid dosage formulations. While Teva

was better at developing LAIs and inhaled drugs, Actavis was more experienced developing semi-solids and liquids, transdermals and ointments, she said.

Complex generics are a big focus of the top generic drug companies because of the high barriers to entry for competitors and the potential for less price erosion. Teva, for example, is one of the companies trying to get to market with a generic version of the inhaled asthma blockbuster Advair, with two candidates in development, one from legacy Allergan and one from legacy Teva.

‘Teva’s diverse portfolio of more differentiated product offering leaves them less exposed to some of the pricing pressures’

Olafsson also talked about Teva’s strategy in biosimilars and its focus on finding a partner soon to help fill a gap in its pipeline for developing biosimilars that could launch from now until 2021. He said Teva has conducted due diligence on 36 potential bio-similar partners.

The combined generics business will have 3,000 employees working in R&D across 26 sites in 20 countries, but Fridriksdottir said there will be some cuts to the complex R&D organization. “At the end of the day, our goal is and our plan is to keep the best of the best, the best people, the best R&D sites and the best locations,” she said.

Teva has guided that it will generated

\$26.7bn to \$27.8bn in revenues in 2019, up from the \$19.7bn it generated as a stand-alone business in 2015, as a result of the merger. EBITDA will be between \$10.7bn to \$11.5bn in 2019, representing mid-point compound annual growth of about 14% from 2015 to 2019.

Olafsson said he believes the generics business will grow 5%, though he acknowledged reaching the goal will require the business to generate double the amount of revenue growth from new products to offset the impact of price erosion, which he expects will be low- to mid-single digits.

No matter how successfully Teva executes on the acquisition of Allergan generics, a lot of the company’s near-term growth prospects rests on the specialty side of the business, namely the fate of the multiple sclerosis blockbuster Copaxone (glatiramer) and how long Teva will be able to maintain exclusivity for the newer 40mg dose of Copaxone.

Some analysts were encouraged by the investor briefing, but acknowledged the risks on the specialty side of the business.

“With investors concerned about generic drug pricing trends and the pipeline of new generic opportunities, we believe management did a commendable job outlining why they are likely better positioned than many of their peers,” Credit Suisse analyst Vamil Divan said in a Sept. 12 note. “Teva’s diverse portfolio of more differentiated product offering (including more complex products) leaves them less exposed to some of the pricing pressures that have been seen in other parts of the generics market. ▶

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Teva First-To-File Launch And 30-Month Stay Expirations 2016/2017

Ampyra	Mirvaso	Quillivant XR
Axiron	Neupro	Reyataz*
Beyaz	Nexium 24-HR OTC	Safyral
Butrans	Noxafil	Trokendi 200mg
Byetta*	Nucynta	Tyvaso
Contrave	Nucynta ER	Uceris
Effient	NuvaRing	Viagra*
Epzicom*	Onglyza	Viread*
Letairis	Pennsaid 2%	Zohydro ER
Livalo	Qsymia	Zubsolv

Source: Teva Investor Day, Sept., 9, 2016; * indicates date certain launch

Sanofi, Google's Verily Enter Diabetes JV To Produce Joined Up Solutions

Sanofi's diabetes head says French drug maker's JV pact with Google's Verily will combine novel therapies for the condition with cutting edge technologies to produce better focused, outcome-based combinations.

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A joint venture being established by Sanofi and Google parent Alphabet aims to combine medicines, devices and software into a joined up portfolio of product offerings for diabetes patients around the world, according to the head of the French drug maker's global diabetes franchise.

The US-based JV, named Onduo, was announced Sept. 12 as a unique alliance focus on helping type 2 diabetes patients better plan their day to day medication management and habits. Based in Cambridge, Mass, Onduo plans to eventually focus on type 1 diabetes, as well as to people at risk of developing diabetes, helping them to better prevent the onset of the disease.

AIM IS JOINED UP HEALTH

"Healthcare hasn't been very good at advancing connectivity so far. Diabetes is an excellent area to pursue and promote this, given the extent to which diabetics use the combination of drug and device, but for the most part there's very little connectivity there," Stefan Oelrich, who heads Sanofi's diabetes franchise, told *Scrip*.

He said Google parent Alphabet and Sanofi plan to invest about \$500m in a joint venture. The joint venture will be independent but can draw on its parents' resources. Sanofi hopes the partnership with Alphabet's Verily Life Sciences will also promote novel ways that diabetes can be monitored and treated, and in the process help the French drug maker better adapt to a changing and increasingly competitive market.

But Onduo will also have the freedom to work with other diabetes product makers.

"Onduo has the right to do work with other pharma companies, and when seen in the solutions perspective we – Sanofi – don't have all the drugs that a physician needs for any given solution, so it is perfectly legitimate that the joint venture as it seeks outcomes solutions will also turn to medicines other than Sanofi medicines. That also reflects the different emphasis of this approach. When focusing on a certain desired

outcome, then that may require other drug classes that we do not offer," Oelrich said.

Oelrich, 48, told *Scrip* that the JV will bring technology and targeted diabetes therapies together with the focus on outcomes. In essence the aim is for innovative medicines to be "joined up" with delivery and monitoring technologies.

'It's turning the current model or approach upside down. That frees us up from thinking just in terms of product portfolio'

"What we have today are the medicines in their various formats – orals or injectables or self-administered pens along with glucose measuring systems and digital platforms that let someone for example count your carbs at certain times of the days that let you titrate better, and so on and so forth; but all of these are pretty much used in isolation and one is separate from the other and so what Sanofi and Verily thought was that together we could start introducing a much higher level of connectivity between existing solutions and upgrade those in terms of technology – which can mean miniaturization as well as connectivity," Oelrich said. "So you can, conceivably, connect an insulin pen to a CGM or a pump to a CGM that's connected to the correct insulin, as well as other solutions. You can think of integration with numerous apps that will coordinate all of them. That's where this may be going."

The end result could eventually be moving from product-centric to outcomes-based offerings.

"It's turning the current model or approach upside down. That frees us up from thinking just in terms of product portfolio and rather to desired outcomes," he said. Sanofi is investing \$248m in cash in Onduo

while Verily is committing an "equivalent" amount, he added.

Asked when Onduo might have its first product ready, Oelrich replied "We're aiming for a product within the next two to three years. That's in sharp contrast to our pharmaceutical research and development timelines of between five to ten years so this promises to be faster."

Regulatory approval time frames should not be too much of a problem either, he said.

"If you really link a medicine to a technology then there is a strong chance that you'll get a needed drug-type approval by the FDA. There is the chance they may want clinical studies before approval, but there are also digital solutions that don't require approvals what so ever."

The first proto-type product from Onduo "might involve integrating a pump, a constant glucose measuring system and a drug in a near autonomous system that optimizes insulin delivery. But that's up to Onduo," he said.

OTHER THERAPY AREAS?

The joined up approach could eventually be applied to other therapy areas.

"You could think of all kinds of therapy areas where this could also apply. The interesting part of diabetes is we have 400 million people out there that live day after day with the condition. But I can well imagine this thinking for other therapeutic areas as well," Oelrich said.

FOLLOWS GOOGLE / GSK PACT

In August, Google life sciences spinout Verily announced it was partnering up with GlaxoSmithKline PLC for a spinout venture focused on bioelectronic devices called Galvani Bioelectronics. Bioelectronic medicine is a new scientific discipline that seeks to treat a number of chronic diseases including diabetes, asthma, arthritis, and inflammatory bowel disease by using miniature devices implanted in the body that are able to modify the electrical signals of nerves in the body. ▶

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Heated Drug Pricing Debate Fanned By Election, Teva's Olafsson Says

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'I can't wait until it's over,' Teva's Generic Medicines CEO Sigurdur Olafsson said of the US Presidential election; then the current debate around drug pricing will return to a discussion of value, he predicted.

Teva Pharmaceutical Industries Ltd. Global Generic Medicines CEO Sigurdur Olafsson weighed in on the contentious drug pricing debate waging in the US, fueled most recently by the high cost of *Epipen*, attributing most of the "heated" discussion to the US presidential election.

The investor briefing Sept. 9 was a platform for management to outline the company's generics pipeline, portfolio and growth prospects now that Teva has completed the acquisition of Allergan PLC's generic drug business for \$40.5bn and the integration is underway.

But the topic of drug pricing was raised by analysts during the meeting. When asked how growing pressure on brand drug prices – specifically the common practice brand drug manufacturers employ of taking big price hikes on mature medicines or on drugs approaching the end of their patent protection – could impact pricing for future generic drug launches, Olafsson predicted that the fundamentals aren't going to change.

"The election is now two months away. I can't wait until it's over," he said. "Then, we can get to reality ... and we can go back to talk about the value that we bring to patients, both the specialty side and the generic side, because there's a tremendous value in many of the brand products."

Next year, Olafsson predicted pharmaceutical manufacturers might be more "careful" when it comes to drug pricing, but he doesn't anticipate sweeping changes longer-term.

LET'S KEEP GENERICS OUT OF THIS

The generics drug veteran also maintained that generic drugs should be kept out of discussions of pricing involving brand products. The perception that there has been significant generic price inflation is "simply wrong," he added. Every year for the last 10 years, price erosion in the generic drug market has been 2% to 7%, he insisted.

High drug prices are back in the media spotlight recently fueled by public backlash over the high cost of Mylan NV's *Epipen* (epinephrine), a commonly used drug to treat anaphylactic shock. The price of *Epipen* has increased more than 500% since 2009 to \$600.

US Presidential candidate Hilary Clinton highlighted *EpiPen* while unveiling a new proposal Sept. 2 to establish penalties for companies that raise drug prices by an unjustified amount.

On Sept 6, Allergan CEO Brent Saunders furthered the debate about how proactive drug manufacturers should be in the face of growing criticism by pledging to limit the company's price increases to once a year and only to low-to-mid single digits, or slightly above the current annual rate of inflation.

Saunders also vowed that Allergan will not engage in taking

major price increases as products near patent expiration unless there are corresponding cost increases, a practice some generic drug manufacturers benefit from when they launch the first generic into the market.



SUPPORTING PLAYER IN EPIPEN CONTROVERSY

Teva is a supporting player in the *EpiPen* controversy because the company has been developing a generic version of the product that was sidelined by FDA. The company reached a patent settlement agreement with Mylan in 2012 to wait until mid-2015 to launch a generic, but the generic has yet to reach the market.

Teva received a complete response letter from FDA in March in regards to its application for a generic copy of *Epipen*, and the company hasn't revealed much in the way of details about the contents of the letter. One issue could be related to concerns about the device for injecting the epinephrine product and the potential for confusion with *EpiPen*'s more familiar injector.

Teva is partnered with Antares Pharma Inc. on the development of the device in the US.

Olafsson said FDA has been more responsive to Teva's request for a meeting following the media attention. "FDA has come back to us and we will have a meeting with them very, very quickly," he said. But despite the increased spotlight highlighting the need for more competition in the market, Olafsson said he still believes the earliest the company could get to market with a generic version of *EpiPen* is late 2017/early 2018.

"I simply haven't communicated enough with the FDA to change my opinion," he added. ▶

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Spectrum Failed To Heed FDA Advice On Apaziquone

Not unexpectedly, Spectrum Pharmaceuticals Inc. found itself on the receiving end of a negative FDA advisory committee review for its bladder cancer drug *Qapzola* (apaziquone) Sept. 14. But had the company heeded the advice received from FDA nearly four years earlier, or made that advice more clear to investors, it might not have gotten to this point. Spectrum argued its case for apaziquone's approval to FDA's Oncologic Drugs Advisory Committee on the basis of two negative pivotal studies and a post hoc, pooled analysis of the trial data, even though FDA specifically recommended against a new drug application filing based on such data in December 2012. The decision to move forward with an NDA submission contrary to FDA advice – the specific nature of which the company appears not to have fully disclosed following the 2012 meeting with the agency – could mean Spectrum will need to take steps to rebuild investor confidence as it moves forward with another Phase III study of apaziquone and prepares for regulatory milestones for other pipeline compounds. Spectrum is seeking approval of apaziquone for immediate intravesical instillation post-transurethral resection of bladder tumors (TURBT) in patients with non-muscle invasive bladder cancer (NMIBC); at the advisory committee meeting, the sponsor further narrowed the proposed indication to patients with low- and intermediate-risk disease.

sue.sutter@informa.com, 16 September 2016

Teva's Cubicin Authorized Generic Is First Rival To Merck's Brand

Teva Pharmaceutical Industries Ltd. has launched an authorized generic of Merck & Co. Inc.'s blockbuster injectable antibiotic *Cubicin* (daptomycin), the first rival that will compete with the brand in the US. The launch of the authorized generic, announced Sept. 15, comes two years earlier than Teva had originally expected to enter the market. The path was

Cokiera EU Withdrawal Signals Abbvie Betting On Glecaprevir/Pibrentasvir

AbbVie Inc. has effectively thrown in the towel on its *Cokiera* Hep C antiviral competing in Europe against Gilead Sciences Inc.'s Harvoni and Merck & Co. Inc.'s Zepatier and has instead signaled it will wait for the launch of its lower-priced next-generation combo glecaprevir/pibrentasvir (ABT-493/ABT-530) to make its mark there. In essence, pursuing *Cokiera*'s EU market authorization didn't make great financial sense for the US drug maker. That's seems the takeaway message from news AbbVie on Aug 3 told the European Medicines Agency's advisory Committee for Medicinal Products for Human Use (CHMP) that it wanted to withdraw an application for a EU marketing authorization for *Cokiera*, for the treatment of chronic hepatitis C. *Cokiera*, a once-daily, fixed-dose antiviral medicine containing the active substances dasabuvir, ombitasvir, paritaprevir and ritonavir, was to be available as tablets for treating adults with chronic hepatitis C, an infection of the liver caused by the hepatitis C virus. All four active substances in *Cokiera* are already available in authorized medicines for treating chronic hepatitis C in Europe and work in different ways. It was expected that combining the substances in a single tablet would make it simpler for patients to take their medicine. Asked why the drug's application was withdrawn, an AbbVie spokesperson said "the CHMP indicated that, for approval of this formulation, drug exposure data from an additional bioequivalence study, evaluating how the size of meals affects absorption of the medicines, would be necessary. This study would not be completed within our commercial timeframe and therefore we have chosen to withdraw the MAA for this specific product," the spokesperson added. The news did not come as a complete shock to some industry observers. "I'm not particularly surprised by the decision," said Michael Haydock, lead analyst at Datamonitor Healthcare. "While it is true that physicians and patients would prefer a once-daily option, in practice I don't think that the dosing schedule is what has prevented AbbVie capturing greater market share from Gilead. Pricing – or cost per cure – is really what has been driving prescribing trends given the shock payers have received in recent years from the massive cost burden of treatment, and based on its dominance of the EU market it seems Gilead has been largely willing to match any discounts offered." Haydock added.

sten.stovall@informa.com, 16 September 2016

made clear when the US Supreme Court declined earlier this year to review a 2014 lower court ruling that had invalidated patents protecting Cubicin in a patent infringement suit filed by Hospira Inc. (now owned by Pfizer Inc.). The 2014 ruling was a stunner at the time because it came just hours after Merck announced plans to buy Cubist Pharmaceuticals Inc. – the maker of Cubicin – for \$9.5bn., a valuation at which many investors balked. Cubicin was Cubist's primary revenue generator, bringing in \$1bn in sales in 2013, accounting for about 75% of the specialty pharma's sales at the time. The patent situation around Cubicin had

also been thought to be fairly secure, at least to Cubist's investors, since the company had previously negotiated a patent settlement agreement with Teva. Under the terms, the company agreed not to launch a generic until June 24, 2018 if Cubist gained a pediatric extension and not until Dec. 24, 2017 if not. Merck said it would appeal the decision and stood by its valuation of Cubist regardless of the outcome. The Delaware court ruling paved the way for generics to enter the market in June 2016, but Pfizer's generic hasn't launched yet.

jessica.merrill@informa.com, 16 September 2016

Business As Usual For Menarini Despite Managing Siblings' Fraud Sentence

Siblings Lucia and Alberto Giovanni Aleotti, respectively president and vice-president of Italian pharmaceutical company Menarini, have been sentenced for tax fraud by a court in Florence. Lucia Aleotti has resigned from the board of Farmindustria, Italy's industry association, but its president Massimo Scaccabarozzi declared his expectation that they would be cleared on appeal. The case is far from closed.

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Lucia Aleotti, president of Italian pharma company Menarini Group, and her brother Alberto Giovanni Aleotti, vice-president, have been found guilty by a court in Florence of tax fraud. The siblings have received sentences of 10 and a half years and seven and a half years, respectively, but it is questionable whether they will end up serving them. They were acquitted of other crimes including defrauding the Italian national health service by charging excessive prices, and a number of co-defendants were also found not guilty.

Menarini told *Scrip* that no Menarini company was involved in the alleged crime, and that it involved fiscal matters relating to the private estate of Alberto Aleotti, the siblings' deceased father and long-time chief of the company.

Menarini told *Scrip* that no Menarini company was involved in the alleged crime, and that it involved fiscal matters relating to the private estate of Alberto Aleotti

It also emphasized that there is a presumption of innocence even after the initial court ruling until the appeals process has been exhausted, something that could take years.

It said that it wasn't issuing an official statement because the case had not come to a final conclusion and the accusation that related directly to the company had been rejected. It did not respond immediately to questions over the continuing role of the Aleottis at the company, but there is no apparent indication that they will step aside from the management of the company that they also own.

FARMINDUSTRIA PRESIDENT SUPPORTIVE

Massimo Scaccabarozzi, president of the Italian industry association Farmindustria, remained loyal to the family that gave Farmindustria its founding president. He issued an official statement declaring that the association trusted that the siblings would be able to prove their innocence upon appeal, and that the company, an important part of Italy's heritage, would be able to continue on its course of international growth. Farmindustria confirmed that Lucia Aleotti had nevertheless resigned irrevocably from the association's 12-member committee of the presidency following the verdict. Her father was the first president of the association.

The Aleotti siblings intend to appeal the ruling, which was made in a Court of First Instance. The Italian system allows for three instances

in court proceedings. Defendants can appeal against a first instance ruling in the Court of Appeal once the reasons behind the first ruling are released after 90 days. The case may also proceed after the Court of Appeal to the Court of Cassation. The sentence issued by the Court of First Instance will not become effective until the following two instances have been concluded. The whole process may take several years, and Menarini points out that there are "numerous practical cases whereby sentences have been completely overturned and a conviction becomes an acquittal."



After taking over at the helm of Menarini in 1964 Alberto Aleotti transformed it into a major multinational firm, pushing for and taking advantage the introduction of new patent protection laws in Italy in the 1970s. He and his family also became the owners of Italy's biggest pharma company. Aleotti senior had his own brushes with the law. One fraud case around kickbacks was settled in 1994, while a second case, to which the current case is related, was brought by the Italian tax authorities in 2010. Aleotti Sr retired from Menarini in 2011, leaving his children in charge, and he died at the age of 91 in 2014.

Alberto Aleotti's widow Massimiliana Landini Aleotti was acquitted by the Florence court, along with Giovanni Cresci, Licia Proietti and Sandro Casini, who have held roles at the company.

The alleged criminality of its owner managers is not the only issue dogging Menarini. The company has seen its revenues declining in recent times as pricing pressures, notably in Europe, take their toll. It is positioned 34th in the *Scrip* 100 league table of the world's pharmaceutical industry by drug sales, and 45th by total revenue (\$4.5bn). It employs around 16,000 people and is present in about 130 countries. It has just completed a €60m investment in expanding facilities at its German business, Berlin-Chemie Menarini. ▶

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Pfizer Is Back In The CTLA-4 Game Via Pact With Oncolmmune

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Pfizer bought an option to license Oncolmmune's anti-CTLA-4 antibody ONC-392 five years after out-licensing its own internal candidate tremelimumab to AstraZeneca following a study failure.

Pfizer Inc. is returning to its cancer immunotherapy roots in a pact with Oncolmmune Inc. that will give the big pharma an option to license a preclinical anti-CTLA-4 monoclonal antibody. Pfizer agreed to pay \$250m in upfront and potential milestones for the option to license ONC-392, which could be less toxic than first generation CTLA-4s.

The deal is tantamount to Pfizer admitting it made a mistake out-licensing its own CTLA-4 inhibitor tremelimumab to AstraZeneca PLC in 2011. The question now is if Pfizer can use its improved immuno-oncology experience to right the wrong by developing a better product. A CTLA-4 inhibitor with less toxicity than existing drugs could become a central component in immuno-therapy regimens.

Years ago, when immuno-oncology was considered a long shot, Pfizer was neck and neck with Bristol-Myers Squibb Co. to bring the first CTLA-4 inhibitor to market for metastatic melanoma. But the Phase III trial testing tremelimumab was halted in 2008 after an interim analysis suggested the treatment

wouldn't improve survival and Pfizer eventually out-licensed the drug to AstraZeneca.

Meanwhile, Bristol's ipilimumab demonstrated a significant benefit in survival in registration studies and went on to become the blockbuster *Yervoy*; the agent has some immune-mediated toxicity issues on its own, but a new dosing regimen has helped and growth has been driven by combination use with Bristol's PD-1 blocker *Opdivo* (nivolumab) in melanoma. There are higher hopes for the duo in lung cancer.

The deal is tantamount to Pfizer admitting it made a mistake out-licensing its CTLA-4 inhibitor tremelimumab to AstraZeneca

The PD-1/L1 checkpoint inhibitors are expected to be the backbone of immuno-oncology combinations, but anti-CTLA-4 agents are also important players – and are less common.

Along with its PD-L1 drug durvalumab, tremelimumab is an integral part of Astra-

Zeneca's ambitions in immuno-oncology. It failed in a Phase III single agent trial, but AstraZeneca expects to have Phase III data on tremelimumab plus durvalumab in non-small cell lung cancer in 2017. The company previously has played up the potential for triple combinations across its portfolio.

While Bristol and AstraZeneca have been focusing intensively on the PD-1/L1 and CTLA-4 combination approach, two other leaders in the immune checkpoint space, Merck & Co. Inc. and Roche, haven't invested in a CTLA-4 blocker; the concern hasn't been efficacy, but the toxicity of the regimen.

A less toxic alternative could represent an important opportunity, however, and a point of differentiation for a late-comer like Pfizer. Oncolmmune said ONC-392 was identified using its propriety in vivo screening model and was designed to reduce immune-related toxicities while retaining potent anti-tumor immunity. Pfizer most likely has its eye on developing the drug in combination with its own PD-1 inhibitor avelumab, partnered with Merck KGAA.

Pfizer's experience in immuno-oncology has advanced considerably in the last eight years since the tremelimumab failure. Not only is Pfizer planning to file avelumab with FDA this year for the treatment of Merkel cell cancer, but the company has developed a robust immuno-oncology assets that will be tested in combinations.

Under the deal with Oncolmmune, Pfizer plans to evaluate ONC-392 up until an undisclosed but agreed upon time before determining whether to exercise its option. The deal includes ONC-392 and any other CTLA-4 antibodies developed by Oncolmmune. If Pfizer exercises its option, the big pharma would be responsible for the development and commercialization of the program.

Oncolmmune, based in Rockville, Md., is a privately held biopharma company focused on the development of treatments for cancer and autoimmune disease. Its lead candidate is a prophylactic treatment of acute graft versus host disease entering Phase II. ▶

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Could \$639m Vitae Buy Give Allergan A New Autoimmune Focus?

Allergan's \$639m purchase of Vitae Pharmaceuticals gives the company an oral drug for a key dermatology indication and the potential to address other autoimmune disorders consistent with its focus on seven key therapeutic areas.

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The \$639m acquisition of Vitae Pharmaceuticals Inc. at first glance seems to be an obvious buy for Allergan PLC, since dermatology is one of the company's seven key therapeutic areas, but Vitae's lead drug candidate could open the door to new inflammation and autoimmune disease programs adjacent to Allergan's existing areas of interest.

Vitae's lead drug candidate is the retinoic acid receptor-related orphan receptor gamma (RORγt) inhibitor VTP-43742, which is in Phase II for psoriasis and autoimmune disorders. By inhibiting RORγt, the oral drug blocks production of interleukin-17 (IL-17) – the target of two recently approved, potential blockbuster biologics from Novartis AG and Eli Lilly & Co. – and it significantly decreased psoriasis severity after four weeks of treatment in Phase IIa clinical trial results revealed earlier this year.

Fort Washington, Pennsylvania-based Vitae also has a topical treatment – VTP-38543, a Liver X Receptor beta (LXRβ) selective agonist – in Phase IIa for atopic dermatitis. It's the only therapy targeting LXRβ in the clinic, according to Biomedtracker's database, and it's one of only two LXR agonists in development; Rgenix Inc. has a program targeting LXR alpha and beta in preclinical cancer studies.

"This deal absolutely fits within one of our key therapeutic areas," Allergan chief research & development officer David Nicholson said in an interview, noting that dermatology/aesthetics is one of the company's largest therapeutic areas in terms of the size of the markets pursued and the number of programs in Allergan's R&D pipeline.

Nicholson also noted, however, that Vitae's focus on autoimmune disorders is an "adjacency" to dermatology and to some of Allergan's other therapeutic areas. Inflammation is a factor in gastrointestinal diseases like irritable bowel syndrome and ocular conditions for which the company is studying treatments in its ophthalmology therapeutic area.

"Yes, [autoimmune disease] is an adjacency, but it's absolutely our strategy to look at adjacencies around the areas we are already interested in," Nicholson said. "From our perspective, Vitae totally fits into our core strategy."

The inflammation seen in psoriasis and other autoimmune disorders is caused by lymphocytes called Th17 cells, which produce the inflammatory cytokine IL-17. Therapies targeting RORγt, thereby modulating IL-17, should be active in a range of disorders where Th17 is the driving force, so Allergan "will be evaluating these other disorders," Nicholson said.

CONTOURING A DRUG DISCOVERY NICHE

The pharma company's R&D chief noted that there were many compelling aspects to Vitae's portfolio, including its drug discovery platform known as Contour.

The structure-based drug design platform builds 3D images of targeted proteins and potential drug candidates to determine how and where the medicine forms the best bond within the hills and valleys of

the target. Vitae uses the technology to develop drugs that overcome potency, selectivity, pharmacokinetics or patentability challenges.

The platform generated VTP-43742 and the preclinical RORγt inhibitor VTP-45489 for autoimmune diseases, which may offer oral alternatives to new injectable monoclonal antibodies that block IL-17 – Novartis's *Cosentyx* (secukinumab) and Lilly's *Taltz* (ixekizumab).

The promise of RORγt inhibition has generated a spate of dealmaking activity, but VTP-43742 remains the most advanced program for the drug target, according to Biomedtracker.

"Other companies have looked at the efficacy of IL-17 monoclonal antibodies and have seen interesting activity," Nicholson said. "But these [Vitae] compounds are orally active and we are of the opinion that orally active drugs will ultimately trump injectable monoclonal antibodies in the marketplace."



He indicated that Vitae's four-week Phase IIa data made a compelling case for VTP-43742, which could make the drug competitive with the IL-17 inhibitors.

As for Vitae's topical treatment VTP-38543 for mild-to-moderate atopic dermatitis, which is in a slightly earlier stage of Phase II development than VTP-43742, anti-LXR molecules have shown activity in inflammation related to skin disorders in animal studies.

"LXR compounds hopefully will show anti-inflammatory activity and healing properties, both of which should be effective in atopic dermatitis. We're quite excited to have the opportunity to continue the development of this compound," Nicholson said.

Vitae at one time also had hoped to develop a beta secretase (BACE) inhibitor for Alzheimer's disease, but the company's partner Boehringer Ingelheim GmbH dropped the program in late 2015.

Vitae went public at \$8 per share in September 2014 and Allergan's \$21 per share acquisition price – showing the pharma's enthusiasm for RORγt and Contour – almost beats the biotech company's all-time high of \$22.01 in December 2014.

The stock suffered since then from the loss of Boehringer as a partner in Alzheimer's disease and from speculation that there were problems with the Phase IIa study for VTP-43742, but it more than doubled to close at \$20.82 on Sept. 14 based on the Allergan transaction. ▶

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Imetelstat Study Blip Beats Geron's Shares Down

Shares in Geron dropped by nearly 20% to \$2.30 on NASDAQ on Sept. 12 following interim clinical data for its lead product, the anticancer imetelstat, from trials conducted by its partner Janssen. While the studies – IMbark and IMerge – are both still ongoing investors were spooked by the news that Janssen was going to drop the lower dose arm in one of them, IMbark, in myelofibrosis. Imetelstat is Geron Corp.'s only real pipeline asset. Janssen R&D LLC is conducting the two late-stage trials of the telomerase inhibitor following a licensing deal signed in November 2014. The deal was a boon for the Menlo Park, California-based Geron, coming just weeks after the FDA lifted a clinical hold on the company's Phase II program for the product. The hold was put in place earlier that year following concerns over the potential for liver injury in March that year. But better news came in November when an investigator-sponsored study showed imetelstat produced four complete remissions and one partial remission in myelofibrosis patients. Telomerase has long been a target in cancer drug development but has produced little fruit so far. In South Korea a vaccine based on telomerase peptides was launched by Samsung in 2015 for advanced/metastatic pancreatic cancer and some other vaccine-type products are in early stage development. The first-in-class imetelstat is a specially designed and modified short oligonucleotide, which targets and binds directly with high affinity to the active site of telomerase.

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14 September 2016

Intarcia Raises \$215m As NDA For ITCA 650 Slips To Fourth Quarter

Intarcia Therapeutics Inc. keeps slipping behind schedule in its quest to submit a new drug application (NDA)

Amgen-Dr Reddy's Build On India Alliance

Dr. Reddy's Laboratories Ltd. has expanded its collaboration with Amgen, gaining rights to market and distribute the Amgen therapies *Xgeva* (denosumab), *Vectibix* (panitumumab) and *Prolia* (denosumab) on the Indian market. *Xgeva* and *Vectibix* were previously marketed by GlaxoSmithKline Pharmaceuticals Ltd. in India, though last December, Amgen Inc. said that it had re-acquired all product rights to *Xgeva*, *Vectibix* and *Prolia* from GSK in 48 countries in Asia, South America, Europe, Australia and other regions throughout the world. The expanded alliance with Dr Reddy's appears to reflect Amgen's recalibrated India plans in this backdrop. *Vectibix* was launched by GSK India in 2014-15, while the British multinational also had in place programs such as "Swasti" aimed at improving patient access for products like *Xgeva* (launched in June 2013) in the country. It's not immediately clear how such initiatives would be transitioned under the alliance with Dr Reddy's. GSK India could not immediately be reached for a comment. *Xgeva* is approved in India for the prevention of skeletal related events in patients with advanced malignancies involving bone, while *Prolia*, which contains the same active ingredient as in *Xgeva*, is approved in India for treatment of post-menopausal women with osteoporosis at high risk for fracture and also for treatment of increased bone mass in men with osteoporosis. *Vectibix* is approved in India for patients with certain types of metastatic colorectal cancer. The latest product additions to the Amgen-Dr Reddy's alliance build on the duo's 2015 collaboration under which Dr Reddy's was to execute a "full range" of regulatory and commercial services to seek approval and launch Amgen's *Kyprolis* (carfilzomib), *Blinicyto* (blinatumomab) and *Repatha* (evolocumab) in India.

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for the once- or twice-yearly diabetes drug candidate ITCA 650 to the US FDA, but that hasn't hampered the private company's ability to raise money as new and prior investors recently supplied \$215m in equity. Boston-based Intarcia said in May when it reported additional positive results from its four-study Phase III program for ITCA 650 – and raised \$75m in new debt – that it would submit its NDA by the end of the third quarter of 2016. However, the company revealed on Sept. 15 that after pre-NDA discussions with the FDA, it will submit the application within the next 30 to 60 days, meaning somewhere between early and mid-fourth quarter of this year. That news was tucked into its disclosure of significant new and anticipated funding. ITCA 650 is a matchstick-sized osmotic pump in-

serted under the skin to provide continuous delivery of the GLP-1 receptor agonist exenatide as a treatment for type 2 diabetes; the device would be replaced every six or 12 months. It bested placebo and Merck & Co. Inc.'s oral DPP-4 inhibitor *Januvia* (sitagliptin) in Phase III studies, but when Intarcia reported top-line data versus Merck's blockbuster oral drug in 2015 the company said it would submit an NDA during the first half of 2016. The successful conclusion of a cardiovascular outcomes study needed to support the NDA filing was unveiled in May along with the \$75m loan commitment from Silicon Valley Bank and MidCap Financial to support manufacturing scale-up for ITCA 650 commercialization.

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16 September 2016



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Merck/Pfizer's Latest SGLT-2 Data Support Attractive Ertugliflozin/Januvia Combo

Overall, data suggest a profile similar to J&J's market-leading Invokana, but analysts still see room for a new entrant to the anti-SGLT-2 class in type 2 diabetes.

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Results from the VERTIS SITA2 study support a combination of Merck & Co. Inc./Pfizer Inc.'s SGLT-2 inhibitor ertugliflozin with the first-in-class DPP-4 inhibitor *Januvia* that could prove attractive in type 2 diabetes, despite the crowded nature of the market.

Merck and Pfizer announced positive results from the study at the European Association for the Study of Diabetes meeting in Munich Sept. 15. In the study, the drug as an add-on therapy to *Januvia* (sitagliptin) and metformin met the primary endpoint of A1c reduction after 26 weeks in type 2 diabetes, with similar rates of side effects to a placebo arm.

Overall, the data suggest a profile fairly similar to Johnson & Johnson's market-leading *Invokana* (canagliflozin), at least on common measures, Biomedtracker analyst Peter Chang told *Scrip*.

The VERTIS SITA2 study is one of nine Phase III trials in 12,600 diabetes patients. The EASD release follows presentation of positive results from the VERTIS MONO monotherapy study and VERTIS FACTORIAL, which also tested ertugliflozin with *Januvia*, at the American Diabetes Association annual meeting in June.

Merck and Pfizer are set to file ertugliflozin with FDA along with two fixed-dose combination applications – with *Januvia* and with metformin – by the end of the year.

If approved, ertugliflozin would become the fourth in the SGLT-2 class, after J&J's *Invokana*, AstraZeneca PLC's *Farxiga* (dapagliflozin) and Boehringer Ingelheim GMBH/

Eli Lilly & Co.'s *Jardiance* (empagliflozin).

However, in a dispatch from the meeting, Datamonitor Healthcare analyst Aine Kyle commented that there still appears to be room for a fourth SGLT-2 inhibitor, as a means of providing more choices to physicians and patients and to allow for potential differentiation to emerge in the class over time.

A fixed-dose combination of an SGLT-2 inhibitor with the popular first-in-class *Januvia* should also be “very attractive,” Kyle said.

As the first and leading DPP-4 inhibitor, *Januvia* is familiar and well-liked by prescribers, Biomedtracker's Chang noted. Furthermore, some DPP-4 inhibitors, namely AstraZeneca's *Onglyza* (saxagliptin) and Takeda Pharmaceutical Co. Ltd.'s *Nesina* (alogliptin), have labels with warnings about heart failure whereas *Januvia* and Boehringer/Lilly's *Trajenta* (linagliptin) do not.

A CLOSER LOOK AT THE DATA

The three-arm VERTIS SITA2 study randomized 463 participants to a dose of either 5 mg or 15 mg daily of the test drug on top of *Januvia* and metformin, versus placebo with the same background therapy.

Both doses of ertugliflozin (5 mg and 15 mg) were associated with significantly greater reductions in A1c at 26 weeks of 0.69% and 0.76%, respectively, compared with placebo, Merck and Pfizer reported.

The reductions were on the order of what is seen with *Invokana*, Chang commented.

Adding ertugliflozin also meant a higher number of people reaching A1c goals compared to placebo, a secondary endpoint.

The patients on triple therapy were more likely to lose weight – a known, desirable class effect – compared to placebo, with statistically significant placebo-adjusted losses of 4.4 pounds and 3.7 pounds for the 5 mg and 15 mg doses, respectively. The weight changes were in line with what would be expected for the class.

Rates of adverse events were generally similar. There was one serious adverse event, a transient ischemic attack, that was deemed related to drug. “Given the single patient, unless it seemed related due to some issue like volume loss, it could well be a chance finding,” Chang concluded.

Rates of genitourinary infection were similar to what has been seen with *Invokana* (see table).

The rate of mycotic infections was actually lower in the VERTIS SITA2 combination study compared to the VERTIS MONO monotherapy study, but this was “probably due to random variability between trials,” Kyle said. There were no cases of acute kidney injury or diabetic ketoacidosis in the study, but Chang notes that it was a moderately-sized trial and that ketoacidosis has been an issue with patients on insulin, which was not included in the study protocol.

All SGLT-2 inhibitors have labels warning of ketoacidosis and serious urinary infections. In June, FDA strengthened label warnings for acute kidney injury for *Invokana* and *Farxiga*, but not *Jardiance*. *Jardiance* also has the advantage of having demonstrated a benefit in a cardiovascular outcomes trial. ▶

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VERTIS SITA2: Highlights Of Adverse Event Rates

ADVERSE EVENT	5 MG ERTUGLIFLOZIN WITH JANUVIA AND METFORMIN	15MG ERTUGLIFLOZIN WITH JANUVIA AND METFORMIN	PLACEBO WITH JANUVIA AND METFORMIN
Genital mycotic infection in men	4.9%	3.7%	0
Genital mycotic infection in women	8%	12.7%	1.9%
Urinary tract infection	2.6%	4.6%	2%
Symptomatic hypoglycemia	3.8%	0.7%	2.6%
Hypovolemia	0.6%	0	0.7%

EU Approval Recommendation Secures Ibrance Domination

The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has recommended that Pfizer Inc.'s *Ibrance* (palbociclib) be granted marketing authorization in the EU for the treatment of women with hormone receptor-positive, human epidermal growth factor receptor 2-negative (HR+/HER2-) locally advanced or metastatic breast cancer. If approved, Ibrance would be the first cyclin-dependent kinase 4/6 (CDK 4/6) inhibitor to be approved in Europe. The CHMP's positive opinion is for Ibrance to be used in combination with an aromatase inhibitor, as well as in combination with fulvestrant in women who have received prior endocrine therapy. "The positive CHMP opinion signals impending approval in the EU. As the first CDK4/6 inhibitor to reach the EU market, Pfizer can establish Ibrance as the leading therapy in HR+/HER2-breast cancer much as it did in the US," Datamonitor Healthcare analyst Zachary McLellan tells *Scrip*. However, he notes that the CHMP panel recommended Ibrance for locally advanced or metastatic patients in combination with an aromatase inhibitor as initial treatment and with *Faslodex* in previously treated patients.

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GSK Shingles Vaccine Adds Evidence It Can Outperform Merck's Zostavax

Chances GlaxoSmithKline PLC can turn the tables on rival Merck & Co. Inc. with its vaccine against varicella zoster, the virus that causes shingles, were strengthened by confirmation GSK's *Shingrix* achieved high efficacy in adults aged 70 years and over in a pivotal Phase III trial. Results from its Phase III ZOE-70 trial assessing its shingles vaccine can-

ECTRIMS 2016: What Future For Merck KGaA's Cladribine?

The 32nd Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS 2016) in London is bearing witness to the reappearance of Merck KGaA's oral induction therapy cladribine, with an ample number of presentations covering the drug's safety and efficacy. And while new safety data in particular might help the drug finally gain approval, the changes in the MS market in recent years mean higher commercial hurdles. Most of the ECTRIMS presentations include analyses of data from already-known trials, namely the Phase III CLARITY, CLARITY Extension, and ORACLE-MS studies, as well as the Phase II ONWARD study. In addition, there is an integrated safety analysis from cladribine's multiple sclerosis (MS) development program, which notably includes data from the ongoing PREMIERE registry and appears supportive of the drug's risk-benefit profile, especially with regards to the risk of neoplasms. As cladribine's potential risk of malignancy was one of the chief reasons behind the European Medicines Agency's (EMA's) previous refusal to approve, the positive data presented at ECTRIMS 2016 are certainly promising. However, approval is far from a shoo-in, not least because of the ongoing lack of direct head-to-head trials involving cladribine versus other MS drugs. If Merck does succeed in convincing European regulators this time around, cladribine could reach the market by October 2017. However, it hardly seems positioned to claim a large share of the MS market. The current competitive landscape is very different to the one that existed in 2010 at the time of cladribine's initial rejection. Numerous drug approvals have occurred in MS in recent years – there are now three oral disease-modifying therapies (DMTs) available: Novartis AG /Mitsubishi Tanabe Pharma Corp.'s *Gilenya* (fingolimod), Biogen Inc.'s *Tecfidera* (dimethyl fumarate), and Sanofi's *Aubagio* (teriflunomide) – diminishing any novelty around cladribine's oral formulation. The recent approval of Sanofi/Bayer AG's *Lemtrada* (alemtuzumab) also means that there is already an effective induction therapy on the market, once again weakening another of cladribine's key competitive advantages. Finally, Roche's *Ocrevus* (ocrelizumab) is poised to further revolutionize the treatment landscape in 2017 as a high-efficacy and well-tolerated B-cell-targeting drug that is effective across a range of MS subtypes.

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didate in adults aged 70 and over were published in the *New England Journal of Medicine* Sept. 14. Promising headline results from the study were initially reported in October 2015, prompting analysts to predict GSK has a potential blockbuster on its hands. Based on the latest results and the previously reported ZOE-50 data in those aged 50 or older, GSK says it expects to start submitting regulatory applications for the candidate vaccine for the prevention of shingles in people 50 years and above later this year. It hopes to launch the vaccine globally in 2017. Merck's *Zosta-*

vax (zoster vaccine live) has been on the market for five years, but limited efficacy especially in older adults has curbed its revenue. Launched in 2011, *Zostavax*'s sales fell 2% to \$749m in 2015. Some analysts note that *Shingrix*'s higher efficacy comes at the cost of a higher shot burden, in that *Shingrix* requires two shots spaced two months apart versus *Zostavax*'s single shot regimen, raising the question of whether compliance would be adequately maintained in this patient group.

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Government Partnerships And Better Payer Engagement: Janssen's Plan For Middle Eastern Growth

Unexpected events like low oil prices and political unrest have made for a very challenging business environment in the Middle East and North Africa and led to a drop in growth. But Khaled Mansour, head of market access and external affairs EMEA Emerging Markets for Janssen, explains how with government partnerships the company plans to build up business from a new baseline.

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First the Arab Spring brought political unrest to the Middle East, and then oil prices took an unexpected plunge, contributing to a decline in the growth of the pharmaceutical market. But Janssen Pharmaceuticals Inc. has a plan, explains Khaled Mansour, head of market access and external affairs EMEA Emerging Markets. The company aims to build business from a new baseline through government partnerships and better engagement with payers in different "funding pools."

Annual growth in the Middle East and North Africa (MENA), worth around \$27bn, is down from a historical 9-12% CAGR to around 6% CAGR, says Mansour. Times have been very challenging. The dip in oil prices means that some governments have had to rein in spending, reduce purchases, delay payments and downsize formularies. "The challenges started really by the end of 2015 and this year we expect big challenges across oil dependent markets, especially Saudi Arabia. But we also expect the market to gradually recover, we expect a new, lower baseline for the business to grow from" he says.

Saudi Arabia, Egypt and Algeria, make up 45% of the market in dollar value. Next come the United Arab Emirates, Lebanon, Iraq, Morocco and Jordan then remaining Gulf Cooperation Council countries Kuwait, Qatar, Bahrain and Oman. However, Mansour emphasizes that Janssen wants to bring its innovative products to every market, not just the most lucrative ones. "Our key guiding principal is to understand the priorities for governments across the region, then we fit our portfolio and our capabilities to these priorities." To this end, partnering with local governments is a key strategy for the company, and happily, governments in the region seem willing to collaborate. "They listen to us and partner with us much better than in other places. That's a big plus for the region." Mansour points to Egypt as an example of how they can work. Hepatitis C is a big problem in Egypt where the prevalence is almost ten times higher than the global average. Janssen is one of the companies behind a revolution in treatment to potentially cure the disease and drugs like Olysio (simeprevir) may promise big long-term savings, but the treatments come at a high and often prohibitive price. However, after identifying hepatitis C as a key priority for the Egyptian government, the company lowered Olysio's price "significantly" to help treat as many patients as possible. Last year the agreement meant that the Egyptian government could treat some 50,000 hepatitis C patients with the drug. Janssen wanted to contribute to solving a national problem, but the Olysio deal also made good business sense. "Partnering with the government in such a critical disease area helps us to positively build on that and get faster access for other products for other diseases." Relations with the Egyptian government are now

far better than they were and the company now has opportunities for other, "more commercially sound" partnerships in other disease areas. Right now the focus is on bringing Janssen's immunology and oncology portfolio to more patients in Egypt.

Similarly, J&J (Janssen's parent company) is working with authorities in Saudi Arabia and the UAE to work out how the J&J companies can help tackle diabetes. Diabetes is a major problem in the Gulf region where the incidence is triple the global level, says Mansour. Talks are still ongoing, but Mansour says Janssen will likely supply the medicines, while its sister companies can supply diagnostics, equipment for surgery and patient education.

Improving access to Janssen's innovative portfolio, according to Mansour, is also "a matter of fitting the portfolio to the funding pool." There is a variety of customers and funding pools across the region. Some markets are driven by private payers, for example Egypt, where private payers – largely out of pocket – make up 80% of the market. The health insurance industry is growing too across the region. Meanwhile, in the Gulf countries, 70% of the market is funded by public payers. Similarly, public payers dominate in Algeria, other Arab countries and Morocco. Public payments come in different forms, some governments, for example, in Saudi Arabia and the Gulf favor purchasing mainly through tenders, while others, like in Algeria operate reimbursement schemes similar to the ones in Europe and reserve tenders for highly specialized products. Mansour says Janssen is starting to create strategies to "address each of these funding pools to create accelerated access to patients." He adds that Janssen's newer, innovative products do better in the Gulf or Algeria where public payers are better able to afford new treatments for their populations, while the firm's heritage portfolio is doing better in Egypt. "The main challenge therefore is how to bring innovative products for treating more serious diseases to countries like Egypt where funding is mainly out of pocket."

One big hurdle for Janssen's mission to bring innovative drugs to the region is the regulatory processes. The markets have their own procedures, which can be long and complicated, and even after EU approval it can still take more than three years to register and launch a product in some countries, he explains. To improve matters, Janssen, along with other pharma companies, is working with regional governments to get innovation to the market faster by improving regulatory frameworks.

Collective efforts are going well, he says. PhRMA, the Pharmaceutical Research and Manufacturers of America, has a well-established presence in the MENA region and under the umbrella of the association, the industry is in continuous discussions with regulators from across the region, says Mansour. ▶

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Stockwatch: Pandora's Interim Analysis

ANDY SMITH

The Medicines Company, Amarin and Geron have all reported interim analyses for clinical studies recently and investors have been left disappointed. Were we better off without the interim analysis?

I was once on a teleconference for middle managers of one big UK pharmaceutical company that was merging with another while the chair of R&D explained the competitive reasons why neither company could look into the box of R&D assets of the other before the merger completed. One wag speculated at the potential for surprise if, when the companies were finally able to look into each other's R&D boxes, both were found to be empty. Investors in a number of biotechnology companies may have had the same sinking feeling in recent weeks as the interim analyses of clinical trials were announced. I was left wondering whether we were better off in the days before the interim analysis.

MEDICINES COMPANY DISAPPOINTS

The Medicines Company provided an update on its dyslipidemia programs that included the planned interim analysis of the MILANO-PLOT Phase I/II study of MDCO-216 (Apo-A1 Milano) in the first 40 of 120 acute coronary syndrome patients. The independent data and safety monitoring board (IDSMB) recommended that the study continue because the pre-defined upper boundary for efficacy had not been met. The share price of The Medicines Company finished down about 2.5% on the day of the announcement and has not regained the dizzy heights of the previous day.

Clearly investors were disappointed as the concept of the interim efficacy analysis is that if efficacy similar to that shown in an earlier study is seen in a larger number of patients, the study can be stopped as it would not be ethical for patients to receive placebo and the company can proceed to the next stage. The analysts from Citigroup pointed out that the efficacy bar in the MILANO-PLOT study was slightly higher than reported in a previous 2003 study because the drug purity and the enrolment criteria had been improved since 2003. The implica-

tion being – as with all interim efficacy analyses – that all things being equal an active drug should have resulted in an early study stop for efficacy. In addition, company managements would not set wildly unrealistic efficacy bars just to entice shareholders into the stock in the hope of a level of efficacy that was unlikely to be achieved.



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Adding to investors' disappointment must have also been the thought that it may not now have been only the rumored manufacturing issues that led Pfizer Inc., – which acquired Esperion Therapeutics Inc. for \$1.3bn in 2003 largely for Apo-A1 Milano – to sell the product on to The Medicines Company for just \$10m plus milestones in 2009. In any event, the failure to halt the MILANO-PLOT study on efficacy grounds on its first interim analysis was probably not a good sign.

Previous clinical failures in studies that have involved perhaps aspirational interim analyses have left a bad taste in the mouths of investors. It is impossible to wipe from the collective memory of UK small cap investors the failure of Antisoma PLC's ASA404 at the first interim analysis in the Phase III NSCLC program.

Then there was the catalog of events that started with the continuation after the first interim review of Sunesis Pharmaceuticals Inc's Phase III VALOR study of Qinprezo (vosaroxin) in acute myeloid leukemia which prompted about a 50% increase in patient numbers. Then after further drawn-out interim safety and efficacy reviews, an extension of the study and everything short of extending animal sacrifice beyond the preclinical phase and distributing Qinprezo-branded lucky rabbits' feet to the IDSMB, VALOR failed.

The 140% share price appreciation over the last six months for Amarin Corp. PLC (against an 18% increase for the NASDAQ Biotech Index) was almost certainly due to

the anticipation of an early halt after 60% of the events due to efficacy at the interim analysis of its REDUCE-IT cardiovascular outcomes study of Vascepa (icosapent ethyl). With the announcement last week and the associated disappointment that the study will continue as planned, that share price performance has started to bleed away. While Amarin had been up-front with the disclosure that it expected the study to run until completion through both interim analyses, the share price volatility demonstrates that when presented with the possibility of a positive event, and despite most drugs failing in development, many investors expect the best outcome.

The negative responses to recent interim analyses do not mean that these analyses should be avoided since clinical studies should be stopped on safety grounds at any time. It would probably be better for neither the existence nor the result of an interim analysis to be publically disclosed unless it resulted in a material event. Unfortunately for Geron Corp., such an event occurred last week when following an interim analysis by its partner Johnson & Johnson, the lower dose of its telomerase inhibitor imetelstat in myelofibrosis was dropped on futility grounds.

While there are also ethical arguments for stopping clinical trials early for the much rarer positive efficacy grounds, perhaps those reviews should also remain confidential as similar events at Orexigen Therapeutics Inc. and Intercept Pharmaceuticals Inc. have come back to haunt for efficacy and safety reasons, respectively.

The Magna Biopharma Income fund holdings include Pfizer

Andy Smith is chief investment officer of Mann Bioinvest. Mann Bioinvest is the investment adviser for the Magna BioPharma Income fund which has no position in the stocks mentioned, unless stated above. Dr Smith gives an investment fund manager's view on life science companies. He has been lead fund manager for four life science-specific funds, including International Biotechnology Trust and the AXA Framlington Biotech Fund, and was awarded the Technology Fund Manager of the year for 2007. ▶

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



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Late-stage clinical developments for the week 9 September - 15 September 2016

LEAD COMPANY	PARTNER COMPANY	DRUG	INDICATION	MARKET
REGULATORY APPROVAL				
Ipsen	Exelixis Inc.	<i>Cabometyx</i> (cabozantinib)	renal cell cancer	EU
Aralez Pharmaceuticals Inc.	-	<i>Yosprala</i> (aspirin and omeprazole)	secondary cardiovascular disease prevention	US
Merck & Co. Inc.	Samsung Bioepis Co. Ltd.	<i>Brenzys</i> (etanercept)	ankylosing spondylitis, rheumatoid arthritis	Canada
SUPPLEMENTAL REGULATORY APPROVAL				
Shire PLC	-	<i>Cuvitru</i> (IgG) sc 20%	primary immunodeficiency	US
GlaxoSmithKline PLC	-	<i>Prepandrix</i>	pandemic flu vaccine	US
Eisai Co. Ltd.	-	<i>Kisplyx</i> (lenvatinib)	advanced renal cell carcinoma	EU
REGULATORY FILING ACCEPTED				
BioMarin Pharmaceutical Inc.	-	<i>Brineura</i> (cerliponase alfa)	neuronal ceroid lipofuscinosis (CLN2 disease)	US
ORPHAN DRUG DESIGNATION				
Boehringer Ingelheim GMBH	-	<i>Ofev</i> (nintedanib)	systemic sclerosis (scleroderma)	US, EU
FAST-TRACK STATUS				
Aptinyx Inc.	-	NYX-2925	neuropathic pain	US
Tesaro Inc.	-	niraparib	ovarian, fallopian tube or primary peritoneal cancer	US
REGULATORY FILING				
GlaxoSmithKline plc	Janssen Biotech NV	sirukumab, sc	active rheumatoid arthritis	EU
Janssen-Cilag International	-	darunavir, emtricitabine, cobicistat, tenofovir alafenamide	HIV-1 infection	EU
Repros Therapeutics Inc.	-	enclomiphene	secondary hypogonadism	EU
ROLLING NDA FILING INITIATED				
Tesaro Inc.	-	niraparib	ovarian, fallopian tube, primary peritoneal cancer	US
REGULATORY REVIEW EXTENSION				
Lexicon Pharmaceuticals Inc.	Ipsen	telotristat etiprate	neuroendocrine tumors	US
SPECIAL PROTOCOL ASSESSMENT AGREEMENT				
Array BioPharma Inc.	Pierre Fabre Group	encorafenib, cetuximab and binimetinib	colorectal cancer	US
PHASE III TRIAL INITIATION				
Innovent Biologics Inc.	-	adalimumab biosimilar	ankylosing spondylitis	China

Source: Informa Pharma Intelligence's Biomedtracker

Biotech Moderna Therapeutics has appointed **Melissa J. Moore** chief scientific officer of Moderna's mRNA research platform – effective Oct. 3, 2016. Moore is currently a member of Moderna's scientific advisory board and joins the company from the University of Massachusetts Medical School (UMMS) where she is currently professor of biochemistry & molecular pharmacology, Eleanor Eustis Farrington chair in cancer research and investigator at the Howard Hughes Medical Institute (HHMI). She is also a founding co-director of the RNA therapeutics institute (RTI) at UMMS.

Synlogic has added executives to its management team with **Todd E. Shegog** having been appointed chief financial officer (CFO); **Aoife M. Brennan** appointed chief medical officer; **Caroline B. Kurtz** head of translational sciences and product development and **Richard M. Schwartz** senior vice president, process development and manufacturing. Shegog was recently senior vice president and CFO at Forum Pharmaceuticals and prior to this, he was the senior vice president and chief financial officer of Millennium Pharmaceuticals Inc., now Takeda Oncology. Brennan joins Synlogic from Biogen where she held various roles, the most recent being vice president and head of the rare disease innovation unit. Prior to this,

Brennan was director of clinical development at a start-up biotech, TolereX. Previously Kurtz was vice president and GC-C platform lead at Ironwood Pharmaceuticals and prior to this she was director of infectious diseases at GellTex/Genzyme. Schwartz is currently the chief of the Vaccine Production Program (VPP) at the Vaccine Research Center (VRC) at the NIAID/NIH. Previously, he was the senior director of process and manufacturing sciences at MedImmune Vaccines.

GlaxoSmithKline's former vice president and site director, **Randy J. Maddux** has joined Aptevo Therapeutics Inc. as senior vice president, operations. He brings over 30 years' biopharmaceutical operations experience and has served in various roles supporting the licensure and launch of several biopharma products including Avonex, Tysabri, Benlysta and Raxibacumab. Prior to GSK, Maddux was vice president of manufacturing operations at Human Genome Sciences and prior to this he held various leadership roles in operations and quality at Biogen and Glaxo.

Exco InTouch has named **Steve Powell** chief operating officer and president and was previously executive vice president at a top 5 clinical research organization (CRO) where he managed a global team. He has 25 years' experience in the healthcare sector with a focus

on operational and technology growth in the CRO and pharma/biotech markets.

Craig Millian has joined **EMD Serono**, the biopharmaceutical business of **Merck KGaA**, Darmstadt, as senior vice president, neurology and immunology. Millian joined EMD Serono in 2010 to lead the fertility and endocrinology marketing team and most recently he was the senior vice president, head of US fertility and endocrinology. He was previously vice president, commercial at Vertex and prior to this he held commercial leadership roles at Pfizer and Sanofi. **Drew Young** has been appointed general manager and managing director, Merck KGaA, Darmstadt, Germany, Biopharma, Australia & New Zealand. Previously Young was senior vice president, neurology and immunology for EMD Serono and joined the company in 2014.

The Swiss biotech company **Novimmune** has appointed **Sven Zimmerman** chief financial officer (CFO) and **Mylène Fleurant** global head of quality. Zimmerman previously was CFO at Auris Medical AG and PregLem SA and prior to this he was European Biotech analyst at UBS Investment Bank. Before joining Novimmune, Fleurant was head of quality affairs at Alvotech and she also spent 10 years as region head quality assurance Europe for Novartis Pharma.

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