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Another Alzheimer's Failure: Crenezumab Bites The Dust

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Roche is discontinuing two Phase III clinical studies of crenezumab after an independent interim analysis concluded the anti-beta amyloid monoclonal antibody is unlikely to meet the studies' primary endpoints, news that continues a long-line of clinical trial disappointments in this therapeutic sector.

Crenezumab was being developed in collaboration with the originator, the Swiss biotech, **AC Immune SA**, and the failure is likely to "weigh heavily on both Roche but particularly partner AC Immune," commented analysts at Jefferies. The failure could also impact others active in the sector, including **Biogen Inc./Eisai Co. Ltd.** with aducanumab, they added in a Jan. 30 note. AC Immune's share price on Nasdaq declined markedly during the morning of Jan. 30, dropping by 69.25% in early trading.

Roche said that the studies' Independent Data Monitoring Committee had concluded that crenezumab was unlikely to show an effect on the change from baseline in clinical dementia rating-sum of boxes (CDR-SB) score, the primary endpoint in the CREAD 1 and CREAD 2 Phase III studies in patients with prodromal to mild sporadic Alzheimer's disease. No safety signals were observed in the pre-planned analysis. The decision casts a shadow over the continuing crenezumab Phase III study taking place in Colombia, which is set to continue, Roche said on Jan. 30. That study, by the Alzheimer's Prevention Initiative (API) is evaluating crenezumab in cognitively healthy individuals who have an autosomal dominant mutation who are at risk of developing familial Alzheimer's. It is being conducted in collaboration with the US Banner Institute and is being funded by the National Institute on Aging.

Further details of the interim analysis were not outlined but will be presented at a forthcoming medical conference. The CREAD 1 and 2 trials each involve 1,500 patients with early AD with confirmed evidence of cerebral beta-amyloid pathology, using four times higher doses than those used in Phase II studies. CREAD 1 started in early 2016, and CREAD 2 in mid-2017.

Roche may have been dismayed by the CREAD results, but it still has an anti-amyloid MAb, gantenerumab, in the Phase III GRADUATE studies, with initial data expected in around three years, and it is collaborating with AC Immune on the development of an anti-tau compound, RG6100, which is in Phase II studies. Jefferies analysts expect data from the Phase II TAURIEL study to be available in the second half of 2020.

Roche noted that gantenerumab is an IgG1 MAb with a mechanism of action distinct from crenezumab; it is designed to bind to aggregated forms of beta-amyloid and has previously shown amyloid plaque lowering in Alzheimer's patients. Gantenerumab is the only late-stage anti-amyloid program being developed for subcutaneous administration, the Swiss multinational said.

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Novartis' blockbuster plans revealed in earnings call. (p6)

Long Time Coming
Mylan's generic Advair finally approved. (p15)

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Takeda's HQ sale adds to company coffers. (p18)

from the editor

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Yet another Alzheimer's candidate failing to show an effect is bad news in a field that has seen so much investment for so little reward. However, all is not completely lost for the drug in question, Roche/Genentech's crenezumab (see cover story). It continues to be studied in people in people who are at higher risk of developing the disease but who have not yet shown cognitive symptoms.

Biogen, which is still optimistic that its Abeta antibody candidates aducanumab and BAN2401 (partnered with Eisai) will prove successful in treating symptomatic Alzheimer's, has also just announced it will launch a trial of aducanumab to prevent the development of the disease before symptoms are evident (see p4).

Catching Alzheimer's early enough has been one of the major challenges that has hamstrung the validation of the beta-amyloid hypothesis, which proposes that the beta-amyloid peptide is the main cause of Alzheimer's and that decreasing its production should treat the disease. One possible reason for the failure of so many Abeta-targeting drugs is that they have been used too late in the the disease to impact its progression. While treating the disease once its symptoms are evident would be more practical, even a preventive drug would be a major breakthrough, if something of a conundrum for cash-strapped healthcare systems.

Meanwhile, Roche continues its work on Abeta also with the ongoing development of gantenerumab, which is in late-stage trials. Given previous challenges with its development, and the generally poor outcomes in the field, hopes are muted. But in the absence of other breakthroughs, patients and pharma companies alike cling to those hopes.

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Celgene Gives Reassurances That Key Products And Programs Remain On Track

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With **Bristol-Myers Squibb Co.**'s $74bn acquisition of **Celgene Corp.** set to close in the third quarter – a deal that requires shareholder approval – Celgene spent its Jan. 31 earnings conference call reassuring investors that sales of its marketed drugs are growing and its pipeline programs remain on track.

In addition to Celgene's four blockbuster commercial products, Bristol highlighted five late-stage assets with US FDA approvals expected by 2020 as a big part of the justification for its big purchase when the deal was announced in early January. Three are crucial for Celgene shareholders to realize the full value of the transaction – payment of a contingent value right (CVR) depends on approvals for ozanimod, lisocabtagene maraleucel (liso-cel or JCAR017) and bb2121 within specific timeframes.

"For Celgene shareholders, it's quite clear how this [deal with Bristol] unlocks and recognizes a lot of the value that the market has not assigned to us more recently," Celgene CEO Mark Alles said during the Q&A portion of the company's fourth quarter earnings call. "The notion that we would create a new company that would have very dramatic leadership in the high specialty areas of oncology, inflammation and immunology is, again, quite clear."

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Among other companies developing candidate Alzheimer's therapies, Biogen said during its fourth-quarter conference call on Jan. 29 that it was starting a new Phase III study of its anti-amyloid beta antibody, aducanumab, for early use to prevent or delay the clinical onset of Alzheimer's disease.

The decision casts a shadow over the continuing crenezumab Phase III study taking place in Colombia, which is set to continue, Roche said on Jan. 30

DIFFERENTIATION

However, Biogen didn't comment on whether or when it might announce details of any interim analysis of the ongoing EMERGE and ENGAGE Phase III studies of aducanumab in early Alzheimer's, and executives were keen to differentiate Biogen's aducanumab from Roche's crenezumab. Aducanumab is highly selective for aggregated forms of amyloid-beta, while crenezumab doesn't have the same level of specificity, noted chief medical officer, Al Sandrock.

AC Immune and Roche have also in the past attempted to differentiate crenezumab from anti-amyloid antibodies that have previously been discontinued during development, saying that it could be used at higher doses to promote microglia-induced phagocytosis and amyloid-beta clearance, while avoiding the activation of microglia-mediated inflammatory responses.

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Biogen To Launch Phase III Alzheimer's Prevention Study

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Biogen Inc. will launch a new Phase III study of its anti-amyloid-beta antibody aducanumab for early use to prevent or delay the clinical onset of Alzheimer's disease. In a fourth-quarter conference call in which executives stood firm in their policy of refusing to comment on whether (or when) they might announce details of any interim or futility analysis of the heavily watched ongoing EMERGE and ENGAGE Phase III studies of aducanumab in early Alzheimer's, observers had to settle for hints of progress in the Alzheimer's arena.

Unveiling 2018 figures that showed it performed solidly if not spectacularly, Biogen said 2019 revenues would rise slightly from $13.5bn to $13.6-13.8bn. But while what happens with spinal muscular atrophy (SMA) antisense drug *Spinraza* (nusinersen) in the coming year will be important, the main variable in Biogen's future growth potential is its late-stage Alzheimer's pipeline, and frustratingly there is no clear sign that there will be any meaningful update on that until early in 2020.

If the Phase III readout for aducanumab proves positive, Biogen will have succeeded in an area of vast unmet need where many others have fallen by the wayside, and will be positioned for a huge sales boost. But if aducanumab follows other anti-amyloid-beta drugs into clinical failure, Biogen's already stated intention of carrying out M&A will become an urgent need if it is to sustain its sales longer term.

Aducanumab is not Biogen's only shot on the Alzheimer's goal: through a partnership with **Eisai Co. Ltd.** it also has a stake in the beta amyloid cleaving enzyme (BACE) inhibitor elenbecestat, and another antibody against the amyloid-beta peptide, BAN2401. *(Also see "Biogen's Busy Pipeline: Continued Confusion On BAN2401, But Other Irons In The Fire" - Scrip, 26 Oct, 2018.)*

Snippets of information were also forthcoming on those candidates during the results call.

ELENBECESTAT UPDATE

Somewhat allaying concerns about trends towards cognitive worsening associated with other companies' now discontinued BACE inhibitors (including **Merck & Co. Inc.**'s verubecestat and **Johnson & Johnson**'s atabecestat), Biogen noted that an independent data monitoring committee had reviewed data from the two ongoing Phase III studies of elenbecestat in early Alzheimer's, and had recommended that they proceed.

It said a cognitive safety monitoring plan had been implemented. Nevertheless, in the absence of an unexpected negative finding, clear indications about elenbecestat's market potential will have to wait until the trial readout in 2020.

BAN2401 INCHES FORWARD

As for BAN2401, Biogen said a Phase III study would begin "following the conclusion of ongoing regulatory dialogues." Although some have questioned whether a clear positive signal on aducanumab would obviate the need for Biogen to invest also in an expensive late-stage trial for BAN2401, Michael Ehlers, VP of R&D, said that "the data for BAN2401 increases the probability of success for both this as-

set as well as aducanumab" since the two candidates share particular features which distinguish them from other anti-amyloid-beta antibodies, and which could provide a rationale for their success where others have failed.

These include specificity for binding aggregated forms of beta-amyloid and data demonstrating robust removal of amyloid plaque in humans, among other things.

For now, at least, Biogen is continuing to advocate the continuing development of both drugs.

Indeed, it seems that positive results for BAN2401 to date have strengthened Biogen's resolve to develop aducanumab. On the reason for pursuing the Phase III trial of the latter at an earlier stage (including in patients who may not have cognitive complaints but who have evidence of amyloid pathology in the brain), chief medical officer Al Sandrock said: "We've been considering doing this preclinical study, we call it, for a few years now and it's part of our broader life cycle management strategy. I'd say the reasons why we're doing it are that many of our advisors and investigators have been encouraging us to do it for some time, and also that the BAN2401 results that we got roughly six months ago increases our level of confidence in aducanumab.

"And then, finally, as you know, FDA put out guidance recently that contemplates how you might get approval for early AD. So, we believe one day the standard of care will be to treat with amyloid lowering drugs as early as possible, and this trial will go a long way toward informing that."

CRENEZUMAB DIFFERENCES

Sandrock meanwhile cautioned against any read-through from the expected upcoming interim readout of Roche's trial of its anti-amyloid-beta antibody crenezumab. (See cover story).

"First of all, these are not the same antibodies, crenezumab binds to sort of a mid-domain in a-beta-42 peptide. Aducanumab and BAN both are N-terminal. Aducanumab and BAN[2401] are highly selective for aggregated forms of a-beta, both soluble oligomers as well as insoluble fibrils. Crenezumab doesn't have that same level of specificity. I think it's important to note that crenezumab is an IgG4, which doesn't have full effector function, whereas BAN and adu[canumab] both have full effector function.

"And finally, we just saw the results published recently on crenezumab Phase II where even their high-dose IV arm, they did not show statistically significant lowering of amyloid plaque whether you used subcortical white matter or cerebellum as a reference region," Sandrock said.

"So, that's another important difference between aducanumab and BAN, both of which show a substantial reduction in amyloid plaque burden in humans. So, I think there's some notable differences, and I'd be cautious about too much of a read-through."

SPINRAZA PROGRESS

Alzheimer's aside, Biogen received a boost in 2018 from Spinraza, with global sales nearly doubling to $1.7bn, but growth flattened in the fourth quarter and while the company is bullish about the ongoing opportunities to expand its market, the expected approval of **Novartis AG**'s gene therapy for SMA in 2019 could dampen its prospects further. *(Also see "Novartis Pruned Pipeline Producing Attractive Respiratory And Neurology Fruits" - Scrip, 13 Dec, 2018.)*

Biogen expects full-year sales to grow in the mid- to high-teens, with increases both in the US and other markets, helped by expected launches in new markets including the UK, Canada, South Korea and China.

Ehlers threw some shade onto Novartis' product, *Zolgensma* (AVXS-101). He commented that "a number of questions remain for this experimental approach as data on the safety, efficacy and durability of AVXS-101 remain limited with results reported to date for only 15 patients followed up for 2.5 years, seven of whom are reported to have subsequently initiated treatment with Spinraza. This is in contrast to the Spinraza clinical trial program which has included more than 300 patient followed up for up to six years."

He noted that Zolgensma "we believe will be initially indicated for infants", whereas Spinraza is approved for pediatric and adult patients. Nevertheless, the gene therapy is not the only threat: Roche is also advancing with an oral SMA therapy which could further curtail Spinraza's trajectory on the market.

BUYING GROWTH?

Biogen CEO Michel Vounatsos confirmed that Biogen would continue to pursue M&A actively, although he said the company would "not go for bridging a potential gap because we are not on a burning platform."

He said the management team had "a broad range of targets" and was "working on that, but with pace and calm."

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Biogen Revenue Details At A Glance

- 2018 revenues $13.5bn (+10%)
- 2018 Spinraza revenues $1.7bn (+95%)
- 2018 multiple sclerosis revenues $9.1bn (-1%; including $478m Ocrevus royalties)
- 2018 biosimilar revenues $545m (+44%)
- 2018 Rituxan/Gazyva revenues $1.5bn (+7%)
- Q4 revenues $3.5bn (+7%)
- Q4 Spinraza revenues $468m (flat vs Q3 2018; +30% from Q4 2017)
- Q4 multiple sclerosis revenues $2.3bn (+2%, including $152m Ocrevus royalties)
- Q4 biosimilar revenues $156m (+28%)
- Q4 Rituxan Gazyva revenues $383m (+13%)

As for BAN2401, Biogen said a Phase III study would begin "following the conclusion of ongoing regulatory dialogues."

Carry On Cosentyx As Novartis Lines Up More Blockbusters

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Novartis AG is aiming to launch 10 potential blockbusters by 2020 but for the moment, the Swiss major is reaping the benefits from an established big seller – *Cosentyx* (secukinumab) – which is continuing to grow at an impressive rate.

Speaking at Novartis' annual press conference in Basel on Jan. 30, chief executive Vas Narasimhan highlighted how much of a key growth driver Cosentyx has become, with the psoriasis, psoriatic arthritis and ankylosing spondylitis IL-17 A inhibitor contributing $806m to the firm's coffers in the fourth quarter. This represents a 33% rise on the like, year-earlier period, a strong showing given how competitive the space has become.

In particular, some observers have been wondering aloud about what effect the success of **Johnson & Johnson**'s IL-23 inhibitor *Tremfya* (guselkumab) in beating Cosentyx on a 48-week primary endpoint in psoriasis in the Phase III ECLIPSE study will have on the latter's rise. According to Paul Hudson, CEO of Novartis Pharma, the effect will not be much. *(Also see "ECLIPSE: J&J's Tremfya Beats Novartis' Cosentyx For Long-Term Psoriasis Clearance" - Scrip, 12 Dec, 2018.)*

In an interview with *Scrip* in Basel, Hudson said that ECLIPSE "is a marketing message and if you ask the dermatology community what they are excited about in the dataset, well there is no interest in getting on a podium and talking about this as a breakthrough insight into the treatment of psoriasis – there is none." He added that ECLIPSE won on one data point "where they missed on everything else."

Hudson went on to say that the IL-23 class has not delivered on the promise of setting the new standard for the disease, adding that Tremfya has actually lost new patient share in the US since ECLIPSE came out. He added that J&J "will campaign it" and "we have to be vigilant about the excitement of their field force but as for physician pull because of breakthrough data? There isn't any."

COSENTYX CONFIDENCE

He is not particularly concerned about the advent of another IL-23 drug, **AbbVie**'s risankizumab, which is expected to be approved soon by the FDA. Hudson claimed that in Europe, "clinically it won't compete," although in the US, AbbVie may "decide to leverage everything they have to get access" by tapping into rebate opportunities but "risankizumab will come and go and ECLIPSE will come and go."

Cosentyx will beat all comers, he argued, because Tremfya and risankizumab cannot compete when it comes to manifestations beyond skin. More than two thirds of psoriasis patients see the condition manifest itself in the nails, scalp, hands, feet and joint. Hudson noted that Novartis has safety and efficacy data for Cosentyx out to five years for PsA and AS, unlike its rivals, saying that "to win, you need to treat more than skin."

A new indication for Cosentyx, in non-radiographic axial spondyloarthropathy, is one of the 10 possible blockbuster launches touted by Novartis from 2018 to 2020 (see table). They include another possible approval for the heart failure drug *Entresto* (sacubitril/valsartan), which also had a strong quarter, with sales shooting up 76% to $318m.

Novartis' biggest seller is the multiple sclerosis therapy *Gilenya* (fingolimod), and while a number of generics players are waiting with their versions of the blockbuster, it looks like they will have to wait a far while longer. Narasimhan told *Scrip* that while the legal situation around Gilenya patents was "extraordinarily complicated," with several generics firms threatening at-risk launches, the company expects no copycat versions to hit the market this year and Novartis is confident of upholding its patents, a view that to date has been backed by US courts. *(Also see "US Court of Appeals Upholds Gilenya Compound Patent, Dealing A Blow To Ezra Ventures" - Generics Bulletin, 11 Dec, 2018.)*

As for new products, fourth quarter sales of the CAR-T treatment *Kymriah* (tisagenlecleucel) came in at just $28m, reflecting in part the struggles Novaertis has had with manufacturing issues. Narasimhan noted that the firm was expanding global manufacturing including collaborations in China and Japan and doubling capacity at Novartis' own Morris Plains facility, adding that progress had been made on access in Europe with commercial orders in five countries. Australia also approved both Kymriah indications

Ten Potential Blockbuster Launches

LAUNCH YEAR	PRODUCT	INDICATION
2018	Aimovig	Migraine
2018	Kymriah	Diffuse large B-cell lymphoma
2018	Lutathera	Neuroendocrine tumors
2019	BYL719	Advanced breast cancer
2019	Mayzent	Secondary progressive multiple sclerosis
2019	RTH258	Neovascular age-related macular degeneration
2019	Zolgensma	Spinal muscular atrophy type 1
2020	Cosentyx	Non-radiographic axial spondyloarthropathy
2020	Entresto	Heart failure with preserved ejection fraction
2020	INC280	Non-small cell lung cancer
2020	OMB157	Relapsing multiple sclerosis
2020	PDR001 combination	Metastatic melanoma
2020	QMV149	Asthma
2020	SEG101	Sickle cell disease

in December, namely B-cell acute lymphoblastic leukemia and diffuse large B-cell lymphoma.

Novartis's new oncology chief Susanne Schaffert declined to give any specific sales forecasts for Kymriah this year sales, but said that the increase in manufacturing capacity is a response to an expected increase in demand.

Much of Narasimhan's presentation to journalists at the Basel press conference focused on the progress made in the year since he took over at the helm. "In 2018 we reimagined Novartis," he said, adding that the firm had advanced its strategic priorities "including building new advanced therapy platforms, ramping up productivity and digital efforts and creating a new culture".

Whether Sandoz will be part of the new culture remains to be seen. The generics unit has had a difficult couple of years, hit hard by pricing pressures in the US and last year Novartis decided to divest Sandoz's US solid-dose and skincare generics operations to **Aurobindo Pharma Ltd.** for around $1.0bn to focus more on biosimilars and complex small molecules.

Narasimhan stressed that he saw Sandoz an integral part of Novartis, but said that the firm would work on transforming the business, telling *Scrip* that the plan was to increase Sandoz's autonomy over the next 18 months. As to what this means in practice is too early to say, he added, noting that one step will involve reducing its geographical footprint. *Published online 30 January 2019*

Pfizer: Time To Face The Lyrica Pain

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Pfizer Inc. CEO Albert Bourla led his first earnings call as the company's chief executive Jan. 29 and stuck to a similar message the company has laid out to investors for close to a year: that Pfizer will be well positioned for growth after cycling through the loss of *Lyrica* to generics beginning June 30, 2019.

Growth will come largely from innovation and the company's internal R&D engine, Bourla said, calling large-scale M&A a potential distraction that could derail the current growth plan. Getting to the second half of 2020 will feel like a long wait to investors, however, if there is not something to fill the void left by Lyrica (pregabalin). The pain drug was Pfizer's number-two seller in 2018, generating $4.62bn, behind only the pneumococcal vaccine *Prevnar 13*.

The company is relying on newer workhorses to pick up some of the slack, drugs like *Ibrance* (palbociclib), *Xeljanz* (tofacitinib) and *Xtandi* (enzalutamide). There is one near-term launch on the horizon, tafamidis for the treatment of transthyretin amyloid cardiomyopathy, which is pending at

the US FDA with a decision expected in July. But while the drug could eventually become a rare disease blockbuster, the launch trajectory is expected to be slow given the current under-diagnosis of the condition. *(Also see "Pfizer Has Tafamidis Data In Hand, But Market Development Still A Challenge" - Scrip, 27 Aug, 2018.)*

Pfizer forecast revenues of $52bn-$54bn in 2019, a range that allows for slightly better or slightly worse performance than the $53.6 bn Pfizer generated in 2018, which represented 2% growth over 2017.

Some investors are hoping the company will patch a near-term revenue generator together through M&A. An acquisition of **Amarin Corp. PLC**, for example, would give Pfizer a near-term commercial opportunity in the fish oil product *Vascepa* (icosapent ethyl).

Bourla confirmed the company is looking proactively at business development opportunities in the commercial arena, but cautioned the focus is on the longer-term.

"We will be proactive, but proactive doesn't mean that our focus is how to change the profile of 2019. Proactive means how we're going to enhance the growth profile of Pfizer in the pivotal moment that is happening after June/July of 2020 or in 2021," Bourla said.

BOURLA: PRICING IS NOT A GROWTH DRIVER

At the same time Pfizer will be facing a steep patent cliff in 2019, the industry is experiencing another challenge when it comes to US drug pricing pressure. The company is among those that pulled back on price hikes on marketed drugs in January. Though it still implemented price increases on 10% of the portfolio, it kept most of those increases to 5% or less. *(Also see "The Inevitable Is Coming: Price Increases, Starting With Pfizer " - Scrip, 19 Nov, 2018.)*

Consistent price increases on marketed drugs have been a reliable source of growth for the industry as new blockbuster drugs have become harder to develop. An analysis of in-line price increases by the top 17 biopharma companies from 2013 through most of 2018 by Leerink found that price growth alone contributed on average 5% a year to industry growth over the last five years. *(Also see "US Drug Pricing: What A Difference A Year Makes " - Scrip, 2 Jan, 2019.)*

> "Oncology drugs are shorter in duration of therapy, so that allows new patients to turn over faster, and it will make it easier for the physicians to initiate new patients on oncology biosimilars"

Bourla signaled that those days are over. "It's very clear that pricing is not going to be a growth-driver for us now, and I think in the future," he said. Pfizer forecast its US net drug prices will be flat in 2019 and globally pricing will decline low single digits.

A 2019 trends report by IQVIA released the same day also forecast industry-wide list prices would increase at a historically low 4% to 7% on an invoice basis, excluding rebates and discounts, and only 0%-3% on a net manufacturer revenue basis, accounting for rebates and discounts.

Pfizer believes its late-stage R&D engine is poised to deliver in the mid-term, with candidates like tanezumab for osteoarthritis pain, rivipansel in vaso-occlusive crisis for sickle cell disease and abrocitinib, a JAK1 inhibitor in development for atopic dermatitis.

The company, with partner **Eli Lilly & Co.**, reported positive data from a second Phase III trial for the NGF inhibitor tanezumab in patients with moderate-to-severe osteoarthritis pain the same day, showing the treatment arm met all three co-primary endpoints at 24 weeks, statistically significant improvement in pain, physical function and the patients' overall assessment of their OA compared to those receiving placebo.

Safety is one potential issue with the class of drugs, but Pfizer believes the profile is shaping up to be manageable. Rapidly progressive osteoarthritis was observed in 2.1% of tanezumab patients and there was one event of osteonecrosis and one of subchondral insufficiency fracture in tanezumab-treated patients in the latest study.

THREE ONCOLOGY BIOSIMILARS

Pfizer also has the opportunity in 2019 for three potential biosimilar launches, all in oncology. The company could launch biosimilar versions of **Roche**'s blockbusters *Rituxan* (rituximab), *Herceptin* (trastuzumab) and *Avastin* (bevacizumab) by year-end, management said. But Pfizer has faced challenges with the launch of its first biosimilar in the US, *Inflectra* (infliximab), a version of **Johnson & Johnson**'s *Remicade*, which has struggled to gain market access around J&J's defensive contracting strategy.

The company is more optimistic about the opportunity for biosimilars in oncology in the US. "Our experience with infliximab in the US really is not a great analogy for what might be to come with our new oncology biosimilars, just because there are just very different dynamics in the I&I space compared to oncology," Pfizer Biopharmaceuticals Group President Angela Hwang said.

"Oncology drugs are shorter in duration of therapy, so that allows new patients to turn over faster, and it will make it easier for the physicians to initiate new patients on oncology biosimilars," she said. Still, no biosimilar versions of cancer drugs have launched in the US and it remains uncertain how physicians will respond to using the drugs initially given the importance of efficacy in the therapeutic area.

Pfizer's biosimilar franchise is picking up some traction, however. Biosimilars generated $769m in 2018, growth of 45%, with the bulk of the revenues, $503m, coming from outside the US.

The company's innovative health business grew 6% in 2018 to $33.4bn, while the Essential Health business declined 4% to $20.2bn.

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New Products Soar And Old Stand Their Ground As Roche Heads Off Biosimilar Threat

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New products accounted for 90% of sales growth at **Roche** in 2018, as the company shrugged off the effects of biosimilar competition to its cancer franchise in Europe. Multiple sclerosis drug *Ocrevus* (ocrelizumab) hit CHF2.4bn in sales in its first full year on the market, shy of consensus but confirming its status as Roche's most successful new product launch ever.

This, added to a faster than expected start out of the blocks for hemophilia product *Hemlibra* (emicizumab), helped more than offset the hit felt by its older blockbuster biologicals, *Herceptin* (trastuzumab) and in particular *Rituxan* (rituximab), which both withstood the advent of biosimilars better than analysts had expected.

Roche's pharmaceuticals division reported sales up by 7% to CHF44.97bn in 2018, ahead of consensus and also driven in large part by its other new products, *Perjeta* (pertuzumab), *Tecentriq* (atezolizumab) and *Alecensa* (alectinib). Group sales were also up 7% to CHF56.85bn.

The 90% figure for growth coming from new products shows "we have been successful in rejuvenating our portfolio," said CEO Severin Schwan, noting that Ocrevus was now "the number one prescribed drug for newly diagnosed patients in the US." The product's sales were up 172% to CHF2.4bn for both the relapsing and primary progressive forms of MS, and strong demand in both indications has continued, although Q4 revenues were lower than consensus.

Jefferies analysts noted that Ocrevus' US growth was partially driven by earlier lines and in 2019 Roche expects to expand use in this segment by displacing oral MS therapies.

Hemlibra too has enjoyed a good market start with sales of CHF224m for the year – "beyond expectations," Schwan said. He attributed this performance to its "fantastic profile which is life changing for hemophilia patients." The product, which can be administered subcutaneously in range dosing options is now approved in more than 50 countries for hemophilia A with inhibitors to Factor VIII, and is now additionally approved in a few markets including the US for patients without inhibitors, thereby extending its reach. A EU CHMP opinion in non-inhibitor patients is expected imminently.

Roche Pharmaceuticals' CEO Bill Anderson told analysts during the results presentation in London on Jan. 31 that although the EU is likely to be restricted to severe patients this is by far the largest segment, accounting for 70% of Factor VIII use. "Over time growth will come from the non-inhibitor market," Schwan said.

But the overall performance was helped by the better than expected performance from established products, Herceptin, *Avastin* (bevacizumab) and Rituxan.

2018 Herceptin sales were up 1% to CHF6.98bn mainly driven by growth in the US (+9%) and in China, which offset a 16% sales decline in Europe after biosimilar competition arrived mid-year. By contrast, Rituxan sales were down 8% to CHF6.75bn on the back of a 47% drop in Europe, but the product managed a 4% rise in the US in both its immunology and oncology segments helped by the subcutaneous formulation. Its international sales were up 11%, again mainly thanks to China.

Avastin revenues were up by 3% in 2018, to CHF6.85bn.

But the impact of biosimilar competition will deepen in 2019, and attention is now squarely on the US, where Rituxan, Herceptin and Avastin are all under threat this year. Schwan confirmed that he does not expect to see biosimilar competition to this trio of drugs until the second half.

Morgan Stanley analysts noted that this was based on "publicly available information from competitor companies", i.e. it was not based on confidential settlement agreements between Roche and biosimilar manufacturers. "We view this guidance as a worst-case scenario and continue to believe that litigation hurdles and settlement agreements will delay US biosimilar entry," they said in a Jan. 31 reaction note.

Roche Pharmaceuticals' CEO Bill Anderson told analysts during the London presentation that there were two reasons why it was difficult to gauge the likely impact in the US this year: no-one knows what will happen with litigation and IP disputes and what launch choices biosimilar companies will take; and no-one knows what the uptake will be when they arrive. "There's not a lot of precedent," he said.

Roche Pharmaceuticals Division 2018 Sales

SALES JAN-DEC 2018	CHF MILLIONS		AS % OF SALES		% CHANGE	
	2018	2017	2018	2017	At CER	in CHF
Pharmaceuticals Division	43,967	41,220	100.0	100.0	+7	+7
United States	23,233	20,496	52.8	49.7	+14	+13
Europe	8,693	9,051	19.8	22.0	-7	-4
Japan	3,701	3,713	8.4	9.0	-1	0
International*	8,340	7,960	19.0	19.3	+10	+5

*Asia-Pacific, EEMEA (Eastern Europe, Middle East and Africa), Latin America, Canada, others

Roche

Roche 2018 Top-Five Best-Selling Products

TOP-5 SELLING PHARMACEUTICALS	TOTAL		US		EUROPE		JAPAN		INTERNATIONAL*	
	CHFm	%	CHFm	%	CHFm	%	CHFm	%	CHFm	%
Herceptin	6,982	1	2,908	9	1,849	-16	249	-16	1,976	10
Avastin	6,849	3	2,904	1	1,820	-1	847	3	1,278	12
MabThera/Rituxan	6,752	-8	4,290	4	916	-47	188	-36	1,358	11
Perjeta	2,773	27	1,325	32	915	15	143	18	390	45
Ocrevus	2,353	172	2,080	144	206	**	-	-	67	**

* Asia-Pacific, EEMEA (Eastern Europe, Middle East and Africa), Latin America, Canada, others ** over 500% Roche

2019 GUIDANCE

Roche guided that 2019 sales were expected to grow in the low- to mid-single digit range, at constant exchange rates. Core earnings per share are targeted to grow broadly in line with sales, at constant exchange rates.

Bryan Garnier analysts said considering this was the first full year characterized by significant erosion of flagship oncology drugs due to biosimilar competition in Europe, it was "remarkable" that Roche was able to post 7% sales growth. "What is even more striking is that the group even accelerated this growth across the year and ended with a last quarter up an incredible 9%, with the two divisions performing extremely well (pharmaceuticals up 9% and diagnostics up 10%), beating consensus expectations by about CHF400m to CHF56.85bn for the full year."

Schwan also reiterated that Roche was not interested in pursuing any mega-mergers, and that its M&A strategy of looking for bolt-on acquisitions to obtain specific technologies or products remained unchanged.

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Amgen Explains How Big A Hit It May Take From Biosimilars, Pricing Pressures

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Amgen Inc.'s 2018 total revenue increased 3% year-over-year to $23.7bn and exceeded analyst consensus of $23.4bn, but the company on Jan. 29 forecast a decline of up $1.9bn for 2019 due in large part to biosimilar competition for *Neulasta* (pegfilgrastim) and *Epogen* (epoetin alfa).

Amgen will rely on new product launches, such as the migraine prophylaxis *Aimovig* (erenumab) and the cholesterol-lowering biologic *Repatha* (evolocumab), as well as volume-driven – not price-driven – sales growth to fill in the revenue gap in the near term. It also will invest in growing its research and development pipeline, including potential acquisitions, but the company's guidance for 2019 shows that those investments will provide a longer-term payoff.

Assurances about Amgen's preparations for this year's looming revenue decline, its hopes for sales growth for newer products and its investments in R&D did little to appease investors, who sent Amgen's stock down 2.4% in after-hours trading to $187.45 following the company's fourth quarter earnings call on Jan. 29.

However, both Mizuho Securities analyst Salim Syed and Jefferies analyst Michael Yee pointed out in same-day notes that Amgen tends to provide conservative financial guidance, so there may be upside later in the year as the company makes progress with its volume-driven sales growth strategy. Both noted that the top end of the current guidance of $21.8bn-$22.9bn is in line with analyst consensus of $22.8bn in 2019 revenue.

Amgen CEO Robert Bradway started the call recapping the company's "transformation" over the past few years, during which thousands of job cuts and other cost reductions resulted in $1.9bn in annual savings. Such efficiencies were needed as the company prepared to see sales decline for its legacy products, including Neulasta, Epogen and other injectables facing biosimilar competition. *(Also see "Q4 Earnings Preview: Pfizer, Amgen, Allergan, Biogen And Novartis" - Scrip, 25 Jan, 2019.)*

Also, with increasing pressure on biopharmaceutical companies to contain high and rising drug prices, Amgen will have to focus on sales volume instead of price increases to drive revenue growth going forward. Bradway noted that "our net selling prices declined in 2018 and will decline further in 2019. For many Amgen medicines, there are no planned price increases."

PRICING AND BIOSIMILARS IMPACT 2019 GUIDANCE

Executive Vice President and Chief Financial Officer David Meline provided more detail on the impact of Amgen's drug pricing strategy going forward, noting that "overall net selling price decreased by 1% in 2018. We expect net selling prices to decline by mid-single digits in 2019."

Meline described net price declines as one of multiple assumptions influencing the company's financial guidance for this year.

"First, our revenue guidance range reflects both continued solid positive growth momentum from our newer products as well as evolving competitive dynamics related to our mature products," he said. "We have important incremental growth opportunities driven by recently launched products including Aimovig, Repatha, and biosimilars and international expansion, as well as our emerging oncology programs."

Meline explained that the company's guidance includes a wider revenue range than usual, because of the uncertainty over the end results of ongoing patent litigation over the hyperparathyroidism therapy *Sensipar* (cinacalcet). **Teva Pharmaceutical Industries Ltd.** briefly launched a generic and quickly took it off the market after reaching a settlement with Amgen in late December/early January.

In addition to potential generic competition for Sensipar, which has had muted growth due to the launch of Amgen's newer hyperparathyroidism drug *Parsabiv* (etelcalcetide), Meline highlighted "continued competitive dynamics" for the TNF inhibitor *Enbrel* (etanercept) and the long-acting anemia therapy *Aranesp* (darbepoetin alfa).

Aranesp sales fell 3% year-over-year to $474m in the fourth quarter and dropped 9% for the year to $1.9bn, impacted in the final quarter by both lower inventories and biosimilar competition for Amgen's short-acting erythropoietin-stimulating agent (ESA) Epogen.

Pfizer Inc.'s 2018 launch of its Epogen biosimilar *Retacrit* (epoetin alfa-epbx) in the US as well as 2019 launches of additional short- and long-acting ESAs are expected to impact both Aranesp and Epogen this year. *(Also see "Pfizer's Epogen Biosimilar Retacrit Launches At 33% Off In A US Market Where Amgen's Already Competitive" - Scrip, 14 Nov, 2018.)* Epogen sales – already impacted by EU biosimilars – fell 2% in the fourth quarter to $264m and 8% for the year to $1bn.

Similarly, sales of Amgen's short-acting neutropenia therapy *Neupogen* (filgrastim) fell 40% to $75m in the fourth quarter and 34% to $365m for the year due to biosimilar competition. Biosimilars that will impact the long-acting product Neulasta hit the market late last year and early this year. *(Also see "Coherus Gears Up For January Udenyca Launch, Prices Biosimilar At 33% Discount To Neulasta" - Scrip, 9 Nov, 2018.)*

However, sales rose 5% to $1.2bn in the fourth quarter of 2018 versus consensus estimates of $990m for the quarter due to a single large purchase and the more than 60% market share captured by *Neulasta OnPro*, its on-body injector.

"Neulasta was a big beat and fared very well despite biosimilar competition. To be clear, there was a $55m government purchase in 4Q, but even if I adjust for that, Neulasta was -1% year-over-year (and still ahead of consensus)," Evercore ISI analyst Umer Raffat said in a Jan. 29 note.

Neulasta sales for the year fell 8% to $4.5bn and will fall further in 2019, of course, due to biosimilar competition, including an expected decline in OnPro's share of the market. However, Meline noted Amgen's wide revenue guidance also accounts for some uncertainty about how much Neulasta biosimilars will impact the company's brand name product this year.

Despite ongoing biosimilar market entries and other competitive threats, Executive Vice President-Global Commercial Operations Murdo Gordon noted during Amgen's call that the company's 3% revenue growth in 2017 was driven by a 5% increase in sales volume, showing that Amgen has been able to increase revenue for some drugs by selling more product rather than simply raising prices.

Sales of the PCSK9 inhibitor Repatha grew 62% in the fourth quarter to $159m after the company introduced a new version of the product at a 60% list price discount. Gordon said about 43% of Medicare patients now have access to the product and that number will grow as payers make off-cycle additions to Medicare health plans. Repatha sales jumped 72% for the year to $550m as volume nearly doubled versus 2017 and the biologic captured 60% of the market.

Aimovig, which launched in the US in 2018 as the first-to-market CGRP inhibitor for the prevention of chronic and episodic migraine headaches, delivered $95m in sales during the fourth quarter, which was almost double analyst consensus of $50m. More than 150,000 patients have been treated with the biologic, marketed under a partnership with **Novartis AG**, since its launch in May. *(Also see "Amgen's Aimovig Aims To Capture As Many Migraine Patients As Possible With $6,900 Price" - Scrip, 17 May, 2018.)*

There have been concerns about the effect on early Aimovig sales of free initial prescriptions that Amgen/Novartis provided for the drug, but as of the fourth quarter about 50% of prescriptions are paid rather than free drug, compared with 35% in the third quarter. *(Also see "Amgen's Aimovig Riding High With Strong Prescriber, Payer Acceptance" - Scrip, 30 Oct, 2018.)* However, Gordon warned that even as more payers add Aimovig to their formularies, its sales trajectory could slow in the first quarter as payers reauthorize previously approved prescriptions for individual patients.

Meanwhile, Enbrel continues to feel the impact of biosimilars for other TNF inhibitors, such as **Johnson & Johnson**'s *Remicade* (infliximab), as well as competition from drugs with new mechanisms of action for the treatment of arthritis and other inflammatory conditions. However, it remains Amgen's top seller despite falling 8% to $1.3bn in the fourth quarter and 8% to $5bn for the year.

The company's only likely near-term launch is the osteoporosis drug *Evenity* (romosozumab), partnered with UCB, which had a generally positive US FDA advisory committee vote earlier this month. *(Also see "Evenity Likely Headed For Approval With Amgen's Proposed Indication, But Postmarketing Requirements Remain Unclear" - Pink Sheet, 16 Jan, 2019.)*

"We continue to see Evenity as a really good complement to our overall focus on bone health," Gordon said. He noted that the advisory committee outcome was mostly "consistent with what we had planned for the product and how it would be positioned in the market. However, there's still a lot of work and discussions still to have with the FDA."

Amgen's bone health franchise is expected to be a source of revenue growth going forward, including *Prolia* (denosumab) for osteoporosis and *Xgeva* (denosumab) for cancer-related fractures. Prolia sales rose 14% to $655m in the fourth quarter and 16% for the year to $2.3bn, while Xgeva grew 17% for the quarter to $456m and 13% for the year to $1.8bn – both driven by volume growth.

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AbbVie's Downward Humira Guidance Worries Analysts

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Much of the attention coming out of **AbbVie Inc.**'s earnings call Jan. 25 was focused on the company's reduction of ex-US revenue estimates for top-seller *Humira* (adalimumab) for the second time in recent months due to the impact of biosimilar competition – raising concerns that the impact of US biosimilars will be greater than AbbVie has suggested.

For the full year 2018, Humira grew 7.4% growth year-over-year to $19.94bn. Broken down, the autoimmune stalwart's US sales of nearly $13.7bn represented 10.7% growth, while ex-US sales of $6.25bn increased just 0.6%. The fourth quarter numbers showed a starker difference, as Humira grew 9.1% domestically to $3.62bn, but declined 14.8% to $1.30bn outside the US.

Noting that "the event that has for many years concerned investors most has been the loss of exclusivity for Humira," Chairman and CEO Rick Gonzalez said AbbVie now anticipates that ex-US sales erosion for the product may be as high as 30% this year. Before biosimilar adalimumab was introduced in Europe last October, AbbVie predicted near-term erosion of 18%-20%, but quickly increased its estimate of the damage during its third quarter earnings call to 26%-27%. *(Also see "AbbVie Hit Harder By EU Humira Biosimilars Than Projected" - Scrip, 2 Nov, 2018.)*

Biosimilar competition for Humira is not expected in the US until 2023. AbbVie finalized the latest of its patent settlements for Humira biosimilars on Jan. 25, allowing **Coherus BioSciences Inc.** to launch its adalimumab biosimilar (CHS-1420) on Dec. 15, 2023 – consistent with the timeline its used in six prior settlements on adalimumab copies. *(Also see "Pfizer Decides Not To Challenge AbbVie's Humira Biosimilar Patents" - Pink Sheet, 1 Dec, 2018.)* An outstanding dispute with **Boehringer Ingelheim GMBH** remains. *(Also see "AbbVie Inks Sixth Humira Biosimilar Settlement, Battles Boehringer's 'Unclean Hands' Claim" - Pink Sheet, 8 Nov, 2018.)*

Gonzalez reiterated AbbVie's strategy for dealing with the Humira patent cliff by building up its successor biologics risankizumab and upadacitinib, under FDA review for psoriasis and rheumatoid arthritis, respectively, and by continuing to grow its hematologic cancer business with *Imbruvica* (ibrutinib), partnered with **Johnson & Johnson**, and *Venclexta* (venetoclax), partnered with **Roche**. Some analysts find that strategy lacking, with Alex Arfaei of BMO Capital Markets insisting the company will need a major M&A transaction to change its fortunes past the introduction of US adalimumab biosimilars.

Leading into the call, Arfaei wrote Jan. 24 that "the question on everyone's mind" was whether AbbVie would pursue a merger with **Bristol-Myers Squibb Co.**, possibly even in a hostile takeover scenario. Citing what he perceived as Bristol shareholder push-back on the pending acquisition of **Celgene Corp.**, Arfaei wrote that this could create an opening for another entity to acquire Bristol and benefit from its leadership position in immuno-oncology, which could offer AbbVie significant diversification away from the autoimmune space. *(Also see "Bristol Values Celgene's Hematology, Immunology Portfolio At $74bn, But Does It Price In Risk?" - Scrip, 3 Jan, 2019.)*

DEALS BIGGER THAN PHARMACYCLICS UNLIKELY

Gonzalez quickly dashed any such speculation, telling a questioner "as far as the appetite for a big deal, I can tell you that is not something that we are contemplating." Further clarifying AbbVie's current approach to business development, he called the 2015 acquisition of **Pharmacyclics Inc.** for roughly $20bn a major deal, albeit a bolt-on acquisition. To date, that deal has proven beneficial for AbbVie, as it brought Imbruvica to its portfolio, which totaled $3.59bn in global sales in 2018, up 40%, including fourth quarter growth of 42% to just over $1bn (including ex-US revenue sharing with J&J).

Prior to spinning out AbbVie, **Abbott Laboratories Inc.** gained Humira through its $6.9bn acquisition of **Knoll Pharmaceutical Co.** in 2000, but AbbVie has been disappointed by some of its M&A gambits. It recently took a $4bn impairment charge related to its $5.8bn purchase of **Stemcentrx Inc.** in 2016 after multiple failed trials for the cancer candidate that drove that deal – rovalpituzumab tesirine (*Rova-T*). The pharma may prefer partnerships and licensing deals to add to its cancer portfolio, as exemplified by the anti-CD39 immunotherapy tie-up signed with **Tizona Therapeutics Inc.** on Jan. 4.

After the call, BMO's Arfaei issued another note that conceded AbbVie's position on large M&A, but asserted "given the magnitude of revenue pressure ahead, we expect AbbVie to be active in sizable business development." The main part of that revenue pressure, of course, is Humira's prospects going forward as the product still accounts for more than half of the company's sales.

Gonzalez said AbbVie has planned for Humira sales erosion from day one of its existence, but that didn't fully placate analysts or stockholders. AbbVie finished the trading day Jan. 25 down 6.3% to $80.51 per share.

Wolfe Research analyst Tim Anderson warned that AbbVie's second rapid revision of the impact of adalimumab biosimilar competition is worrisome for the pharma and reminiscent of how peer companies have responded to challenges to key franchise products. "AbbVie has revised down again its assumptions for EU biosimilar erosion – twice in a three-month window," the analyst wrote in a Jan. 25 note.

"These revisions will make investors nervous that AbbVie is under-calling the long-term impact of biosimilar erosion, beyond 2019, including in the US (2023), where Humira currently generates the majority of its sales. These downward revisions also reconfirm a trend that we have often seen among big pharma management teams, not limited to AbbVie, i.e., underestimating the declines with big legacy franchise that start to roll over."

Anderson cited **GlaxoSmithKline PLC**'s respiratory blockbuster *Advair* (fluticasone/formoterol) and **Sanofi**'s diabetes titan *Lantus* (insulin glargine) as examples of that trend.

USING HUMIRA TO GAIN FORMULARY ACCESS FOR FOLLOW-ONS?

Morgan Stanley analyst David Risinger noted Jan. 25 that AbbVie's US Humira sales growth guidance of 7% this year is below expectations; it would account for domestic sales of about $14.6bn, while consensus projections are roughly 3% higher at about $15.1bn, while Morgan Stanley expects 8% growth to $14.8bn. However, Risinger opined that with both risankizumab and upadacitinib likely to gain US approval this year, AbbVie may employ a rebate strategy with Humira to "garner strong formulary" access for both launches.

Risankizumab has an April 25 action date for psoriasis, while the action data for upadacitinib in RA has not been disclosed. The FDA filing was announced by AbbVie Dec. 20, meaning the regulatory decision likely would occur during the second half of 2019.

Although AbbVie tested 15 mg and 30 mg doses of upadacitinib in Phase II RA studies, its filing seeks approval of the lower dose. Analysts offered competing theories on why the lower dose was requested, with Leerink Partners Geoffrey Porges noting that several assays showed reduced selectivity for the JAK1 inhibitor at higher doses.

Morgan Stanley's Risinger noted that the 15 mg dose proved only slightly less effective than 30 mg in RA and achieved superiority to Humira in the SELECT-COMPARE trial, which did not test the 30 mg dose. By contrast, competing JAK1 inhibitors now on the market – **Pfizer Inc.**'s *Xeljanz* (tofacitinib) and **Eli Lilly & Co.**'s *Olumiant* (baracitinib) – have not demonstrated superiority to Humira.

Pointing out that novel candidates for RA typically are subject of FDA advisory committee reviews, AbbVie President Michael Severino said it's early in the review cycle, but that a panel review would not surprise AbbVie.

Referring to Severino's recent promotion to president from heading R&D, one questioner asked Gonzalez to speak about a possible transition plan. "I've heard all the rumors about potentially me retiring," the exec said. "I can tell you they are not true. As many of you probably know, I retired once and I can tell you I'm heck of a lot better at running AbbVie than I was at retirement." Gonzalez retired from Abbott as president in 2007 and came out of retirement in 2009 ahead of the AbbVie spin-out.

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Allergan Thinks It's Ready To Withstand Restasis Generics

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Allergan PLC is coming to grips with imminent generic competition for *Restasis* in the US. As the loss of exclusivity looms for its second-biggest seller, the company is counting on continued growth for top-seller *Botox* in both therapeutic and aesthetic indications, an expected label addition for *Vraylar* in bipolar depression and the potential of several other late-stage pipeline assets.

The Dublin-headquartered firm took a hit in 2018, as fourth quarter net sales income decreased 5.7% to $4.1bn and full-year revenues dropped 1% to $15.8bn. Execs pointed to the beginning fall-off of Restasis (cyclosporine ophthalmic emulsion 0.05%) as a key reason, but also disclosed a set of impairment charges totaling $5.4bn. The write-downs reflect disappointing commercial performance from aesthetic brand *Kybella* as well as weakness overall in the general medicine unit, Chief Financial Officer Matthew Walsh explained on the Jan. 29 investor call.

Restasis global sales declined 14.4% during 2018 to $1.26bn, all but $65m of that realized in the US. The decrease was attributed to lower net pricing and inventory reductions. With generic versions possibly just around the corner at **Teva Pharmaceutical Industries Ltd.** and **Mylan NV**, US Restasis sales may begin to fall off as badly as ex-US sales have. *(Also see "Q4 Earnings Preview: Pfizer, Amgen, Allergan, Biogen And Novartis" - Scrip, 25 Jan, 2019.)* Leerink Partners predicts Restasis revenues will drop another 71% this year to $344m, and shrink to just $77m in 2023.

The US specialized therapeutics unit – which includes Restasis and both aesthetic and therapeutic Botox (onabotulinumtoxinA) – saw a 3.9% decrease in net sales during the fourth quarter, as volume demand growth for the neurotoxin was offset by Restasis. Botox cosmetic revenues were $258.1m, up 13% year-over-year, while therapeutic use of the product brought in $433.3m, up 12.8%, continuing positive trends reported in third quarter 2018. *(Also see "Allergan's Botox Holds Its Own In Migraine, Despite CGRP Competition" - Scrip, 30 Oct, 2018.)*

For full-year 2018, Botox brought in $2.55bn in the US, up roughly 18% from $2.25bn in 2017. Global Botox revenues totaled $3.58bn for the year, up 12.9%. This helped drive a 1% growth rate for Allergan's international sales in the fourth quarter to $870.2m.

In a Jan. 29 note, Leerink Partners analyst Marc Goodman said Botox therapeutic's strong performance likely indicated better-than-expected sales in migraine prevention, "which is great to see," he added.

Morningstar analyst Michael Waterhouse called Botox's growth in both therapeutic and cosmetic indications "a key positive" for Allergan. "Botox maintained a 13% growth rate in both cosmetic and therapeutic indications within the US during the quarter despite the launch of competing CGRPs for migraine," he said Jan. 29. "Management noted very limited prescription losses to CGRPs, but we think this might be difficult to sustain even though Botox has so far performed better than we initially expected."

KYBELLA DISAPPOINTMENT LEADS TO LARGE WRITE-DOWN

Kybella (deoxycholic acid) – a cosmetic product intended to reduce double-chin – brought in $38.1m in 2018, down 32.3% from 2017. Allergan bought out **Kythera Biopharmaceuticals Inc.** for roughly $1.9bn in 2015 largely on the promise of Kybella; management attributed $1.6bn of the new impairment charge as related to that product.

Noting that the Kythera acquisition "has not worked out as planned" and that another $622m of the impairment charges was attributed to performance by anti-infective products, Credit Suisse analyst Vamil Divan wrote Jan. 29 that "given questions around past deals and management's ability to execute, we think the Street will likely view this large write-off negatively." Allergan's stock finished the trading day Jan. 29 down 8.55% to $145.12 per share.

Allergan also disclosed that it still intends to sell off its infectious disease business, which is part of its struggling general medicine division, but now plans to keep and attempt to grow its women's health unit. *(Also see "No Fire Sale: Allergan May Sell Women's Health, Infectious Disease Units" - Scrip, 30 May, 2018.)* General medicine net revenues fell 8.4% during the fourth quarter to $1.4bn total, driven by patent expiries for *Namenda XR* and *Estrace*. Namenda (memantine) products brought in $10.7m in the fourth quarter, down from $97.8m in fourth quarter 2017, and full-year sales declined 382% to $71m. Likewise, *Estrace* (estradiol vaginal cream) tumbled 318% on the year to $49m.

"On anti-infectives, we are in the final stages of this process and believe that this business is more likely than not to be sold," CEO Brent Saunders said. "While we do not yet have a completed transaction to announce at this time, and there are always risks to completing a transaction, current facts and circumstances are indicating that a sale of anti-infectives is probable over the near term."

The August "complete response" letter from the US FDA pertaining to the filing for approval of ulipristal acetate (branded *Esmya* in Europe) in uterine fibroids probably altered Allergan's plan to sell off its women's health unit. *(Also see "Allergan's Ulipristal, Dogged By Liver Concerns, Gets An FDA Rejection" - Scrip, 22 Aug, 2018.)*

"For women's health, we have concluded that the highest value proposition for this business at this time is to continue managing it and optimizing it," Saunders explained. He added that the company is "winding down" the advisory process on a potential sale and will look to other ways to unlock the unit's economic potential.

STRATEGY FOR RESTASIS DECLINE

While Allergan talked up multiple ophthalmology candidates as part of its strategy for overcoming the Restasis patent cliff, a pair of neuropsychiatric drugs and an oral calcitonin gene-related peptide (CGRP) inhibitor for migraine may offer its best near-term growth opportunities, according to Cowen analyst Ken Cacciatore. The anticipated addition of bipolar

depression to *Vraylar*'s (cariprazine) label is one likely source of growth.

Currently approved for schizophrenia and bipolar mania, Vraylar realized US sales of $151m during the fourth quarter, up nearly 72% year-over-year. Full-year sales of $487m represented 199% growth. Bipolar depression could be added to the drug's label in May, if the FDA okays a supplemental approval.

Meanwhile, the Phase III N-methyl-D-aspartate (NMDA) receptor modulator rapastinel may offer Allergan another big-seller in neuropsychiatry. Multiple Phase III data readouts in major depressive disorder for the candidate are expected during the first half of the year. Cacciatore called it the "most interesting" NMDA receptor drug in development, offering important differentiation against **Johnson & Johnson**'s esketamine, because the latter likely will be a scheduled substance requiring 90-minute monitoring after administration and a 24-hour prohibition on driving for the patient.

"Ketamine [the active ingredient in esketamine] is well known to be effective in treating depression, though psychomimetic effects limit its wide use commercially," Cacciatore said. "Rapastinel works through the same receptor and has not shown any psychomimetic effects to date. Ketamine-like efficacy without a 'high' would be a potential blockbuster, and we are within 1-5 months of pivotal data."

The analyst also is bullish on the market potential of ubrogepant, Allergan's Phase III oral CGRP inhibitor for acute migraine. An FDA submission is expected this year, which could mean approval in 2020, if not before. "Given that Allergan already has a large and comprehensive migraine commercial effort via Botox migraine, this product will be able to be rapidly leveraged and complement Allergan's already leading prophylactic migraine program," Cacciatore said. "We continue to believe that this opportunity could easily exceed $500m."

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Generic Advair: Finally Approved, A Long Time Coming

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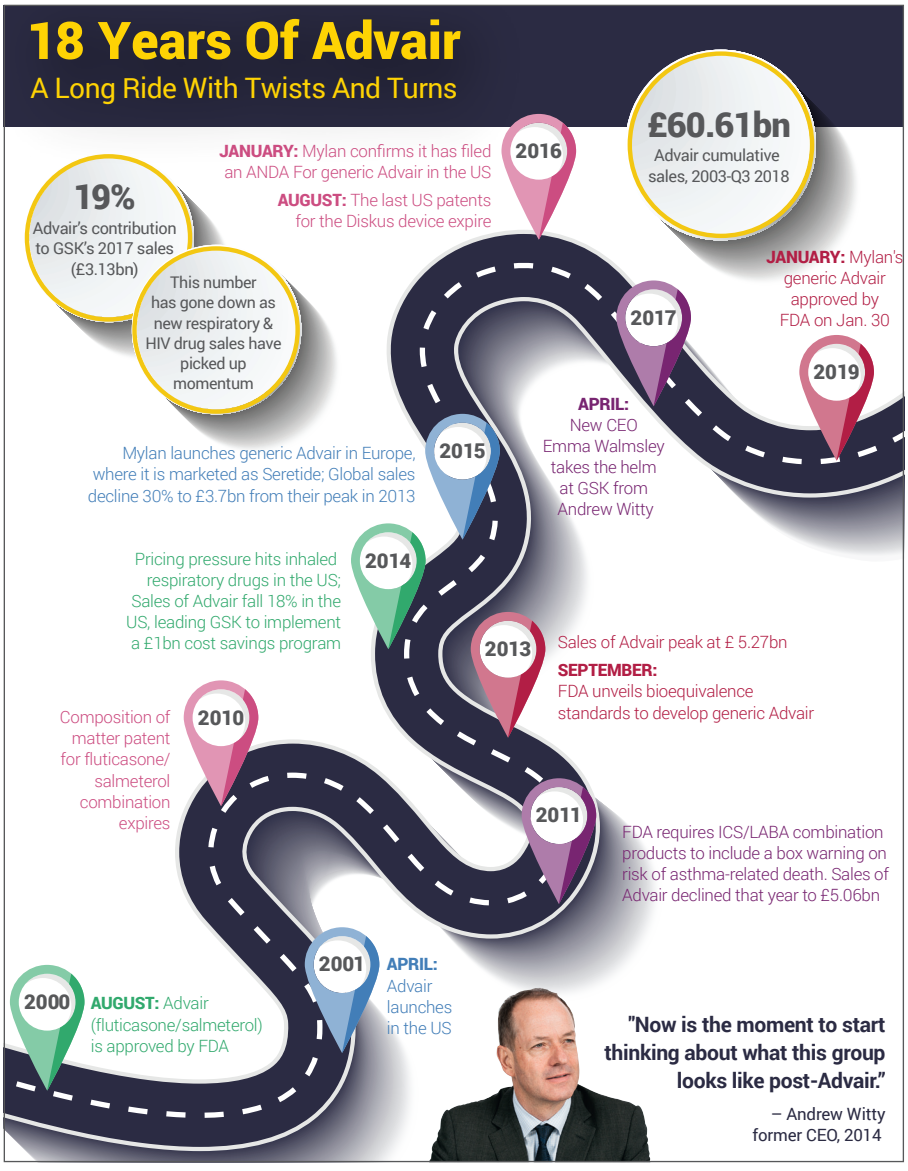
The US FDA approved the first generic version of **GlaxoSmithKline PLC**'s blockbuster asthma drug *Advair Diskus* (fluticasone propionate/salmeterol) Jan. 30 in a big win for **Mylan NV**. The approval underscores the R&D investment the company has put behind developing complex generics and biosimilars.

For GSK, the launch of a substitutable generic presents an overhang going into 2019, but one the company has long prepared for and one that has greatly diminished in the last five years. (*See timeline.*)

Sales of Advair peaked in 2013 when it generated £5.27bn ($6.91bn); in the first nine months of 2018, Advair generated £1.78bn ($2.33bn). The drug began facing generic competition in Europe in 2014, and GSK has diversified its respiratory portfolio with some success to include next-generation drugs like *Breo Ellipta* (fluticasone furoate/vilanterol) and *Anoro Ellipta* (umeclidinium/vilanterol).

The time it took to get a generic version of Advair across the finish line at the FDA gave GSK the opportunity to reduce its reliance on Advair. The drug, approved for asthma and chronic obstructive pulmonary disease (COPD), lost its patent protection years ago. The composition of matter patent on the two active ingredients expired in 2010, while the patents protecting the Diskus device expired in 2016.



But the FDA has been careful about approving an interchangeable generic, given the complex nature of the inhaled combination drug administered through a device. FDA Commissioner Scott Gottlieb has made approving complex generic drugs a high priority at the agency.

Mylan has been in a tight race with others, including **Novartis AG**'s **Sandoz International GMBH** generic drug unit and **Hikma Pharmaceuticals PLC**, to get the first approval. The company received two complete response letters to its ANDA filed in 2017 but quickly turned around with the information FDA was requesting, most recently in mid-July. The company had been anticipating FDA action by October, but had not received any official word from the agency.

The company has planned to sell the generic under the brand name *Wixela Inhub*.

For GSK, the loss of Advair will certainly be felt. For many years, Advair almost single handedly propped the pharmaceuticals business up. Over the past three years, however, the company has launched a portfolio of newer next-generation drugs under the *Ellipta* umbrella. Sales of Ellipta drugs were £1.4bn in the first nine months of 2018, closing in on Advair. **GlaxoSmithKline PLC**'s HIV business **ViiV Healthcare** has also strengthened, as has its vaccines, particularly with the launch of the shingles vaccine *Shingrix*.

The loss of Advair will not be nearly as painful for GSK as it would have been if a generic had come in 2016, as some investors worried at the time.

The lackluster launch of some other complex generics in the US has also highlighted how branded companies can successfully retain market share by lowering prices. It's a lesson Mylan has learned all too well. It launched the first generic of **Teva Pharmaceutical Industries Ltd.**'s *Copaxone* 40 mg late in 2017, but Teva has managed to hold a significant amount of the market share by competing on price.

GSK, meanwhile, under its new leadership team, led by CEO Emma Walmsley, has pivoted to oncology as an area for future growth, and has barely given the anticipated launch of a generic Advair more than a cursory backward glance. Advair represented about 8% of the company's nine-month revenues, down from 19% of 2017 revenues.

Advair launched in 2001 and generated roughly £60.61bn in cumulative revenues through the third quarter 2018.

Published online 31 January 2019

Novartis' Entresto Faces Challenge From Natco In India

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Could **Novartis AG** be heading for another tough patent battle in India? It may be too early to predict how things will play out, but **Natco Pharma Ltd.**'s cut-price version of Novartis' heart failure therapy *Entresto* (sacubitril/valsartan) has just made its debut on the Indian market, in what appears to be an "at-risk" launch.

The Hyderabad-based company said that it had launched *Valsac* (valsartan/sacubitril) tablet at an "affordable price"- the 50 mg and 100 mg strengths come at a maximum retail price of INR45 ($0.63) and INR55, per tablet, respectively.

Entresto, sold as *Vymada* by Novartis in India, is available at about INR74.5 per tablet for the 50 mg version, while the product's second brands *Cidmus* and *Azmarda,* marketed by **Lupin Ltd.** and **Cipla Ltd.**, respectively, are both available at INR69.82/tablet, according to pricing data on some online pharmacies in India.

POST-GRANT PATENT OPPOSITION

While specifics around Natco's at-risk launch strategy for Valsac were not clear, sources indicated that the Indian firm had moved a post-grant patent opposition against the innovator product. The exact grounds of the opposition could not immediately be ascertained.

Novartis told *Scrip* that it is aware that Natco has announced the launch of a generic version of valsartan-sacubitril and is "evaluating its options." The Swiss multinational shared no further specifics on the issue, including the patent status of Entresto in India.

India's Patent Regulations provide for both pre-grant and post-grant patent opposition opportunities. Under Section 25(2) of the Indian Patents Act, a post-grant opposition notice would require to be made to the Patent Controller by any "person interested" at any time after the grant of patent but before the expiry of a period of one year "from the date of publication of grant of a patent." Under the regulations, a "person interested" includes a person "engaged in, or in promoting, research in the same field as that to which the invention relates."

There are several grounds for such opposition including if the patentee has wrongfully obtained the invention or the invention was publicly known/used in India before the priority date of that claim, or the invention is obvious and does not involve any inventive step, or if the subject-matter is not an invention or not patentable under the regulations.

DULLING THE MOMENTUM?

A cut-price version may well just "dull the momentum" for the Swiss multinational in a market where heart failure affects about 8-10 million patients, an industry analyst said.

Novartis needs no reminding of the crucial patent battle pertaining to its anticancer *Glivec* (imatinib mesylate) in India, which did not go its way. In 2013, India's Supreme Court declined a patent for Glivec – the court held that the beta crystalline form of imatinib mesylate failed in both the tests of invention and patentability as provided under specific clauses and Section 3(d) of India's Patent Act.

Natco is a tough customer; not only does it sell its imatinib version in India, it also successfully pursued a compulsory licence for Bayer's *Nexavar* (sorafenib tosylate) some years ago. In 2012 India approved its first compulsory license in the area of medicines, allowing Natco to self-manufacture and sell a version of Nexavar for just over 3% of the price that the German company sold it for in India at the time.

Published online 29 January 2019

Fresh EU Okay For Rubraca Boosts Clovis

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Despite lagging behind its PARP inhibitor rivals, a new approval for *Rubraca* in Europe has put **Clovis Oncology Inc.** back into the spotlight and possibly in the shop window for potential acquirers.

The European Commission has approved the use of Rubraca (rucaparib) for a second indication, as monotherapy for the maintenance treatment of adults with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response to platinum-based chemotherapy. It was approved for third-line BRCA-mutated recurrent ovarian cancer in Europe in May 2018 but importantly, this second thumbs-up, similar to one granted last year in the US, means patients will be eligible for treatment regardless of BRCA status.

> Zejula and Lynparza "have fairly significant head starts in this particular setting."

The green light, which was expected given that Clovis received a positive opinion from the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) in December, is based on the Phase III ARIEL program, specifically the ARIEL3 study. The latter trial demonstrated 13.7 months of median progression-free survival (PFS) in the all-comers population for Rubraca compared with 5.3 months for those on placebo.

Clovis CEO Patrick Mahaffy said in a statement that "as the only PARP inhibitor that has shown further tumor shrinkage as well as prolonged PFS in this maintenance setting, we believe Rubraca represents an important step forward for women with advanced ovarian cancer."

Commenting on the latest approval, Hardik Patel, an analyst at Informa's *Datamonitor Healthcare* arm, told *Scrip* that while this is important news for Rubraca, as it expands its target population, "I don't necessarily think this particular expansion will go a long way in improving its competitive positioning" in Europe versus fellow PARP inhibitors, namely **AstraZeneca PLC**'s market-leading *Lynparza* (olaparib) and **Tesaro Inc.**'s *Zejula* (niraparib).

Lynparza was approved in the EU for the maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete response or partial response to platinum-based chemotherapy way back in December 2014. This was expanded to include patients without BRCA mutations in May 2018.

Zejula was also approved in the EU as a monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete response or partial response to platinum-based chemotherapy back in November 2017.

As such, Zejula and Lynparza "have fairly significant head starts in this particular setting," Patel said. Rubraca is indeed the first drug to be approved in the EU for both the maintenance and third-line treatment setting but the other two "shouldn't be too far behind in adding further indications to their EU labels," he added.

Clovis is planning its initial launch of Rubraca as a maintenance therapy in Germany before the end of the first quarter, with additional roll-outs across the continent through the year. While the firm started building its commercial infrastructure in Europe following the initial marketing authorization in May 2018, it did not launch Rubraca at that time, choosing instead to wait until it got the expanded broad second-line maintenance label and not be in a later line of treatment than Lynparza and Zejula.

The company told *Scrip* that its EU commercial and medical affairs organizations are in place "and we are actively preparing for our Q1 2019 launch in Germany." Clovis added that for the rest of Europe, the majority of additional hires, including sales reps, will coincide with reimbursement approval in the individual countries "and will occur in late 2019 and early 2020, as will any meaningful revenues from those territories."

In an investor note following the CHMP opinion, Andrew Berens at Leerink wrote that "we see the European landscape as a significant opportunity for both Rubraca and Zejula, given that the European payors place more emphasis on the caliber of the registrational data than in the US." He noted that Lynparza has a broad label in the second-line maintenance setting, but that approval was based on Phase II data rather than Phase III data.

However, Clovis continues to face a major battle with Lynparza, especially now that **Merck & Co. Inc.** has put its marketing muscle behind the drug after inking an alliance with AstraZeneca, while Tesaro is in the process of being acquired by another pharma giant, **GlaxoSmithKline PLC**, in a $5.1bn deal. *(Also see "GSK Embraces PARP Promise With Tesaro Buy" - Scrip, 3 Dec, 2018.)*

That latter transaction increased rumors that Clovis is going to be an M&A target soon. Berens argued that "speculation Rubraca could be a valuable asset for an oncology company looking to expand European presence is likely to increase."

Speculation certainly went up around the time of the J.P. Morgan Healthcare Conference in San Francisco earlier this month where Clovis unveiled preliminary fourth quarter 2018 results that forecast US Rubraca sales of $30.3-$30.8m, up 33% from the third quarter and well above consensus estimates. Full-year sales were $95.3-$95.8m and the firm ended the year with $518m-$521m in cash.

Leerink's Berens said that this gives the company a strong foundation to advance the clinical development pipeline and further develop the commercial organization. Late last year at ESMO, it also presented promising data from the TRITON trial which could see Rubraca become the first drug in the PARP class to get approval for prostate cancer.

Importantly, he added, "we see the recent return of M&A to the targeted oncology space as improving investor sentiment, providing a further tailwind to the shares."

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Real Estate Sale, Including Osaka HQ, To Raise $347m For Takeda

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Takeda Pharmaceutical Co. Ltd. is to transfer the ownership of selected real estate assets in Japan – including its Osaka headquarters – to an undisclosed buyer to raise around JPY38bn ($347m) before tax ahead of the end of its current fiscal year on March 31.

The move, initially involving the formation of a new wholly owned subsidiary under existing Tokyo-based Takeda Pharmaceutical Real Estate (TPRE, itself 100% owned), will raise significant cash to help pay down borrowings related to the recently completed $61bn (in equity value) acquisition of **Shire PLC**.

While the deal will raise substantial money, it is also likely to generate some controversy among the company's more conservative investors given the inclusion of the company's main building in Osaka, Takeda's ancestral home, even though this will continue in its present form and function.

Company CEO, Frenchman Christophe Weber, came in for some criticism ahead of the Shire merger for what detractors saw as his attempts to move 237 year-old Takeda away from its Japanese roots, something he refuted.

As part of the run-up to the Jan. 8 completion of the Shire deal, Takeda stated repeatedly that its intention was to pay down the roughly $48bn in net debt associated with the transaction through a variety of means, to 2x adjusted EBITDA (earnings before interest, tax, depreciation and amortization) within three to five years.

The company's various financing arrangements, which it sees as "highly competitive", give a blended interest rate of around 2.3% for the debt.

Under the new move, a portion of the real estate businesses of Takeda and property management company TPRE (originally established in 2006) will first be taken over by the new entity (formed in January 2019 as TYK Business Preparation Company KK under TPRE).

Takeda Sells Off Properties, Including in Osaka, To Raise Cash Post-Shire

TYK will issue 59,423 shares, with 54,640 of these to be allocated to TPRE and the remainder to Takeda. All these shares will then be transferred on the March date by the latter two companies to the end recipient, which at this transferee's request is remaining unidentified.

The new owner will thereafter hold 21 assets, including Takeda's flagship Osaka Mido-suji Building headquarters in Osaka, although business activities at all the affected sites will continue as normal, presumably under lease-back arrangements.

The total book value of these assets as of March 31, 2018 was JPY12.9bn, Takeda noted.

PLANNED BUSINESS DISPOSALS

The company said again that: "Takeda will continue to look into possible sales of non-core assets worth up to 10 billion US dollars to further decrease Takeda's leverage (net debt to adjusted EBITDA ratio) and optimize its business resources."

Speculation continues around the size and shape of these divestments, with Shire's eye care business, and more recently Takeda's mature emerging markets portfolio, being put forward as possible candidates, although nothing has been confirmed.

It appears that Takeda's large over-the-counter and consumer healthcare business in Japan is not on the block, given Weber's recent assertion that this already has "critical mass."

Takeda has already included JPY80bn in planned gains on sales of real estate in its current fiscal year, which it noted includes the anticipated proceeds of the newly disclosed plan.

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From the editors of PharmAsia News.

Embattled Midatech Receives Lifeline From China To Save Cancer Candidate

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Just days after its share price went south by 50%, UK biotech **Midatech Pharma PLC** has detailed plans that may save the development of its carcinoid cancer drug candidate. The arrangement will see a Chinese drug distributor take majority ownership of the firm.

In a trading update last week, the Oxford-based company said it had "very limited cash to enable it to continue as a going concern" and "will urgently look to conclude its discussions" with an unnamed potential strategic investor. In September, the company made $13m through the sale of its US subsidiary to Kanwa Holdings. However, net proceeds were only $4.2m after the company repaid a loan, leaving it only enough working capital to last it until the end of the first quarter. *(Also see "Midatech Divests US Unit To Focus On Its Rival Drug To Novartis' Sandostatin LAR" - Scrip, 28 Sep, 2018.)*

CHINESE INVESTMENT

In a new statement issued Jan. 29, the company has put together a range of actions that it hopes will ensure the company can operate for longer, but it will have to issue new shares and sign away rights to its pipeline of drugs in China and other Asian territories.

Chinese drug distributor China Medical Systems (CMS), chaired by Chinese billionaire Lam Kong, has signed a deal to develop and commercialize Midatech Pharma's lead product MTD201, its childhood brain cancer candidate MTX110 and any new pharmaceutical products or line extensions in China and certain Southeast Asian countries including Singapore, the Philippines and Malaysia.

CMS said the products would have "broad market prospects" once commercialized in the territory.

Midatech will earn a manufacturing margin in the low double-digit percentage range. In addition, it will be eligible to receive regulatory milestone payments for each product up to seven figures, and cumulative sales-based milestone payments of seven to eight figures.

CMS will also make an equity investment of £8m, at 3.85 pence per share. This will give CMS a 77.3% stake in Midatech. CMS is listed on the Hong Kong stock exchange, and has a HK$18.40bn (£1.8bn) market capitalization. Its founder and chairman Lam Kong has a net worth of $1.5bn, according to *Forbes*.

Huaizheng Peng, a director of CMS subsidiary CMS Venture and CEO of A&B, another CMS subsidiary, will be appointed as a non-executive director of Midatech. Ex-**Shire PLC** CEO Rolf Stahel chairs Midatech's board.

However, the company has made it clear that money raised through the subscription offer is expected to only provide working capital for the group until the fourth quarter of 2019.

AIM-listed Midatech also intends to raise further funds through a placing and open offer on the same terms as offered to CMS, at the issue price of 3.85 pence. A meeting of shareholders is due to take place on Feb. 18, and if the measures are approved the shares will be issued and listed on AIM.

It is also continuing to explore opportunities for out-licensing MTD201, MTX110 and the company's technology platforms *Q-Sphera*, *MidaCore* and *MidaSolve*.

Midatech is focused on getting its lead candidate, MTD201, to a market which is worth $2bn, according to the biotech.

The market leader for the treatment of carcinoid and acromegaly is Novartis' *Sandostatin LAR*. Midatech believes MTD201 could be a good alternative to SLAR because of its sustained-release formulation, which should improve injectability, avoid needle blockage, enable the use of smaller needles and reduce injection site pain. Both products are formulations of octreotide.

Guidance from the FDA has driven Midatech to pursue a pivotal trial, either a multi-dose study in healthy volunteers or a study in patients.

Costs for this type of study may be about £5-7m, excluding the cost of production. A new drug application is planned for 2021, subject to the successful commercial scale-up of MTD201 manufacturing. The company says it is now seeking further funding in the form of loans or grants to support the manufacturing scale-up costs of MTD201, which are expected to be about €15m.

Midatech says it is "seeking the quickest, most efficient and potentially valuable route to market for MTD201," and in addition to ongoing talks with the FDA, is now also seeking EMA feedback on the MTD201 trial design.

EIGHTEEN MONTHS AND BEYOND

Within the next year and a half, Midatech is expecting clinical data readouts from three programs: carcinoid cancer and acromegaly, brain cancer, and the group's autoimmune diabetes vaccine.

It recently received a regional Basque government Gauzatu loan of €1.5m, and the company is in the process of applying to the Spanish Government for a loan to further support manufacturing scale-up. If successful, it is expected that the loan will cover up to 75% of the manufacturing scale-up cost of approximately €15m.

While MTD201 is clearly the front runner to solving Midatech's money worries, its other candidate, MTX110 for for diffuse intrinsic pontine glioma (DIPG), an aggressive and fatal brain stem tumor, is expected to generate data this year. Interim data from the Phase I safety component of the study are expected in 2019. This will also establish the recommended dose to be used in the follow-on Phase II efficacy component of the study program, with the objective of assessing overall survival after 12 months. The Phase II component of the study is not covered by the net proceeds of the share sale.

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Shaken MorphoSys 'Assessing Options' After Losing US Darzalex Patent Ruling

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MorphoSys AG said it was "disappointed" about a US court ruling against the German biotech in its three-year patent dispute with Danish biotech **Genmab AS** and pharma giant **Johnson & Johnson** over blood cancer blockbuster *Darzalex* (daratumumab). The ruling has blocked the start of a jury trial.

MorphoSys Hit By Patent Lawsuit Ruling Over Blood Cancer Drug

The complaint, filed in 2016 by MorphoSys with the US District Court of Delaware, alleges that Darzalex, an antibody-based biologic drug approved to treat multiple myeloma, infringes MorphoSys patents on the use of human antibodies.

MorphoSys held that Darzalex infringed on three of its patents, those with US patent numbers 8,263,746 and 9,200,061 and 9,758,590 that cover its own anti-CD38 antibody, MOR202.

But a summary judgment order issued Jan. 25 by the Delaware court declared all three patents invalid due to "lack of enablement" and so a jury trial due to assess the matter in February will now not take place.

A ruling in favor of MorphoSys could have triggered a significant royalty stream on Darzalex to the German group.

MorphoSys' management in a terse reaction said the company was "disappointed" with the court decision and that it was considering all of its options, including an appeal to the Federal Circuit Court.

MorphoSys, which is in the early stage of building its own in-house pipeline, had sought redress for alleged infringement by J&J's and Genmab's CD38-directed monoclonal antibody.

"This court decision has no bearing upon the composition of matter patent protection for MorphoSys' own CD38 antibody MOR202 and thus MorphoSys' ability to develop MOR202 in various indications," the Munich, Germany-based company said.

MorphoSys is developing the therapy on its own after **Celgene Corp.** in 2015 ended a collaboration to develop the differentiated antibody. However, it decided last year not to continue development of MOR202 in multiple myeloma after completion of its Phase I/IIa trial.

That decision was partly in response to the huge success that Darzalex has enjoyed, as well as because MorphoSys has not found a replacement partner to progress MOR202 in western markets.

MorphoSys does however expect its Chinese partner **I-MAB Biopharma** to continue preparations for clinical development in multiple myeloma using MOR202 and to soon start a pivotal evaluation of it in China, a spokesperson for the German biotech told *Scrip*.

MorphoSys also decided not to continue studying MOR202 in non-small cell lung cancer (NSCLC) "for the time being" following the discontinuation of a clinical study by J&J of its CD38 antibody in combination with a checkpoint inhibitor.

It will still explore other indications with MOR202 and plans to start a Phase II trial testing it in an unidentified autoimmune disorder in the third quarter of this year, the spokesperson said.

"This court decision has no bearing upon the composition of matter patent protection for MorphoSys' own CD38 antibody MOR202 and thus MorphoSys' ability to develop MOR202 in various indications." - MorphoSys AG

MUTED ANALYST REACTION

Analysts at Deutsche Bank said they were taking a sanguine view on the US court ruling and maintaining their 'buy' rating on MorphoSys.

They pointed to the fact MorphoSys today has 115 antibody drug candidates in development, of which 103 are partnered and 12 proprietary.

"The company's first product on the market, Tremfya, which is partnered with J&J, is on its way to becoming a multi-billion blockbuster, and late-stage data for its proprietary lead candidate MOR208 are very encouraging, suggesting further upside to peak sales estimates," they concluded.

Published online 29 January 2019

Amicus To See If Its Fabry Drug Galafold Can Benefit From Mis-Diagnosed MS

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Amicus Therapeutics Inc.'s oral enzyme replacement therapy *Galafold* (migalastat) for the rare condition Fabry disease has enjoyed a strong initial launch in the US, Europe and Japan and the upward trajectory remains steep, largely thanks to the drug's relative ease of use, efficacy and price, according to the rare disease specialist's president.

Added sales momentum for Galafold could also come with better diagnosis of multiple sclerosis, "because Fabry can get mis-diagnosed as MS," Bradley Campbell told *Scrip* in an interview.

IMPROVING FABRY DIAGNOSIS

"Fabry has a significant under-diagnosis rate. There also appears to be a significant mis-diagnosis rate of Fabry disease," Campbell said.

"Other market players in the past have looked in renal dialysis clinics, in cardiovascular and stroke clinics and found mis-diagnosed Fabry disease. Similarly, we're now seeing that around 5.5% of patients who are believed to have multiple sclerosis in fact had Fabry disease."

"One of the things that characterizes MS is white matter lesions in the brain; it can be weakness, or systemic pain, and those same characteristics exist in some portions of the population having Fabry disease," Campbell explained. "Because Fabry disease is so much less common, it's understandable that someone might assume multiple sclerosis rather than a condition being Fabry disease."

The challenge is to know that that incorrect diagnosis is possible.

"But if you can convince physicians that it is possible that between 3% to 5% of their patients suspected of having MS might actually have Fabry disease, you can very easily run a genetic test for Fabry disease and come up with the appropriate diagnosis." Campbell said.

Potentially mis-diagnosed Fabry disease could theoretically be corrected and 'tapped' in other clinics by Amicus.

Amicus Therapeutics Inc. President Bradley Campbell

> "If you can convince physicians that it is possible that between 3% to 5% of their patients suspected of having MS might actually have Fabry disease, you can very easily run a genetic test for Fabry disease and come up with the appropriate diagnosis" - Bradley Campbell

"In dialysis clinics we have seen patients who thought they had kidney failure for more general reasons and in fact had Fabry disease and that's what led to their kidney disease. So that's the kind of model that we're looking at. The same goes for GI and irritable bowel syndrome, as Fabry disease also involves GI stress," Campbell told *Scrip*.

GALAFOLD STEEP LAUNCH

Orally-administered Galafold is Amicus' first approved drug. It was launched in the US and Japan in 2018, having been approved in Japan in June and launched in July, while US approval and launch both occurred in August. Galafold was launched in Germany in 2016. and has been rolling out into Europe's other main economies since then.

Sales of the therapy in 2018 beat both internal estimates at the company and market projections, and came in at the end of the year with total preliminary revenue of $91m with 650 patients under treatment globally.

The New Jersey-based company expects Galafold revenue in 2019 of between $160m to $180m worldwide, propelled by a number of growth drivers.

"Key dynamics are the continued launch of Galafold in the US and Japan – it will be the first full year on the market in those two geographies – while continuing to grow in the European region," Campbell said.

"We have more than half the market for Fabry treatment in Europe's big five economies. We plan to continue to expand market share there, while launching in other countries around the world."

The company foresee sales of Galafold of $500m by 2023 and eventual peak sales of $1bn for the therapy.

Amicus is also busy with its development program for AT-GAA treatment for Pompe disease, which is soon entering pivotal stage.

The company also has an early-stage gene therapy pipeline.

CONTINUED ON PAGE 23

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

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

PIPELINE WATCH, 25–31 JANUARY 2019

Event Stage	Lead Company/Partner	Drug Name	Indication	Comments	Change To LOA (%)	LOA (%)
Phase III Published Results	Johnson & Johnson	cadazolid	Clostridium difficile-Associated Diarrhea	The Lancet Infectious Diseases, Jan. 29, 2019	0	0
Phase III Updated Results	Shield Therapeutics plc	Feraccru (ferric maltol)	Anemia Due to Chronic Renal Failure, Dialysis-Independent	AEGIS-CKD; Improved Hemoglobin, Well Tolerated	0	53
Phase III Top-Line Results	Pfizer Inc./Eli Lilly	tanezumab	Osteoarthritis Pain	Positive Results, Met Primary Endpoints	0	65
Phase III Top-Line Results	Takeda Pharmaceutical	TAK-003 Tetravalent Vaccine	Dengue Fever	TIDES; Met Primary Efficacy Endpoint, Well Tolerated	0	61
Phase III Top-Line Results	Scynexis, Inc.	ibrexafungerp, Oral	Mucocutaneous Invasive Fungal Infections	FURI; Positive Results At Interim Analysis	4	62
Phase III Top-Line Results	Alexion Pharmaceuticals, Inc.	Ultomiris (ravulizumab-cwvz)	*Atypical Hemolytic Uremic Syndrome*	Treatment-Naïve; Sustained Efficacy	5	65
Phase III Top-Line Results	Johnson & Johnson	Erleada (apalutamide)	Prostate Cancer, Metastatic, Castration-Sensitive	*TITAN; Met OS And PFS Endpoints*	0	100
Phase III Top-Line Results	Mithra Pharmaceuticals SA	Estelle (estetrol/drospirenone)	Contraception	E4 FREEDOM; Met Primary Efficacy Endpoint	4	71
Phase III Top-Line Results	Sylentis, S.A.	tivanisiran (SYL1001)	Dry Eye Disease	HELIX; Pain Symptoms Improved	0	51
Phase III Trial Initiation	Theravance Biopharma, Inc.	ampreloxetine (TD-9855)	Orthostatic Hypotension	0169; A Noradrenaline Re-Uptake Inhibitor	34	44
Phase III Trial Announcement	Quest PharmaTech Inc.	oregovomab	Ovarian Cancer, Front-Line	w/Chemotherapy; An Anti-CA-125 Antibody	0	12
Phase III Trial Announcement	Entera Bio, Ltd.	Oral PTH (1-34)	Osteoporosis	vs Forteo; 12-Month Study In US	0	14
Phase III Trial Announcement	PellePharm, Inc.	patidegib gel	Basal Cell Carcinoma	926-301; A 150-Patient Study	0	10

Source: Biomedtracker | Informa, 2019

CONTINUED FROM PAGE 21

PIVOTAL POMPE PHASE III

Campbell said 2019 would be an important year for Amicus's clinical development of AT-GAA as a treatment for Pompe disease, an inherited lysosomal storage disorder that can be can be debilitating, and is characterized by severe muscle weakness that worsens over time.

"We had discussions in 2018 where we came into alignment both with the FDA and EMA on a registration study, which will be a registrational Phase III study for AT-GAA," Campbell said.

"We will therefore by the end of this year enroll about 100 patients, at more than 90 sites around the world."

The study will compose a combination of 'switched' patients and treatment 'naive' patients, he said.

"The primary endpoint will be the six-minute walk test and it's a 12-month endpoint, so we'll hope to see data towards the second half of 2020 and we'll use that data to approach regulators on a potential submission," Campbell told *Scrip*.

Published online 30 January 2019

APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
Kevin Finney	Abide Therapeutics Inc	President, Chief Operating Officer and Director	Zavante Therapeutics	Chief Operating Officer	1/24/19
Cynthia Pussinen	Actinium Pharmaceuticals Inc	Executive Vice President, Technical Operations and Supply Chain	Pfizer Inc	Head, Strategic Portfolio Management, Worldwide Research and Development	1/23/19
Christopher C. Young	Akorn Inc	Executive Vice President, Global Operations	Actavis	Vice President, Operations	1/28/19
Mehrdad Mobasher	Corvus Pharmaceuticals Inc	Chief Medical Officer and Vice President	Genentech/Roche	Hematology/Oncology Development, Global Clinical Leader	1/28/19
Dimitris Voliotis	CureVac AG	Chief Development Officer	Eisai Inc	Senior Vice President, Global Clinical Development, Oncology Business Group	1/28/19
Jean Monin	Ethypharm Group	Chief Commercial Operations Officer	Amgen Inc	Vice President and General Manager, France	1/29/19
Alexander Hardy	Genentech	Chief Executive Officer	Roche	Head, Global Product Strategy	3/1/19
Richard Pascoe	Histogen Inc	Chairman and Chief Executive Officer	Apricus Biosciences Inc	Chief Executive Officer	1/28/19
Robert Jacks	Indalo Therapeutics Inc	Chief Executive Officer and President	Symbiomix Therapeutics	Co-Founder, President and Chief Financial Officer	1/28/19
Brandon Brega	Ology Bioservices Inc	Chief Operating Officer	Merck & Co	Associate Vice President, Plant Management	1/23/19
Sheldon Koenig	Portola Pharmaceuticals Inc	Chief Commercial Officer and Executive Vice President	Sanofi	Senior Vice President and Head, Cardiovascular Franchise	1/28/19
Andreas Maderna	Sutro Biopharma Inc	Vice President, Chemistry	Pfizer Inc	Associate Research Fellow	1/29/19
George Spencer Green	Taiwan Liposome Co Ltd	Chief Medical Officer	Pfizer Inc	Vice President and Clinical Head, Biosimilars Development Program	1/25/19
Josep Infesta	Valbiotis	Head, Global Business Development	IZ3	Founder	1/24/19

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