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Payers Must Brace For Coming Wave Of Cell And Gene Therapies

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When cell and gene therapies were coming one at a time, initially for rare diseases, the impact on payers could be minimized. But now that a big wave of regenerative medicines for a wider array of diseases is hitting the commercial market, they could have a significant impact on the bottom line, companies acknowledged during the Alliance for Regenerative Medicine's (ARM's) recent Cell and Gene Meeting on the Mesa.

Given the complicated nature of these products, cell and gene therapy developers emphasized the importance of engaging with payers early and often to explain why a particular product is worth a health plan's or public payer's investment. Therapies with complex administration combined with significant pre- and post-treatment care can add to the product's price tag, but may also provide life-saving benefits to patients and reduce overall health care costs. *(Also see "Progress Being Made With Cell And Gene Therapy Market Access, But Challenges Remain" - Scrip, 8 Oct, 2019.)*

Enzyvant Sciences Ltd., for instance, expects US Food and Drug Administration approval for RVT-802 in pediatric congenital athymia before the end of this year. But the Roivant Sciences Inc. subsidiary understands that while its treatment for an ultra-rare disease isn't a big budget line item on its own, it adds to the coming flood of new cell and gene therapies for payers.

CEO Rachelle Jacques said in an interview with *Scrip* that in Enzyvant's pre-approval discussions about its tissue-based therapy "it was interesting to see payers having a very adverse reaction to comments of 'Oh, it's a small patient population, so it won't hurt your budget.' I think that's an old argument we need to be sensitive to … we do have to recognize it's a tidal wave coming for payers."

Spark Therapeutics Inc. chief commercial officer Ron Philip also pointed out during a commercial trailblazers session at the meeting that one or two cell or gene therapies probably aren't problematic for payers. However, Philip said, health plans and public health agencies will have to figure out a longer-term economic model to handle the increasing number of regenerative medicines on the market. "If the value is there, we benefit from that," he said.

Enzyvant's early talks with payers about the value of RVT-802 have been fruitful, Jacques said, noting that "we start the discussions at different places and a lot of them are coming to the same conclusions."

The Meeting on the Mesa, held 2-4 October in Carlsbad, CA, offered multiple opportunities for companies with products on or nearing the market to talk about how they are working with payers to illustrate the complexities and the benefits of their therapies.

NOVARTIS: A PIONEER IN CELL AND GENE THERAPY MARKET ACCESS

In anticipation of launching its cell and gene therapies, Novartis AG was able to craft favorable reimbursement deals – both outcomes-based agreements and payment via installments over multiple

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Roche and J&J report rises (p5-6)

Getting Ready For NASH
Genfit on approaching this new market (p19)

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Deal with bluebird targets hemophilia (p7)

from the editor

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Among the early reporters of quarterly results, Johnson & Johnson and Roche have set an upbeat tone for the final earnings season of 2019 before full-year financials are unveiled in early 2020. Both companies have upped their guidance for annual sales, vaunting strong performance by new products which has offset sales erosion of older mainstays by generics and biosimilars.

The longer it takes for biosimilars to gain real traction in the US, the more time these companies and their peers have to bolster their new product portfolios and drive commercial uptake, reducing reliance on lucrative but aging biologics. See p5-7 for full details of J&J and Roche's Q3 reviews.

The relative frequency of updates in the world of rare diseases and gene therapies compared with drugs for large patient populations highlights both the great progress that is being made in once intractable spaces, and the challenge that represents for payers. Regulatory incentives and technological breakthroughs have fuelled activity in once neglected diseases, but we're reaching a time when convincing payers to pay top dollar for therapies by pointing out the rarity of the cases becomes a losing argument.

As highlighted in our cover story, payers are bracing for a tidal wave of new specialized therapies that cumulatively will place increasingly significant pressure on overall budgets, regardless of the patient populations targeted by any one therapy.

Despite the challenge, optimism prevails: development of advanced therapies continues apace, while early and in-depth engagement between payers and developers has begun to yield innovative solutions to the cost conundrum.

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Galloping India Growth For Sacubitril/ Valsartan Under Shadow Of Challenge

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The Indian market for the sacubitril/valsartan combination appears to be growing in leaps and bounds, suggesting that Novartis AG's efforts to expand reach and access for its heart failure therapy via partnerships is paying dividends. Nevertheless, the shadow of an ongoing suit for a cut-price version of the product looms.

Novartis's Entresto (sacubitril/valsartan) is sold as Vymada in India, along with its second brands Cidmus and Azmarda, marketed by Lupin Ltd. and Cipla Ltd., respectively. Natco Pharma Ltd. earlier this year introduced its valsartan/sacubitril combination (Valsac)) at risk, with Novartis moving court against the Indian company for allegedly infringing its Indian patent on the product.

Data from the market research agency AIOCD AWACS indicate that the Indian market for the sacubitril/valsartan combination was valued at INR2.25bn ($31.5m), growing by 68% on a moving annual total (MAT) basis for September. This represents a significant jump from comparable numbers in December last year when the sacubitril/valsartan combination was valued at INR1.24bn. Impressively, the September data also suggest that sacubitril/valsartan has been driving growth in the cardiac segment, which reported MAT sales of INR170.76bn (+12.6%) for the month.

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years – based on conversations with payers that began months before approvals for the leukemia and lymphoma treatment Kymriah (tisagenlecleucel) and the spinal muscular atrophy (SMA) gene therapy Zolgensma (onasemnogene abeparvovec).

Kymriah is one of only two chimeric antigen receptor T-cell (CAR-T) therapies approved in the US; the other is Gilead Sciences Inc.'s Yescarta (axicabtagene ciloleucel). Both are one-time, autologous products in which T-cells removed from patients are genetically engineered to target the antigen CD19 on cancer cells.

Kymriah launched with a list price of $475,000, but Novartis pursued outcomes-based contracts and indication-based pricing from the start.

"Novartis rolled this out to all of the hospitals participating in the Kymriah network and we continue to offer it today," John Coombs, patient access lead for Novartis CAR-T therapies in the US, said in a panel on novel payment arrangements. For pediatric patients who don't respond to treatment by a certain time, the company won't bill the hospital for Kymriah.

"The hospital agrees not to bill a third-party payer and therefore this agreement extends to all third-party payers; so commercial payers benefit from it, Medicare benefits and Medicaid benefits," Coombs said.

He advised: "If you're going to be thinking about any kind of outcomes-based approach, start running it by your stakeholders – start to talk with them early."

Later he added, "understand your patients and how they move through the health care system and see which [pricing and reimbursement] option may be best for your therapy."

Doctors also spoke about the unique challenges of CAR-T therapies. Specialists involved in CAR-T programs at the University of California, San Diego (UCSD) and City of Hope in Los Angeles noted in a session about their experience with the treatments that managing potentially severe side effects – primarily cytokine release syndrome (CRS) and neurotoxicity – requires specialized care teams.

"These are the sickest of the patients that we have; these are the patients who are dying from a hematological malignancy and they need tremendous amounts of support," said John Zaia, director of the Center for Gene Therapy at City of Hope. He noted that these patients need a lot of care before and after CAR-T therapy, because they're already suffering from neutropenia, B-cell deficiency and many other side effects from prior lines of treatment and their disease.

> "Understand your patients and how they move through the health care system and see which [pricing and reimbursement] option may be best for your therapy." – John Coombs

Dimitrios Tzachanis from the UCSD Blood and Marrow Transplant Program noted that patients aren't admitted for CAR-T treatment unless the hospital has a neurologist trained in the treatment of CAR-T-induced neurotoxicity available. Also, a bed in the intensive care unit (ICU) and ICU staff trained to treat CRS and neurotoxicity must be ready for the patient. However, none of this is lined up until the payer that covers the patient has approved treatment with a CAR-T therapy.

Nevertheless, Tzachanis said he's never had a patient who progressed after several prior treatments and was essentially cured by CAR-T therapy complain about the complexity of their care – even individuals who spent a few days in the ICU due to severe neurotoxicity.

LUXTURNA: A GENE THERAPY ADMINISTERED IN SPECIAL CENTERS

Like Kymriah and Yescarta, which must be administered in certified cancer treatment centers, Spark's Luxturna (voretigene neparvovec) also must be administered at specialized eye surgery centers. Luxturna was approved in the US in December 2017 to treat patients with biallelic RPE65 mutation-associated retinal dystrophy, an inherited form of blindness.

The treatment is delivered by a subretinal injection, which must be administered by surgeons at centers where retinal specialists are available to deliver supportive care, Spark's Philip explained at the meeting.

"We used the benefits of the 21st Century Cures Act to be able to go early to the payers, probably six to nine months [ahead of approval] with some of them, and just have dialogues and try to explain to them" how Luxturna should be delivered and the benefits the treatment provides, including improved vision and the prevention of blindness.

"It was multiple engagements to try to get them comfortable with each one of those facets and to be able to get them to that point where we were able to get that feedback that was relevant," Philip said. "That feedback was enormously important for us to kind of shape the package or the set of solutions that we needed to put forward. I would recommend to anybody that is going to be launching, go early, talk to them and try to absorb that feedback."

The advice has proven out in ex-US markets as well. Spark's European partner Novartis recently attributed rapid approval for reimbursement of Luxturna's costs in the UK to early and constructive engagement with the National Health Service's National Institute for Health and Care Excellence (NICE). *(Also see "Novartis Prepares for UK Luxturna Rollout After Rapid NICE OK " - Scrip, 8 Sep, 2019.)*

That early engagement with payers is important, Philip noted, because reimbursement decisions are not going to be the same for every cell and gene therapy. Drug developers will have to make the case for specific products based on the standard of care for the disease they're treating, the specifics of their therapies and many other factors, he said.

Spark spent a lot of time talking publicly about the potential $1m cost of its therapy prior to Luxturna's approval before settling on its $850,000 list price.

ENZYVANT'S RVT-802: A COMPLICATED COMPLEX THERAPY

Enzyvant's RVT-802 has a slew of peculiarities that only starts with its ultra-rare patient population – 20 children in the US each year with congenital athymia, versus 1,000-2,000 patients with biallelic RPE65 mutation-associated retinal dystrophy for Luxturna.

It's also manufactured at a single good manufacturing practice (GMP)-certified site at Duke University, where RVT-802 originally was developed for congenital athymia associated with DiGeorge syndrome and other diseases.

Contributing to RVT-802's unique challenges, athymia patients are born without a thymus, so they don't produce normal functioning T-cells and suffer from severe immunodeficiency that usually leads to death around 24 months of age due to their susceptibility to infections. That means when patients travel for treatment with RVT-802 they require special medical flights, because they can't risk exposure to infection on commercial flights.

Also, athymia patients must be well when they're treated with RVT-802, so they require significant pre-implant care. Post-implant care at Duke and at home is extensive as well, because it takes several months for patients to generate enough T-cells to effectively fight infections and other illnesses.

However, the implantation itself is not difficult, Enzyvant CEO Jacques said, and survival to date far exceeds the natural history for these young patients.

"We have 90 patients in our data set that have been treated over time at different time intervals with the oldest patient who is 26 years old, so we have 25.5 years of data for her," Jacques said.

The one-year survival rate for RVT-802 is 75% and overall survival is 72%, so early efficacy largely is preserved over time. The median follow-up is eight years.

"The payers haven't been particularly focused on the pre- and the post-care," Jacques said. "As they do with all of these one-time novel therapies, they want to understand what's coming. We have been able to tell them about Enzyvant, we have been able to tell them about RVT-802, what it is and the benefits it brings, but there's more detailed discussions that can happen later."

So far, she said, payers are open to Enzyvant's outcomes-based proposals, which the company hopes will remove any barriers to access for athymia patients and enable rapid treatment with RVT-802.

"The patients are in a situation where it's a ticking clock for them, so every day that goes by that they don't get treated is a day that they're at risk, so we're keeping that sense of urgency in mind," Jacques said.

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J&J's Tremfya Gets Its Blockbuster Wings

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Johnson & Johnson's Tremfya (guselkumab) is securely on track to become a big blockbuster this year, after the first-in-class IL-23 inhibitor grew 69% in the third quarter. Tremfya was one of 10 J&J medicines that grew double digits in the quarter, prompting the company to raise its sales and earnings guidance for the year.

"Our growth was broadly based with 10 of our key brands growing at double-digit rates, which more than offset the erosion due to biosimilars and generics," worldwide chairman, pharmaceuticals Jennifer Taubert said during the company's third quarter earnings call on 15 October.

Tremfya is one of J&J's rising stars, but the drug is launching in a competitive therapeutic area that includes older anti-TNFs and newer IL-17 inhibitors like Novartis AG' Cosentyx (secukinumab) and Eli Lilly & Co.'s Taltz (ixekizumab). Investors have had some concerns about how Tremfya would differentiate itself in the competitive market.

In addition, AbbVie Inc. – an experienced immunology market leader – just launched a second IL-23 blocker, Skyrizi (risankizumab). *(Also see "AbbVie's Humira Succession Plan Begins Taking Shape With Skyrizi US Approval" - Scrip, 24 Apr, 2019.)* The launch of Skyrizi got underway earlier this year, so investors will be curious to hear more about uptake during AbbVie's third quarter call.

J&J said it is confident that the data supporting Tremfya, including a head-to-head trial versus Cosentyx, makes a strong case for the product.

"We believe we've got a real competitive profile versus the IL-17s," Taubert said. "We've also got a competitive profile versus the IL-23s, and we don't see that they're bringing anything to the market that is any different."

Tremfya is currently approved for moderate-to-severe plaque psoriasis, but as with other drugs in the therapy area, it will likely be approved for more indications, which will drive additional growth. J&J submitted a supplemental new drug application (sNDA) for Tremfya with the US Food and Drug Administration for psoriatic arthritis in September. *(Also see "Keeping Track: A Duo Of RTOR Approvals, Thumbs Up For First Oral GLP-1 Treatment, And First Ebola Vaccine Nears US Market" - Pink Sheet, 21 Sep, 2019.)*

Tremfya sales are soaring

Tremfya was one of several drugs that contributed to a solid quarter for J&J. Stelara (ustekinumab) grew 30% to $1.7bn in the third quarter. The multiple myeloma drug Darzalex (daratumumab) grew 55% to $765m, and Imbruvica (ibrutinib) for certain blood cancers grew 31% to $921m. As a result pharmaceutical worldwide sales grew 5.1% to $10.89bn in the quarter, with generic and biosimilar competition, including to Zytiga (abiraterone), down 23%, and Remicade (infliximab), down 18%, offsetting some of the growth.

J&J slightly raised group sales guidance for the year to $81.8bn to $82.3bn from

prior guidance of $80.8bn to $81.6bn, and earnings per share guidance to $8.62 to $8.67 from $8.53 to $8.63.

J&J is also in the midst of launching another drug it hopes will be a commercial winner – Spravato (esketamine) for treatment-resistant depression. But the company did not provide a detailed update on the launch or breakout sales. Management said that more than 2,000 sites have been certified under the Risk Evaluation and Mitigation Strategy (REMS) program for Spravato and that 500 sites are actively treating patients with the drug.

The company filed an sNDA for Spravato for the treatment of patients with major depressive disorder who have suicidal ideation with intent, a very severe patient population that has typically been left out of clinical trials. The filing was based on the results of two Phase III clinical trials that focused on the challenging patient population and met the primary endpoint of reducing depressive symptoms.

PRODUCT LIABILITY: THE OVERHANG THAT WON'T GO AWAY

Despite the positive momentum, a consistent overhang for the diversified big pharma is ongoing liability litigation on multiple fronts, including cases related to talc in the consumer products business and opioid liability litigation.

The company has been a defendant in several high-profile opioid cases, including in Oklahoma and a bellwether multidistrict litigation (MDL) case in Ohio. But in October, J&J reached a settlement in Ohio, agreeing to pay $10m to two county plaintiffs, reimburse $5m in legal fees and direct $5.4m in charitable contributions to non-profit organizations connected to opioid-related programs. *(Also see "J&J Settlement Leaves Teva As Sole Opioid Maker In Bellwether Trial" - Pink Sheet, 2 Oct, 2019.)*

The amount of the settlement was viewed as favorable for J&J, especially compared to the $572m judgement issued against J&J by a judge in the Oklahoma case that went to trial. The award had been viewed as a potential benchmark, although J&J is appealing the decision.

"In Ohio, you saw something different. We saw a reasonable amount in proportion to other companies that are involved as defendants," chief financial officer Joseph Wolk told investors. "We were particularly pleased to see that the funds were going to victims of opioid addiction, and so for many reasons there, we thought the best path for all stakeholders was a settlement, and that is something that we will always take into account."

Another potentially enormous payout grabbed headlines earlier this month when a jury decided that J&J should pay $8bn related to its marketing practices for the antipsychotic Risperdal (risperidone). Wolk said the judgement is "egregious," citing US Supreme Court precedent. "We don't expect that to stand," he said, noting the company is appealing the ruling.

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Roche Ups Outlook, Sees Spark Buy By Year-End

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Roche's strong growth has continued into the third quarter. Propelled by recently launched drugs, the Swiss group on 16 October again beat market forecasts and raised its 2019 full-year outlook for the third time this year.

Roche's management is increasingly confident that it can ride out a wave of biosimilars entering the US market in coming months and continue growing earnings into 2020.

The family-led Swiss drug group said third-quarter group sales grew 13% at constant exchange rates, with the pharma division revenue up 15%, driven mainly by multiple sclerosis medicine Ocrevus (ocrelizumab), cancer drugs Perjeta (pertuzumab) and Tecentriq (atezolizumab), as well as the new hemophilia therapy Hemlibra (emicizumab).

Roche CEO Severin Schwan told journalists that third-quarter sales of the group's newly launched products had been stronger than management had previously predicted, and that "based on the strong demand for our new medicines and continued progress of our product pipeline, we have raised the outlook for 2019, and I am confident that we will continue to grow beyond this year."

The robust performance in the last three months meant that in the first nine months of 2019, group sales rose 10% to CHF46.1bn ($46.2bn) from a year earlier, while sales for the pharmaceuticals division were up 12%, at CHF36.6bn.

Given that overall performance, Roche raised the lower end of its full-year guidance and now sees sales growing "in the high single digits", up from mid-to-high-single digits previously foreseen, with Core EPS (earnings per share) still growing in line with sales growth.

Schwan said the strong uptake of newly introduced medicines from Roche more than offset lower sales of Herceptin (trastuzumab) and of MabThera/Rituxan ((rituximab) in the latest quarter.

All regions contributed to third-quarter growth, including Europe, where Roche returned to sales growth, offsetting the arrival there of biosimilar rivals, the CEO said.

"In the quarter in Q3 we were up 5% in Europe. This really reflects the diminished impact of biosimilar losses in Herceptin and MabThera where most of the impact has already been felt and more than offset by the launches of the new products," he said.

Growth was particularly strong in Roche's US pharma operations, with sales there up 14% in the latest quarter over the same year-ago period.

That advance was helped by the very limited impact of US biosimilars to date, with the US still showing positive growth for Avastin (bevacizumab) and no increase in the rate of decline for Herceptin despite the launch of biosimilars versions of both products in July. *(Also see "US Market For Therapeutic Cancer Biosimilars Will Be Tested By Mvasi, Kanjinti Launches" - Scrip, 19 Jul, 2019.)*

The three-month sales update came one month after Roche held an R&D seminar in London, where senior executives outlined Roche's unfolding success story and showcased more pipeline products

which could deliver further expansion in 2020 and beyond. *(Also see "Bucking Biosimilar Threat, Roche Sees Further Growth" - Scrip, 17 Sep, 2019.)*

Asked on 16 October for a likely timeline of when more biosimilar rivals would arrive in the US market, pharmaceutical division CEO Bill Anderson replied: "we think a first biosimilar to Rituxan would come sometime in Q4, and in the next six months we would expect to see at least a couple of more biosimilars for Herceptin and on Avastin – and there will probably be at least one more biosimilar around the year end or early 2020."

But CEO Schwan said that scenario was manageable because "we are rejuvenating our portfolio at a fast pace."

"To put things into perspective, the new medicines that we've launched already represent 30% of pharma sales at this point," the Austrian CEO said on 16 October. That's up from 29% in the second quarter and 23% of total pharma sales in third-quarter 2018.

That message is resonating, and optimism is clearly growing amongst analysts over Roche's growth prospects and its ability to overcome looming threats from biosimilars in the US and possible US pricing reforms. *(Also see "Roche's Pipeline Prospects Promise Steady Sailing To More Growth " - Scrip, 1 Aug, 2019.)*

Bryan, Garnier & Co, which has made Roche its top pharma pick for the fourth quarter, summarized the situation in a 7 October preview research note, saying that Roche "is making the most spectacular recovery move."

"A couple of years ago, the market was looking at the wall of patent expiries becoming closer and closer and was considering that Roche could not be able to avoid a period of declining sales and profits of three years, those being 2018-2020. The group convinced the market that it could do better than that in 2018 and then 2019 and now the very first comments about 2020 suggest no decline at the top line level."

Reacting to the strong third-quarter update, the brokerage firm on 16 October said that "now of course the question is far more about 2020, since a lot of the biosimilar impact has been postponed to next year. We believe Roche can at the very least deliver stable numbers, but some growth looks achievable too."

NO SPARK UPDATE

Roche had no news during its update, however, on the continuing delay to its plan to acquire Spark Therapeutics Inc., a US gene therapy group, saying only that it still expects the transaction to close by the end of this year.

Roche announced in February plans to acquire Spark for $4.8bn, but since then the deal has been postponed several times, with concerns from US and UK antitrust authorities about a potential monopoly in hemophilia seen by many analysts as being the most likely reason. *(Also see "Roche $4.8bn Buy Sparks Hemophilia Gene Therapy Race " - Scrip, 25 Feb, 2019.)*

Roche's management during its third-quarter update declined to be drawn on the topic, either by journalists in the morning or on the analyst call later in the day. CEO Schwan would only say during both updates that the group "remains confident of closing the transaction this year."

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Roche Expects Better Xofluza Sales After New Indication: **https://bit.ly/2P6l0pT**

Novo Nordisk, Bluebird Targeting 'Lifelong' Gene Therapies

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Novo Nordisk AS, a late entrant in the gene editing field, hopes it can leapfrog current competitors in the hemophilia space by linking up with US-based bluebird bio Inc. to develop a one-time, life-long therapy for the condition, starting from childhood.

The Danish group best known for metabolic disease products in diabetes and obesity has been trying to refocus its underperforming biopharm business in recent years. Its longstanding portfolio of hemophilia treatments has meanwhile come under increasing pressure since the arrival in 2017 of Roche's successful hemophilia A product Hemlibra (emicizumab).

So it is perhaps not so surprising that Novo Nordisk this month decided to link with bluebird bio in a three-year collaboration making use of a genome editing technology called MegaTAL, which the US-based biotech says can be combined with viral or non-viral delivery methods.

"The expertise from Novo Nordisk in this alliance will be in hemophilia R&D, whereas the bluebird effort is going to be concerned with MegaTAL design. Together we're going to identify a development candidate by the end of the three years, if not sooner," Daniel Brunicardi Tim-

merman, corporate VP of Novo Nordisk's Biopharm Transformational Research Unit, told *Scrip*.

MegaTALs are a single-chain fusion enzyme that combines the natural DNA cleaving processes of Homing Endonucleases (HEs) with the DNA binding region of transcription activator-like (TAL) effectors. TALs are easily engineered proteins that recognize specific DNA sequences.

While the initial focus of the alliance is hemophilia, the two partners will also jointly investigate other severe genetic diseases.

Timmerman said it was premature to say exactly what those therapeutic areas might be, however.

"Novo Nordisk has, for the past few years, been looking into how it can expand its biopharm part of the business for the longer term, including looking at new types of diseases in the immediate vicinity of where we're currently at, so hemophilia and growth disorders," he explained.

"Since a common denominator in the biopharm area is rare diseases, which in many cases have a well-defined genetic identity, then gene therapies are something that lend themselves naturally to that category of diseases," Timmerman said.

"So here, we're focusing on hemophilia A at the start, but we have a long-term outlook for also including other diseases in collaboration with bluebird."

Partners Pfizer Inc. and Sangamo Therapeutics Inc. are jointly working on their hemophilia A gene therapy SB-525, which is designed to deliver a copy of the Factor VIII gene to a patient's liver cells.

Spark Therapeutics Inc., which Roche is hoping to acquire, is working on two investigational hemophilia gene therapies, SPK-8011 and SPK-8016 , for hemophilia A.

And gene-editing specialist CRISPR Therapeutics AG has an ongoing collaboration with Germany's Bayer AG around hemophilia and other indications, first entered in 2015. *(Also see "Bayer And CRISPR Form Cutting Edge Gene Editing JV" - Scrip, 22 Dec, 2015.)*

ONE-TIME, LIFETIME GENE THERAPY

Being a relatively late starter in the race, along with the disruptive potential of bluebird's MegaTAL technology platform, could work to Novo Nordisk's advantage, said Timmerman.

"Most people in the sector believe that the gene therapies that we're currently seeing in clinical development will be great for adults – apart from risks that the expression might wear off over time – but they're not very likely to be for kids anytime soon," he told *Scrip*.

"Our thinking with bluebird is that, if one can actually make genetic changes at the level of the genome, then that could resolve a lot of questions, because if we could make this work then that would mean that, for example, when cells divide, the genetic manipulation that we're thinking of introducing would naturally be passed on to cell progeny, and that would actually eliminate the risk of expression wearing off over time."

"From a differentiation perspective, we're aspiring to create a product which would with greater certainty ensure a lifelong duration of therapy, and something that could be given to all patients – both kids and adults."

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Takeda Sheds Select Product Assets In Mid-East, Emerging Markets To Acino

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Following strengthening rumors in recent weeks, Takeda Pharmaceutical Co. Ltd. has confirmed it has finalized an agreement to shed a selected portfolio of over-the-counter (OTC) and prescription pharmaceuticals in multiple markets in the Near/Middle East and Africa to Swiss firm Acino Holding AG, for a total value of around $200m.

The proceeds from the divestment will go some way towards further deleveraging the mountain of debt taken on to fund the acquisition of Shire PLC, while honing Takeda's focus on core strategic therapeutic and growth areas.

The Japanese firm has said it will divest up to $10bn in non-core assets with the aim of paying down some $46.5bn in debt taken on to finance its $62bn purchase of Shire, completed in early January. The ultimate aim is to bring Takeda's net debt to adjusted EBITDA ratio down to 2x within three to five years of the close of this M&A deal, helped also by improving cash flow.

"The divestment…represents the continued execution of our strategy to optimize our portfolio, invest in the defined core business areas, and accelerate our progress toward reaching our target leverage ratio," said Costa Saroukos, Takeda's chief financial officer.

THIRD DIVESTMENT SO FAR

The deal with Acino is the third major post-Shire divestment move by Takeda, following the sale of ex-Shire dry eye drug Xiidra (lifitegrast) to Novartis AG for up to $5.3bn (completed on 1 July) and a smaller agreement to divest the TachoSil surgical bleeding control patch to the Johnson & Johnson medical equipment subsidiary Ethicon Inc., for $400m in cash upfront.

> The proceeds will go some way towards further deleveraging the mountain of debt.

But given that perhaps there is another $4bn or so to go to reach the $10bn target, there continues to be market speculation over the shape of other divestment moves, possibly including a similar streamlining of portfolios in Western Europe.

The Acino transaction, expected to close in January-March 2020, involves roughly 30 undisclosed products across the OTC and Rx sectors in Takeda's Growth and Emerging Markets Business Unit, and which are marketed in Egypt, Saudi Arabia, South Africa, Turkey, Ukraine and United Arab Emirates plus other countries.

Privately-held Acino will acquire the rights, title, and interest to the products exclusive to these countries, and a number of primarily sales and marketing staff supporting the portfolio will be transferred to the Swiss firm at closing.

Takeda will also enter into a multi-year agreement to manufacture and supply the products to Acino, which has a focus on selected markets in the Middle East, Africa, the CIS Region and Latin America.

While specific products were not identified, Takeda said they are mostly outside of its core areas of gastroenterology, rare diseases, plasma-derived therapies, oncology and neuroscience.

NORDIC CAPITAL THREAD

It seems likely that the divested lines could include a number of drugs acquired as part of Takeda's $13.7bn buy of Nycomed SPA in 2011. In an interesting twist of fate, Nycomed was majority-owned at the time by the private equity group Nordic Capital, which along with Avista Capital Partners also acquired Zurich-headquartered Acino for $439m in 2013 and still co-owns it.

Takeda stressed it remains committed to the geographies where the products are being divested, but it is changing focus to accelerate the commercialization of its innovative portfolio in such markets and to develop its access to medicines program.

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Alexion Buys A Complementary Business With Achillion

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Alexion Pharmaceuticals Inc.'s acquisition of Achillion Pharmaceuticals Inc. will add two clinical-stage drugs that will build on Alexion's own expertise in complement alternative pathway-mediated rare diseases. Achillion is developing oral small molecule Factor D inhibitors for diseases like paroxysmal nocturnal hemoglobinuria (PNH), where Alexion is the current market leader with its C5 inhibitor Soliris (eculizumab) and second-generation drug Ultomiris (ravulizumab).

"The addition of clinical-stage oral Factor D inhibitors that have potential to advance the standard of care for multiple rare, complement-mediated diseases provides an opportunity to diversify our complement portfolio beyond C5," CEO Ludwig Hantson said during a call detailing the transaction on 16 October. Factor D is one of three pathways in the complement system.

Alexion agreed to pay $930m up front, or $6.30 per share, for Achillion, to be paid in cash, the company announced on 16 October. Achillion will bring $230m in cash to the combined balance sheet, which is reflected in the value of the deal. The $6.30 per share offers represents a solid premium over Achillion's closing share price of $3.65 the day before. For Achillion investors, the deal represents an exit after big disappointment and strategic shift in 2017, when the company lost Janssen as a development partner for its NS5A inhibitor in hepatitis C.

The transaction also includes contingent value rights (CVRs) to be paid to Achillion shareholders based on certain clinical and regulatory milestones and specified timelines, including $1.00 per share for the US Food and Drug Administration approval of danicopan and $1.00 per share for the Phase III initiation of ACH-522.

Danicopan is Achillion's most advanced drug, currently being studied in two Phase II trials. One of the studies is exploring the treatment as an add on to a C5 inhibitor like Soliris for patients with PNH who are experiencing clinical extravascular hemolysis (EVH), a condition that affects less than 10% of patients receiving standard of care. A second trial is in patients with C3 glomerulopathy (C3G), a rare disorder that causes chronic kidney disease and for which there are no approved treatments. The condition results in permanent kidney damage and kidney failure.

Alexion has found a business match in Achillion

ACH-522 is a second-generation oral Factor D inhibitor, which could offer a best-in-class pharmacokinetic profile with more potency than danicopan with less dosing. Achillion completed a Phase I trial, and Alexion believes the drug could have potential in a range of diseases.

"Given our deep expertise in complement biology and our rare disease developments and commercialization capabilities, we believe we are uniquely positioned to create value for patients and shareholders," Hantzen said. "We see great opportunity to accelerate Achillion's efforts in treating PNH patients with EVH and advance the strong progress they have made towards developing the first treatment for C3G.

ANTITRUST ISSUES MAY RAISE CONCERNS

One potential issue for the deal could be securing antitrust approval from the US Federal Trade Commission. There have been some concerns in biopharma that regulators are taking a harder line when it comes to portfolio overlap. *(Also see "When It Comes To FTC M&A Review, The Times May Be A Changin' " - Scrip, 8 Jul, 2019.)* Roche's planned acquisition of Spark Therapeutics Inc. has been pushed back several times while the deal awaits

antitrust clearance, with speculation the holdup is related to the companies' overlapping hemophilia portfolios. Industry watchers were also surprised when Bristol-Myers Squibb Co. agreed to sell Celgene Corp.'s commercial blockbuster Otezla (apremilast) to Amgen Inc. to appease antitrust concerns about portfolio overlap of the product with one of Bristol's late-stage pipeline drugs.

Management said it believes the Achillion pipeline drugs address a broader range of indications than the small subset of PNH patients targeted for danicopan, which will help the deal secure regulatory approval. Soliris is approved for multiple rare diseases, however, and the company secured FDA approval late in 2018 for Ultomiris, a long-acting C5 inhibitor that can be dosed very eight weeks versus every two weeks with Soliris.

SVB Leerink analyst Geoffrey Porges said the decision to double down on the complement pathway makes sense. "We, however, view the FTC as the largest risk to the transaction, given the obvious, and quite significant, overlap in therapeutic focus," he added in a same-day research note.

ANOTHER PIPELINE STEPPING STONE

Alexion has been working to diversify its portfolio beyond Soliris for some time, but in the second quarter, Soliris accounted for around 87% of Alexion's $1.2bn in total product revenues. Ultomiris generated $54.2m in the second quarter. The company has made more progress on building out the pipeline and been active on the deal-making front. In April, Alexion partnered with Affibody AB to co-develop a Phase I asset, ABY-039 for rare immunoglobulin G (IgG)-mediated autoimmune diseases, and signed a drug discovery deal with Zealand Pharma AS. *(Also see "Scandinavia Serves Up Two Partners For Alexion, In Its Rare Disease Sweet-Spot" - Scrip, 21 Mar, 2019.)*

The company also announced an option deal with Stealth BioTherapeutics Corp. on 10 October to co-develop and co-commercialize elamipretide, currently in Phase III testing in people with primary mitochondrial myopathy (PMM). Elamipretide is a potential first-in-class therapy that targets mitochondrial dysfunction, and could be the first treatment approved for PMM, a disease characterized by debilitating skeletal muscle weakness, chronic fatigue and exercise intolerance.

Alexion agreed to pay an initial payment to Stealth of $30m, including an option fee, an equity investment and development funding.

With the Stealth option and Achillion agreement, Alexion head of R&D John Orloff said the company will have 23 programs in clinical development.

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Ipsen Doubles Down On FOP With Blueprint Pact

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With filings imminent for palovarotene, Ipsen has added a second drug for fibrodysplasia ossificans progressiva (FOP) to its pipeline after inking a licensing deal with Blueprint Medicines Corp. of the US, confirming the company's plans to be a major player in rare disorders.

The French drug maker is paying $25m up front to get hold of BLU-782, an oral ALK2 inhibitor being developed for the treatment of FOP. Blueprint is eligible to receive up to another $510m in potential development, regulatory and sales-based milestones, plus tiered royalties.

BLU-782 recently completed a Phase I dosing study in healthy volunteers which showed that the drug was well tolerated at all doses tested. Ipsen plans to commence a potentially pivotal Phase II trial next looking at BLU-782, which has been granted rare pediatric disease, orphan drug and fast track designations by the US Food and Drug Administration.

FOP, which is caused by a mutation in the gene for ALK2 known as ACVR1, is characterized by the abnormal transformation of muscle, ligaments and tendons into bone. As the disease progresses, extra-skeletal bone increasingly restricts joints, resulting in severe disability, loss of mobility, compromised respiratory function and increased risk of early death.

COMBINATION POTENTIAL

As well as evaluating BLU-782 as monotherapy, Ipsen could also be looking at combining the Blueprint drug with its own FOP candidate palovarotene. The Paris-headquartered group got hold of palovarotene, a retinoic acid receptor gamma selective agonist, through its acquisition of Canada's Clementia Pharmaceuticals Inc. in February 2019 for $1.04bn.

Palovarotene was licensed by Clementia in January 2014 from Roche, which discontinued development following Phase II studies in chronic obstructive pulmonary disease. The Montreal-based group developed the drug initially for episodic treatment of FOP. Filings are thought to be imminent.

Ipsen told *Scrip* that palovarotene has not been filed yet and that it will provide an update on the drug and its other pipeline programs during its third-quarter conference call on 24 October. It is eyeing a potential launch of palovarotene in the middle of 2020 and getting US approval could secure the firm a valuable priority review voucher. Although not the cash cows they were previously, the vouchers still raise a tidy sum when sold – most recently, AstraZeneca PLC paid $95m to Swedish Orphan Biovitrum AB for one. *(Also see "AstraZeneca Buys Priority Review Voucher With Two Big Filings On The Horizon" - Scrip, 22 Aug, 2019.)(Also see "Priority Review Vouchers Post Lower Average Approval Times Than Priority NMEs" - Pink Sheet, 15 Oct, 2019.)*

Ipsen CEO David Meek said, "Our strategy has been to build a leading rare diseases franchise, and through the recent acquisition of Clementia, we gained a first-in-class asset in palovarotene. Now, with the addition of BLU-782, we have two strong complementary drug candidates."

The Blueprint deal has gone down well with analysts. Jefferies issued a note on 16 October saying that the pact boosted Ipsen's "sub-scale orphan franchise providing the next phase of growth." As for

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EVONETIX'S DNA SYNTHESIS PLATFORM
Cambridge, UK-based Evonetix is developing technology to enable a new approach for synthetic biology, making it possible to produce high-fidelity DNA at scale. Evonetix is using its proprietary technology to develop a bench-top DNA writer suitable for all research laboratories that will transition DNA synthesis from a service industry to one where scientists can make genes at will, which will impact a wide range of industries, including pharmaceuticals and biotech.

INVITROGEN EVOS M7000 MICROSCOPE
The Invitrogen EVOS M7000 microscope is a fully automated digital microscope that delivers high-quality cell imaging and data to scientists. It is designed to meet the increasingly demanding applications of cutting-edge biological research, from looking at samples to better diagnose disease to analyzing the effect of drugs on tumor cells. The user interface was developed by biologists for biologists.

KALEIDO'S MICROBIOME RESEARCH PLATFORM
Kaleido's human-centric proprietary product platform allows it to more effectively advance optimized, data-rich product candidates called Microbiome Metabolic Therapies (MMTs) to treat disease and improve human health. The platform captures human data at the earliest stages of ex vivo screening and testing, and then is able to rapidly advance MMT candidates into human clinical studies making it potentially faster and more cost-efficient than traditional drug development.

LYNDRA THERAPEUTICS' ULTRA-LONG ACTING PILL
Last November, Lyndra Therapeutics released the first clinical data showing that it is possible to convert a once-daily therapy into a weekly dosage. On a broader scale, the positive data means Lyndra is one step closer to reaching its goal: making daily pills a thing of the past to help solve the issue of medication adherence, a global epidemic that costs up to $300bn in the US alone.

MOGRIFY'S DIRECT CELLULAR CONVERSION TECHNOLOGY
Mogrify has developed a proprietary direct cellular conversion technology that allows the transformation of any human cell type into any other without having to go through a pluripotent stem cell or progenitor cell state. This technology opens up the opportunity to develop and scale up any autologous and allogeneic cell therapies across every therapeutic area, as well as create a new class of therapies: in vivo reprograming.

NEUBASE THERAPEUTICS' PATROL PLATFORM
Unlike other antisense oligonucleotides (ASOs), which have a sugar backbone like natural RNAs, NeuBase's PATrOL platform is designed with a different approach: a peptide backbone, which allows them to wedge into target RNA bound up in conformations inaccessible to traditional ASOs. PATrOL has performed well in preclinical studies to date and has the potential to become a viable therapeutic that addresses many different rare diseases with a single, cohesive approach.

Masters Speciality Pharma's Best Company in an Emerging Market Award

BEIGENE
The Beijing-based firm achieved a number of significant milestones to cement its reputation as the bellwether Chinese biotech: it completed a secondary offering on the Hong Kong Stock Exchange, raising HK$7.3bn ($933m); signed five unique partnerships including the "three-in-one" deal with Zymeworks; and had regulatory filings for tislelizumab and zanubrutinib accepted by China's National Medical Products Administration.

CIPLA
Cipla is dedicated to high-quality branded and generic medicines, offering one of the world's largest portfolios of inhalation products, with 27 molecules and combinations across a range of devices to cater to diversified patient needs. Cipla puts patient requirements to the fore, initiating the 'Breathe Free' public service initiative to increase adherence levels to medications and educate patients on correct inhaler technique.

HIKMA PHARMACEUTICALS
Hikma has a large and varied product portfolio focused on three key areas: injectables, generics and branded, delivering growth in challenging and varied markets. 2018 saw a new CEO, Siggi Olafsson, and increased focus on R&D, with 6% of group revenue invested in core R&D and an increase in investment in injectables and branded R&D programs, plus an improved financial performance.

HUTCHISON CHINA MEDITECH
Headquartered in Hong Kong, Hutchison China MediTech (Chi-Med) is one of the first movers in China's biotech industry. In November 2018, it announced the first commercial launch of Elunate (fruquintinib) for treating metastatic colorectal cancer, making Chi-Med the first ever biotech company in China to bring an oncology drug from discovery all the way through to unconditional approval.

MUNDIPHARMA SINGAPORE
Mundipharma Singapore had notable successes during the year: it joined forces with Singapore's Biofourmis to develop painfocus, a new end-to-end pain management solution to increase the objectivity of pain measurement; gained exclusive rights to the P'tit Bobo range of children's OTC products for the Middle East, Turkey and Africa from France's Yslab; and expanded its biosimilar portfolio by acquiring Spain's Cinfa Biotech and its pegfilgrastim biosimilar.

WUXI APPTEC
WuXi AppTec is a full-service clinical provider bringing in additional parts of the discovery and development value chain, including small-molecule R&D and manufacturing, cell and gene therapies CDMO services, testing and genomics. Through its platform, it has enabled more than 3,500 innovative collaborators from more than 30 countries to bring innovative healthcare products to patients. Company revenues increased 29.3% year-on-year – reaching RMB2,769m in Q1.

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palovarotene, the broker is forecasting $350m worldwide peak sales for FOP, assuming US approval for flare-up and chronic treatment; final data from the Phase III MOVE chronic dosing trial is expected in the second half of 2020.

Palovarotene is also in a potentially registrational Phase II trial for another rare bone disorder, multiple osteochondromas (MO). Jefferies is forecasting blockbuster worldwide peak sales of $1.5bn given the higher prevalence and assuming US approval in the second half of 2022; acceptance of a US filing for MO could trigger Ipsen paying a $263m contingent value right to Clementia shareholders.

Bryan Garnier analyst Jean-Jacques Le Fur issued a note on 16 October saying that "It is clear now no other competitor may have a better portfolio to target FOP [as] Ipsen makes an ally from a potential competitor." He claimed that the FOP market is hard to estimate because it mainly depends on the penetration of treatments, though Ipsen believes it can reach about 1,000 patients out of a total estimated to be 9,000 worldwide.

With the Clementia acquisition and the Blueprint deal, Ipsen is "preparing the post-Somatuline (lanreotide) era," Le Fur said. The latter, a somatostatin for neuroendocrine tumors and acromegaly, is comfortably the company's biggest seller, bringing in €479m in the first half of 2019.

However, Somatuline generics have recently been approved in Europe, where the arrival of the first generics to Novartis AG's rival product Sandostatin LAR (octreotide) represents a further challenge. Credit Suisse analysts said in a 11 October note, however, that the impact on Somatuline sales is expected to be very modest and the Q3 figures should see continued strong growth for the product in the US.

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Dainippon's Cynata Quest Falls Through As Sides Remain Apart

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Sumitomo Dainippon Pharma Co. Ltd. (SDP) says it has decided to withdraw its offer to acquire Cynata Therapeutics "as the parties have been unable to reach mutually agreed terms on the proposed acquisition."

The major Japanese pharma firm first confirmed in July that it was in negotiations with the Australian stem cell and regenerative medicine venture over a possible deal, although both sides noted at the time that a final agreement still needed to be reached.

Cynata has also now stated that it could not reach any deal "on terms to its satisfaction" and that the two sides had ended further negotiations.

One other possible factor that remained unsaid by both firms is that they have recently struck other alliances, which in Cynata's case are providing new funds and in SDP's instance will divert much of the attention of corporate management.

SDP had made an indicative, non-binding and conditional proposal for all shares in Cynata for A$2.00 ($1.41) per share in cash. The company had around 101.89 million shares outstanding, valuing the potential deal at around $204m.


Dainippon, Cynata Fail To Agree Terms

SDP was the sole bidder in the running after Cynata confirmed at the time that similar acquisition discussions with all other parties had ceased, and so it seems unlikely that any alternative suitor will emerge immediately.

Cynata shares on the Australia Stock Exchange had slumped by around 8.4% in early afternoon trading on 17 October after the breakdown of the possible acquisition was announced.

PIPELINE PROGRESS TO CONTINUE

Melbourne-based Cynata, formed in 2011 and acquired in 2013 by Australian firm Eco-Quest Ltd., said that it will continue to progress its clinical pipeline, led by Phase II programs in osteoarthritis and critical limb ischemia, plus an existing graft-versus-host disease (GvHD) partnership with Fujifilm Holdings Corp.

Cynata also stressed that it remains "actively engaged in commercial discussions with parties interested in partnering to develop the company's unique Cymerus therapeutic mesenchymal stem cell (MSC) technology."

Agreement on any deal would have provided SDP with access to novel technology for the large-scale commercial production of stem cells along with these early clinical stage candidates, as it looks to build its strategic presence in regenerative medicine.

Cynata's main proprietary technology is the Cymerus platform, which uses induced pluripotent stem cells (iPSCs) and precursor mesenchymoangioblasts (a common precursor for both MSCs and endothelial cells) to enable the economic, large-scale production of MSCs.

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The system uses a master bank of iPSCs with unlimited expansion potential, derived from a single blood donation. Relatively few MSCs can usually be isolated from each donation and the cells can lose potency as normal culture expansion progresses, requiring new donors.

The Cymerus platform has also shown preclinical promise across a broad range of other potential indications including asthma, diabetic wounds, heart attack and cytokine release syndrome related to CAR-T therapy.

Cynata's in-house pipeline is led by the MSC therapy CYP-001, which met its clinical endpoints in a Phase I study for steroid-resistant acute GvHD. This showed a 93% overall response rate by day 100 with 14 of the 15 patients showing an improvement of least one grade versus baseline.

Fujifilm, which already holds a minority stake in Cynata, had a license option for CYP-001 in GvHD, which it exercised in mid-September and now plans to take into the clinic. The deal is worth $3m upfront to Cynata, plus up to $43m in future milestones and a 10% sales royalty rate.

Cynata also plans to start this year a Phase II program with its MSCs in critical limb ischemia and a 448-patient Phase II trial in osteoarthritis, which would be one of the largest ever trials with this form of cell therapy. The latter plan recently received a boost through an agreement with the University of Sydney, which means the study should now start in the first quarter of next year.

The trial is being "substantially funded" through a grant from the Australian National Health and Medical Research Council, Cynata said. In SDP's case, the company is now needing to focus attention on the execution of its major $3bn deal with Roivant Sciences Inc. to acquire stakes in up to 11 of its subsidiary "vant" companies, for which a definitive agreement is expected this month.

The transaction gives the Japanese firm access to multiple clinical-stage assets, including several that are close to approval filings in the US. *(Also see "Will 'Vant' Deal Really Fulfill Dainippon's Needs? " - Scrip, 9 Sep, 2019.)*

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Need For Partnering Won't Change But Shape Might – BioJapan

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The pharma industry's traditional methods of discovering new medicines are becoming increasingly outdated and risky, as evidenced by the global fall in overall R&D productivity in recent years. This at least was the view of some of the speakers at the BioJapan meeting in Yokohama last week.

This assessment seems to be backed up by hard data, with one report published late last year for instance showing that the projected returns on R&D investment for the top pharma firms had fallen to an all-time low of 1.9%.

Against this background, major companies are continuing to "move towards an externally leveraged paradigm," Saikatendu Kumar Singh, associate director of Global Research Externalization at Takeda Pharmaceutical Co. Ltd., told the meeting, held 9-11 October.

The leading Japanese pharma company is certainly living by this credo, currently running more than 200 external partnerships, mostly out of its major global R&D hubs in the US and Japan.

While the need to access external innovation and expertise will not change, what will be considered as therapeutics in the future may be different, Singh predicted, stressing he was giving his own personal views and not those of his company.

"These might include cell-sized 'nanodrones' that can seek out, diagnose and treat disease within the body, the increased use of artificial organs, and the augmentation of neurological function with 'silicon-neurones' and brain and optic implants."

> "Pharma needs to be respectful and humble."
> – Saikatendu Kumar Singh

SIMILAR PROCESSES

Despite the prospect of such changing technology, how large pharma companies go about identifying partners will not fundamentally change. "We can still both approach each other but a key point will be the need to understand common goals upfront," he said in a session on public-private partnerships (PPPs) and pre-competitive research collaboration.

"The same challenges will remain, including the need to be honest if PPPs are actually really needed and appropriate [in specific cases] - there also need to be transparent expectations."

PPPs involving genetic data initiatives, such as those profiling patients to determine responders to targeted therapies, may pose particular considerations, especially if they are cross-border. "Genomic data could rightly be considered by governments as a national resource and there is a need to respect ethics and confidentiality over access to anonymized data," Singh noted.

"Pharma needs to be respectful and humble."

Takeda's director of PPPs Akiko Otani also told the meeting that "we [pharma] cannot do drug R&D alone" any more.

In her role, she is particularly keen to raise awareness of the concept of PPPs in Asia - where Takeda is already involved in 80 such live consortia across the spectrum from discovery to global health policy - and to share the potential benefits and role of these.

One key aspect will be "engaging regulators and this needs alignment with broader [PPP] goals. We hope we can foster a collaborative spirit and engage them from the beginning along with patient groups," Otani said.

IMPACT OF EXTERNAL INNOVATION

The impact of partnerships with, or the acquisition of, external companies to access outside innovation were highlighted by Gurkeerat Singh, Eli Lilly & Co.'s vice-president of Emerging Technology and Innovation.

In a dedicated session on the US giant's partnering activities, Singh noted that: "These have helped Lilly cut the time from first human dose to launch by 30% over the past 10 years, to 7.2 years. We expect 20-plus new molecular entities to be launched globally in the 2013-24 period."

In fact, over 75% of the current top-selling medicines were originated externally from their marketers, and external innovation (mostly via M&A, licensing) accounted for over 65% of the combined sales of the top 30 pharma companies in 2018, he told BioJapan.

Western Europe, and the east and west coasts of the US (mainly the San Francisco and Boston areas) are the source of over 75% of deals and major pharma external assets, and "the location of major pharma firms does not impact the source of their external innovation," Singh noted.

CHINA EMERGENT?

China is now gradually building its credentials as a pharma innovator, leapfrogging in areas such as CAR-T therapies, where the number of clinical trials in the country now exceeds that in the US.

Meanwhile, major companies there are increasingly pursuing the discovery and development of in-house molecules, rather than licensing these in. If in-licensing is pursued, Chinese firms may now more often be seeking global rights, rather than just in the greater China area, as they look to expand internationally.

As to the future shape of innovation in the country, the Lilly executive told *Scrip* that China is seen by big pharma as a still emerging source of innovation. "Korea has put a stake in biologics and Japan in regenerative medicine, but in China further significant developments [in innovation] could still be five years out," he said.

Nevertheless, "there is certainly a shift towards heightened activity and novel molecules but the volume is still low."

Positive points for the development of the sector in the country include "strong government support and the easy availability of funding for start-ups, and a move towards the harmonization of regulations to global norms," he said.

(Japan policies to support the bioventure sector formed another major theme at BioJapan. *(Also see "Shake It Off? Japan Mulls Routes Out Of Bioventure Doldrums " - Scrip, 16 Oct, 2019.)*)

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Evenity Gets CHMP Nod

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UCB Group has secured a green light in the EU for the osteoporosis drug Evenity (romosozumab). Winning over the European Medicines Agency's Committee for Medicinal Products for Human Use after it issued a negative opinion in June is a boon for the Belgian firm, which is responsible for sales in Europe, and its partner Amgen Inc.. However, commercial success is by no means assured.

Following a re-examination hearing which included advice from patient representatives and experts in osteoporosis and cardiovascular disease, the CHMP on 18 October decided to recommend market authorization but to restrict its use to postmenopausal women with more severe disease (low bone density and a previous fracture) at high risk of fracture and without a history of heart attack or stroke. It is to be given as a monthly subcutaneous injection for one year. The agency said additional measures and studies were foreseen to follow its use in practice and ensure it is used correctly. Final approval by the European Commission is expected by the end of 2019.

The challenges en route to approval in Europe mirror those Evenity experienced in the US, where the Food and Drug Administration issued a complete response letter in 2017 before eventually approving it in April 2019 with a black box cardiovascular safety warning. The drug is also approved in Japan, Canada, Australia and South Korea.

Those cardiovascular safety issues – which were identified in clinical trials of Evenity – were behind the EMA's initial reluctance to recommend approval, and may have a bearing on the drug's commercial success. Although it is a first-in-class product with a dual mode of action to both increase bone formation and restrain bone resorption that sets it apart from rivals in the space, its efficacy is offset by its safety.

Analysts at Deutsche Bank in an 18 October note increased their peak sales forecast for Evenity to €580m from €350m on the "welcome surprise" from the CHMP, noting that the drug is on track to exceed €120m in sales in 2019 following better than expected launches in the US and Japan. Others, however, were less enthusiastic about its prospects.

"Despite Evenity's interesting new mechanism of action, we remain cautious regarding its commercial success since there are multiple generics on the market, since Prolia [Amgen's denosumab] is a great commercial success with good efficacy and also considering the potential question mark about doctors' appreciation of the cardiovascular safety profile," commented Jean-Jacques Le Fur in an 18 October reaction note for Bryan Garnier.

Meanwhile, biosimilar versions of another treatment for severe osteoporosis, Eli Lilly & Co.'s Forteo (teriparatide), were launched in Europe following patent expiry in August, adding downward pricing pressure on the new entrant.

"Overall, Evenity is a decent drug," commented Wimal Kapadia at Bernstein in an 18 October note. Nevertheless, "it is tough for us to see practicing physicians giving patients a drug that helps 50% of the time, but could lead to CV events 44% of the time," he wrote.

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Kiadis Crushed By EMA Rejection Of T-Cell Therapy

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Shares in Kiadis Pharma Netherlands BV have tanked after the cell therapy specialist admitted it no longer expects to get the green light in Europe next year for its blood cancer immunotherapy ATIR101.

Kiadis has been seeking approval for ATIR101, an allodepleted T-cell therapy to be used to deplete T-cells that would cause graft-versus-host disease, as an adjunct to hematopoietic stem cell transplantation (HSCT) in adults with late-stage blood cancer. Specifically, the therapy is being evaluated where the donor is haploidentical, or half-matched.

Changing treatment landscape scuppers Kiadis approval hopes

However, the company expects that the Committee for Medicinal Products for Human Use of the European Medicines Agency will issue a negative opinion and recommend against conditional marketing authorization at its meeting in November. Kiadis and the agency held a scientific advisory group (SAG) meeting in September to review the file but the changing treatment landscape since the submission was made two years ago means that the EMA needs more data and plans for a possible approval in 2020 has gone up in smoke.

Kiadis CEO Arthur Lahr noted that the company filed a marketing authorization application (MAA) in 2017 with single-arm Phase II ATIR101 data and historical T-cell deplete haploidentical HSCT control data. The decision to file was "based on input from the EMA that these were considered adequate for review," he said.

Feedback from the regulator "now indicates that the original data do not provide adequate support for a marketing authorization," Lahr added, "due to the evolution of the standard of care with the post-transplant cyclophosphamide (PTCy, also known as the Baltimore) protocol."

The CEO said the news from the EMA was "very disappointing" but all is not lost. Kiadis is currently enrolling a global, 250-patient, Phase III trial, comparing patients treated with ATIR101 after a T-cell deplete HSCT with those whose treatment is based on the PTCy protocol.

Completion of enrolment and interim readout of the Phase III trial are expected in 2021 and Kiadis is confident that if positive, the study will be enough to back a filing with the US Food and Drug Administration and submission of a new MAA to the EMA. Lahr said the randomized trial should address the EMA's concerns, as it compares ATIR101 to the current standard of care.

On the money side, chief financial officer Scott Holmes added, "We do not believe that this setback significantly changes the long-term revenue potential for ATIR101 or the near-term cash needs of Kiadis." He admitted that in any case "revenue expectations in the initial years of European launch were minimal and would not have provided a positive operating margin."

Analysts at Jefferies issued a note on 18 October saying, "This is a disappointing outcome, with conditional EU approval a key part of our thesis and a significant de-risking event even though limited initial commercial revenues were anticipated." They added that it leaves Kiadis "with a lack of data catalysts until 2021 and likely increased perceived ATIR101 risk, plus less than 12 months cash runway."

Jefferies said that Kiadis, which raised €27.6m through a private placement in May, had about €62.7m in cash at the end of June which should be sufficient to last until the second quarter of 2020. However, as well as the Phase III ATIR101 trial, the company is looking at starting studies in 2020 of KNK002, bought when Kiadis acquired private US biotech CytoSen Therapeutics Inc. earlier this year. *(Also see "Kiadis Raises €28m As Cell Therapy Nears Commercialization" - Scrip, 31 May, 2019.)*

KNK002, a natural killer (NK) cell therapy candidate, has completed a 25-patient proof-of-concept study in haploidentical HSCT. Jefferies noted that with an 8% relapse rate and 66% progression-free survival (PFS), the results were not dissimilar to the 9% relapse rate reported with ATIR101 in Phase II trials.

ECHOES OF MOLMED'S ZALMOXIS

Kiadis's setback comes just a week after rival MolMed decided to withdraw European marketing authorization for its own cell therapy product Zalmoxis, several months after an interim analysis on a Phase III trial of the product showed it to have no benefit on disease-free survival.

The drug had been conditionally approved as an add-on therapy to support stem cell transplantation in patients with high-risk blood cancer. Zalmoxis had been a flop commercially and the Italian company said it would "direct its investments and resources, until now destined to Zalmoxis, to activities that better contribute to its business objectives."

Kiadis investors are clearly concerned about its business. Its stock, listed on Euronext Amsterdam and Brussels, had crashed 52% to €2.43 by 2.15pm UK time (18 October).

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Sofinnova Raises €333m For European Biotech Fund

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Venture capital firm Sofinnova Partners has raised a substantial €333m in its latest funding round, which will help it support predominantly Europe-based biopharma and medical device start-ups.

One of Europe's biggest and best known venture capital (VC) players in life sciences, the company now has more than €2bn under management with more than €1bn raised in the last four years across a number of specialized funds.

The latest €333m fundraising announced on 17 October is for its early-stage healthcare venture capital fund Sofinnova Capital IX.

Antoine Papiernik, managing partner and chairman of Sofinnova Partners, said the latest success was down to an "experienced team, stable strategy and exit track record" which convinced investors to take part.

The firm has enjoyed a remarkable run of success in recent times, completing nine exits in the portfolio and raising a total enterprise value of almost €4bn.

This has included the sale of Belgium's Ablynx to Sanofi for €3.9bn in 2018 and Switzerland's Actelion to Johnson & Johnson in 2017 for $30bn. *(Also see "J&J's $30bn For Actelion Buys Immediate And Longer-Term Value" - Scrip, 26 Jan, 2017.)*

Another success was the sale earlier this year of inhaled medicines specialists Breath Therapeutics for up to €500m to Italian pharma company Zambon completed its exit after just two and a half years of involvement, and only three years after Breath was first set up. *(Also see "Breath Therapeutics Snapped Up Post Series A By Specialty Company Zambon" - Scrip, 25 Jul, 2019.)*

The company operates from offices in Paris, London and Milan, and says it will continue the strategy it has pursued in recent years, investing as a founding and lead investor in start-ups and corporate spin-offs.

Its focus is "on therapeutic, paradigm-shifting technologies and products alongside visionary entrepreneurs."

Sofinnova Capital IX will invest about two thirds of its funds in European companies, and one third outside Europe, primarily in North America.

The new fund has commitments from leading institutional investors across Europe, as well as the US, Canada and Asia. These are predominantly endowment funds, insurance companies, pension funds, sovereign funds, corporates and family offices, many of them having established relations with the Sofinnova family of funds.

In the last three years it has also launched Sofinnova Crossover I, a fund investing in pre- and post-IPO companies; Sofinnova MD Start III, a medical device acceleration fund; Sofinnova Industrial Biotech I, a fund dedicated to industrial biotech; and Sofinnova Telethon Fund I, dedicated to seed investments in gene and cell therapies based in Milan, Italy.

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Woodford Debacle Is A Test Of UK Biotech's Resilience

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The fall of Neil Woodford, the UK's most prominent fund manager in life sciences and biotech, is at last reaching its conclusion – ending the career of a former star investor whose endorsement was once highly valued by UK life sciences companies, but which simply became bad news.

A series of misplaced investment decisions over the last few years came to a head earlier this year, with his flagship Woodford Equity Income Fund (WEIF) this year losing two-thirds of its peak value of £10bn.

The decision has now been taken by administrators Link Fund Solutions to shut down the WEIF, although investors will have to wait until January to see how much of their money will be returned to them.

Woodford said he opposed the decision, but has now been dismissed from his position as investment manager of the fund.

The fate of the separate Woodford Patient Capital Trust (WPCT), which holds large stakes in several promising UK life sciences and biotech firms, has not yet been decided, but it looks likely to be wound up in the near future as well.

Included in this portfolio are companies such as biotech Autolus Ltd., life sciences machine learning specialists BenevolentAI and drug discovery tech company Oxford Nanopore Technologies Ltd. Shares in the WPCT plunged on the morning of 15 October in response to the news of the sister fund's closure, adding to the existing problems for these companies,

Woodford's Woes And UK Biotech

Top 10 Investments In Woodford Patient Capital Trust

COMPANY	SECTOR
Rutherford	Healthcare
Ratesetter	Financials
Oxford Nanopore	Drug discovery
Mission Therapeutics	Biotech
Kymab B Pref	Biotech
Industrial Heat	Industrials
Immunocore A Pref	Biotech
Benevolent AI	Technology
Autolus	Biotech
Atom Bank	Financials

which need to distance themselves from the fund.

Publicly listed Autolus and privately held Benevolent AI have both suffered setbacks in recent months, with Woodford's involvement dragging down investor views of both companies. In the case of Autolus, its share price decline was largely due to delays to its CAR-T pipeline announced in August. Woodford is now understood to have sold his stake in Autolus, with a new investor acquiring a 19% stake in the firm recently. *(Also see "Autolus Faces Life After Woodford With New Czech Backer" - Scrip, 18 Sep, 2019.)*

Then in September, Benevolent AI saw its valuation cut in half to $1bn (£800m). This followed its securing a new investment from Singapore sovereign wealth fund Temasek - a welcome cash injection for the tech firm, but necessitating a considerable downsizing of its value.

Over the weekend, *The Telegraph* newspaper reported that Woodford wanted to bring Oxford Nanopore to an initial public offering – in part to allow him to recoup his investment and help save his cash-strapped fund - but plans for this last throw of the dice were always unrealistic.

This is another unfortunate instance of Woodford generating bad press for one of his investments, and has little to do with the company's own strengths and weaknesses.

The DNA/RNA sequencing company tripled its revenue last year to £32.5m ($41m) in 2018, but is still a minnow in a market dominated by Illumina. In addition, the reason why an IPO currently looks out of the question is the prevailing unfavorable market conditions. Several biotech firms which were ready to float on the US NASDAQ abandoned their plans in recent weeks, while those that did launch have under-performed. *(Also see "BioNTech Falls Short In Jittery IPO Market" - Scrip, 11 Oct, 2019.)*

While 2019 will be looked back on as a tricky period for UK biotech because of Woodford and the uncertainties of Brexit, the sector still looks far stronger than it did a decade ago. The science, financing and corporate governance and quality of management have all improved significantly in that time, with companies much more likely to survive when the inevitable clinical development setbacks arrive.

Syncona CEO Martin Murphy

In counterpoint to Woodford, one of the bright spots for the UK is the emergence of Syncona. This publicly listed life sciences specialist venture capital firm has invested heavily in UK biotech over the past few years.

That means the loss of Neil Woodford as the UK life science sector's number one investor advocate won't be such a blow. While performing a much more hands-on role in financing and supporting life science start-ups, Syncona is emerging as a new champion for the sector.

'STRESS TEST'

It is also an investor in Autolus and a host of other cell and gene therapy companies, providing management guidance, scientific oversight as well as long term funding – a package which looks superior to Woodford's increasingly wayward fund management decisions.

However, one could argue that current challenges represent a useful "stress test" for UK biotech: can the companies overcome these doubts with the strength of their science and executive leadership?

Speaking last week at the Endpoints conference in London (before the latest developments) Syncona's chief executive Martin Murphy was confident this would happen.

Asked about the Woodford debacle, Murphy said: " We just have to get over it."

He added: "Global capital moves around, it will go to where the opportunities are and judge on the quality of the starting science, the commercial opportunity and the quality of the talent to execute."

Syncona can point to a number of successes this year, most recently the £100m Series B fundraising for new UK biotech Achilles Therapeutics Ltd., for which it was the founding backer, and into which it attracted further investors.

Syncona also had a successful exit from one of its investments earlier this year, with the sale of Nightstar Therapeutics PLC to Biogen Inc. for $800m. *(Also see "Biogen By Buying Nightstar Targets Ophthalmology As Emerging Growth Area" - Scrip, 4 Mar, 2019.)*

Murphy remarked: "We are building those businesses, and those businesses are getting financed, and will [continue to] get financed."

Autolus and other promising UK biotechs, such as Kymab Group Ltd. (another Woodford investment), have pivotal clinical readouts over the next few years, which will be the true make-or-break moments for the companies.

It seems like only a matter of time before the Neil Woodford debacle is concluded. This should help the sector to move on, and allow investors to focus more clearly on the company fundamentals rather than the travails of its once-star investor.

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Preparing For The NASH Market: A Conversation With Genfit Execs

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Lille, France-based Genfit SA generally is seen as the second-place player in the non-alcoholic steatohepatitis (NASH) space, behind presumed leader Intercept Pharmaceuticals Inc., but some market watchers don't even rank the firm that highly because the Phase II study for its candidate elafibranor failed until the results were measured against a revised definition of NASH resolution.

Newly promoted CEO Pascal Prigent – a commercial-side veteran of Eli Lilly & Co. and GlaxoSmithKline PLC – and his team are fighting against those perceptions. *(Also see "Genfit Addresses Multiple Transition Issues With CEO Change" - Scrip, 4 Sep, 2019.)* Prigent and chief operating officer Dean Hum, a Genfit co-founder, argue that elafibranor will offer a better safety and tolerability profile than Intercept's obeticholic acid (OCA), for which a new drug application (NDA) was filed in late September. *(Also see "Intercept's NASH NDA Positions OCA For May 2020 Approval, Then Launch" - Scrip, 30 Sep, 2019.)*

They also believe that the ability of elafibranor, a dual agonist of PPAR alpha and delta, to resolve NASH by reducing hepatocyte ballooning and lobular inflammation could prove to be a more important therapeutic benefit for NASH patients than the fibrosis reduction that OCA, an FXR agonist, has demonstrated. *(Also see "Genfit Hopes To Make Case For First-Line Treatment In NASH" - Scrip, 4 Apr, 2019.)*

In a wide-ranging interview with *Scrip*, which has been lightly edited for length and clarity, Prigent and Hum detailed what Genfit is focusing on now as it prepares to unveil data from the Phase III RESOLVE-IT study in the first quarter of 2020. They anticipate filing an NDA with the US Food & Drug Administration during the fourth quarter of 2020, with a European filing to follow within three to six months. Intercept's recent NDA submission places it on track for potential approval in May 2020 in a therapeutic space with no approved drug therapy. *(Also see "Intercept Retakes The Lead In NASH" - Scrip, 19 Feb, 2019.)*

Genfit CEO Pascal Prigent

Q: Now seems to be a time of transition at Genfit. How would you describe the status of the company and its top priorities right now?

PASCAL PRIGENT: The catalyst for all these moves was a personal decision from [founder and departing CEO] Jean-Francois Mouney. Essentially, what he wanted was to take a step back professionally, but still stay very much involved with the company. [Mouney remains as Genfit's chairman.] Once the decision was taken, it made quite a bit of sense because of where Genfit was in its life, sort of shifting from a company that was a pure R&D-focused biotech to a more like a biopharma with important commercial challenges. Having somebody with a different profile at the head of the company made sense.

The other major transition was our greater focus on the US, and it was important that I have [product] launch experience in the US. [Genfit raised $155m in a US initial public offering this past March and said it would build up its US presence in Boston.

In a few months, we'll have our Phase III data and it could be one of two things. It could be great results, or it could be disappointing results. If they're great results, we're going to get into an accelerated mode to discuss [opportunities] with potential partners, maybe discuss M&A, and accelerate as much as we can the filing with the FDA. It's really not the time where you'd want a leadership change.

Conversely, if the results are disappointing, we have other things we can do – we have a primary biliary cholangitis program [for elafibranor in Phase II], a diagnostic program [partnered with LabCorp on an NIS4 diagnostic for NASH], a combination therapy program – so there are many things we can do, but clearly it will be a little bit of a hurricane for the organization and we'll need to readjust.

DEAN HUM: One major thing was that Mouney wanted to take a step back and focus on his role as chairman of the board, and he communicated to us that he'd be a very active chairman, strongly engage with the company and continue to provide his strategic vision. And I can confirm that that has been the case.

Q: Based on your experience with drug launches, what do you think will be the keys to a successful commercial launch in NASH?

PRIGENT: Eighteen months ago, there was a lot of enthusiasm about NASH, with people saying it could be a $30bn market … and I felt people were brushing aside some of the challenges a little bit too quickly. Now, I think the pendulum has swung a bit too much the other way, with people asking is this really a disease, what are payers going to think and will patients be willing to get treated, etc. I think the fundamentals are there. We know that unfortunately all these metabolic diseases that come from our lifestyle, eating too rich, not exercising enough – these sorts of trends are here to stay. We see

the rise of diabetes, obesity, and NASH moves with that. We also know that NASH is real and next year in the US, it's probably going to be the number-one cause for liver transplants. So, the medical need is there.

Commercially, you probably have three main issues – the first issue is the one of diagnostics. As long as biopsy is seen as the way to enter treatment, then NASH is going to be a very small market. Nobody wants to do a biopsy, patients hate it, it's expensive, and what people sometimes don't get is the math. Even if everybody loved biopsy, you probably have 1,000 hepatologists doing biopsies in the United States. And you have 20m NASH patients. So, if all the hepatologists were just doing biopsies 24/7 for one year, we would only scratch the surface in terms of diagnosing patients.

The second issue is the payer viewpoint – what are they going to be willing to pay and at which stage of the disease, and whether they are going to require biopsy [for diagnosis.] The third challenge for me is patient compliance because this is an asymptomatic disease, so will patients be willing to seek treatment and stay on treatment?

We've done a lot of market research this year. What we found out we felt was very encouraging. First of all, there is no way around the biopsy: you have to find an alternative solution, which is why we've accelerated the development of our blood test diagnostic tool, which we think is going to be the key to unlock market potential, not just for us but for everybody.

The thing that was positive was payer sentiment. From a payer standpoint, there was a price point at which they were not going to require a biopsy, it was only going to be necessary if the [drug] price was high. If you choose to price for access, more than two-thirds of payers are not going to require a biopsy – and that price is just below $10,000. We've always felt that this was a mass market, and in a mass market you have to price according to what a large market like diabetes allows. At that price level, we think most payers will be comfortable with not having a biopsy.

Then, from the compliance standpoint and the willingness of patients to seek treatment, we feel that it's going to be very important to provide more than a drug. We'll need to provide a suite of services to the patient, recognizing that it's a complex disease, it's multi-factorial and therefore there is not one silver bullet. This approach has been pioneered by our colleagues in the diabetes space and we think something similar will be needed here. This is why we've initiated discussions with people in the nutrition field, in weight loss, in compliance programs, etc.

Q: Genfit has licensed development and commercialization rights for elafibranor in greater China to Terns Pharmaceuticals Inc., but what is your partnering strategy for North America, Europe and Japan? Do you intend to keep all those rights in-house?

PRIGENT: What we've said is that we're going to be very open and that we have no preconceived ideas. It's probably very unlikely that in the US we'll do something all by ourselves, especially because we see this as a mass market, a primary care market, so we'd probably need a sales force of about 5,000 reps. We think it's a market where a direct-to-consumer campaign is going to be likely; if you do TV, it's easily $100m or more.

So, the likelihood that we go it alone is relatively low, but when we say partnership, that can have multiple definitions – it could be anything from M&A, a license, co-marketing, co-promotion, a joint venture. We're open to anything, we'll do whatever is best to realize the potential of the drug and value for our shareholders. If it's an M&A, it's an M&A. If it's a series of partnerships, it's a series of partnerships.

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For part two of this interview, focusing on the clinical challenges for elafibranor and the coming competition with OCA: **https://bit.ly/2P6EB9J**

GSK Puts Faith In Next Gen Respiratory, Real World Studies

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2019 has been a turning point for GlaxoSmithKline PLC, with the loss in February of US market exclusivity of Advair (salmeterol/fluticasone), the asthma/COPD blockbuster which has been its flagship for more than 15 years.

GSK is also changing fast, thanks to efforts led by CEO Emma Walmsley and R&D supremo Hal Barron, the latter having identified cancer and immunotherapy as the most important fields for growth. That doesn't mean GSK is abandoning respiratory medicine, where it launched its iconic Ventolin (salbutamol) 50 years ago, and has set itself the task of repeating this trick of leading innovation.

Competition in respiratory medicine is growing again however, and GSK and its long-term rival AstraZeneca PLC is competing in two key growth markets: COPD 'closed triple' therapies and severe eosinophilic asthma (SEA).

GSK currently has the upper hand in SEA, where Nucala (mepolizumab) is the market leader, but AstraZeneca's Fasenra (benralizumab) is gaining ground.

Meanwhile in COPD Trelegy Elipta (fluticasone/ vilanterol/umeclidinium) is the only ICS/LABA/LAMA triple therapy approved in the US, and AstraZeneca's Breztri Aerosphere (budesonide/glycopyrronium/formoterol fumarate) was recently rejected by the FDA. *(Also see "Blow To AZ As FDA Rejects COPD Contender" - Scrip, 1 Oct, 2019.)*

Competition doesn't just come from this old rivalry, however: Sanofi and Regeneron

Pharmaceuticals Inc.'s Dupixent (dupilumab). added a US license in eosinophilic asthma in 2018, and analysts predict it could overtake both Nucala and Fasenra to become the market leader.

REAL WORLD RESPIRATORY

Against this background, GSK is trying to keep one step ahead. One of the boldest moves is a large-scale commitment to real world studies for its big new respiratory brands.

The company pioneered the field with the real world Salford Lung Study in England, and is building on this valuable experience with real world studies of Nucala and Trelegy Elipta.

Full results from the REALITI-A trial are due in 2021, with two similar studies of Trelegy, INTREPID and LEGEND, expected to read out in 2020 and 2023 respectively.

GSK's championing of real world studies addresses the fact that only around 7% of COPD and 3% of asthma patients would be eligible for traditional respiratory clinical trials.

But opening up these studies to 'all comers' including patients with severe disease and co-morbidities and hoping for positive results is a risky business.

Interim results of the REALITI-A study were presented at the recent European Respiratory Society congress in Madrid.

The first study of its kind, it produced encouraging early results. After 12 months of use, Nucala cut severe eosinophilic asthma attacks by 69% as an add-on treatment to corticosteroids.

The treatment was also shown to reduce exacerbations leading to hospitalizations and emergency room visits by 77%, and allowed 34% of patients taking standard-of-care corticosteroids to stop using them.

Mike Crichton is senior vice president, global therapy area head, speciality and primary care at GSK. He was recruited earlier this year, joining the company from Sandoz, where he was head of Asia Pacific, and before that vice president of AstraZeneca's cardiovascular diabetes unit.

"It's a valuable data set, to be able to add to what the randomised control trials have demonstrated, and what our label says. We're looking at the effectiveness of our medicines in a broader group of patients who have a lot more background therapies or complicated disease or comorbidities.

"I think that's exciting for most physicians, and there is a value to healthcare systems as well, where they can see how the RCT plays out in the real world."

But there remains great uncertainty about how regulators can and should evaluate real world data. The greatest commercial advantage is to be gained when a study convinces the FDA to update a product label – but will regulators be sufficiently convinced by such real world studies to do this?

"I think that's something that we would talk to the regulators about," said Mike. "We would ask them, where do they see this data?"

Clearly, GSK is taking a calculated risk that regulators and payers will take compelling real world data seriously.

"As leaders, the onus is on us to continue to evolve the science. Whether it ends up being in the label or not, it's our responsibility to do the research and get it out there in public. That's what we're doing with REALITI-A study and certainly with Trelegy INTREPID and LEGEND trials as well."

Commenting on the result, Mike said: "A 77% reduction in the annual rate of exacerbation - that's profound. Reducing stays in hospital is great for the patient, and great for the cost benefit and for the physician." The reduction in corticosteroid use was also "pretty massive, when you talk about the impact on patients," he adds, pointing out the burden of this current treatment paradigm on patients and their quality of life.

These results are broadly consistent with results from Phase III trials, and GSK will look to gain the edge with payers and doctors in its competition with Fasenra and Dupixent.

NUCALA IN COPD

Both GSK and AstraZeneca hope to expand the use of their IL-5 agonists into COPD – but this has proven problematic for both companies.

GSK saw Nucala rejected by the FDA last year, while AstraZeneca's Fasenra failed to show efficacy in two Phase III trials. Neither company are giving up, however, though Mike Crichton isn't giving too much away about his company's next move. *(Also see "AstraZeneca: Don't Write Off Fasenra In COPD Just Yet" - Scrip, 30 Sep, 2019.)*

"We hope to be able to update people not in the future, but we're certainly not done in the space," says Mike.

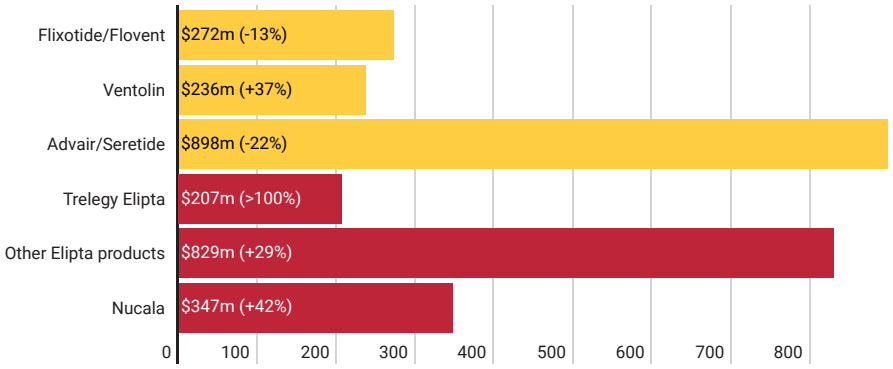
"We've got a very robust pipeline when it comes to tackling the problems with COPD. We are continuing to look at Nucala in COPD. We've looked at results from our trials, and we've learned a lot from those. We think there's a path forward for IL-5 and eosonophilic treated disease in the future."

In the meantime, both GSK and AZ are looking to expand their drug's reach into further niche settings – Nucala in severe hypereosinophilic syndrome (HES) nasal polyposis, while Fasenra recently gained orphan designation in eosinophilic esophagitis, and is also chasing a HES approval.

Published online 16 October 2019

In transition: GSK's respiratory franchise

H1 2019 revenues of major respiratory brands, growth/decline in brackets. Older, post-patent brands, including Advair/Seretide, in yellow, new products in red.



Source: GSK H1 2019 results.

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, 11–17 OCTOBER 2019

Event Type	Lead Company/Partner	Drug Name	Indication	Comments	Change To LOA (%)	LOA (%)
Phase III Updated Results	RedHill Biopharma Ltd.	RHB-104 (rifabutin, clarithromycin, clofazimine)	Crohn's Disease	MAPUS; Positive Results	0	61
Phase III Updated Results	Pfizer Inc.	abrocitinib	Atopic Dermatitis	JADE Mono-1; Met All Endpoints	0	68
Phase III Updated Results	GenSight Biologics S.A.	GS010	Leber's Hereditary Optic Neuropathy	RESCUE; Encouraging Results	0	47
Phase III Updated Results	ObsEva SA	nolasiban (OBE001)	IVF Fertility Treatment	IMPLANT2; Positive Results	0	68
Phase III Updated Results	Aldeyra Therapeutics, Inc.	reproxalap	Allergic Conjunctivitis	ALLEVIATE; Ocular Itch Improved	0	58
Phase III Updated Results	Protalix BioTherapeutics/Chiesi	pegunigalsidase alfa	Fabry's Disease, Switched Therapy	BRIDGE; Improved Renal Function	-3	63
Phase II/III Updated Results	Stealth BioTherapeutics/Alexion	elamipretide	Barth Syndrome	TAZPOWER; Improved Cardiac Function	0	40
Phase III Top-Line Results	RedHill Biopharma Ltd.	RHB-104 (rifabutin, clarithromycin, clofazimine)	Crohn's Disease	MAPUS2; Positive Results	0	61
Phase III Top-Line Results	Shionogi & Co. Ltd.	cefiderocol	Complicated Urinary Tract Infections	Positive Results	0	61
Phase III Top-Line Results	Shionogi & Co. Ltd.	cefiderocol	Gram-Negative Infections	CREDIBLE-CR; Mixed Results	0	69
Phase III Top-Line Results	UCB SA	bimekizumab	Psoriasis, Moderate-To-Severe	BE VIVID; Met Primary Endpoints	2	63
Phase III Trial Initiation	Novavax, Inc.	NanoFlu, quadrivalent vaccine	Seasonal Influenza In Elderly	Recombinant Vaccine	34	64
Phase II/III Trial Initiation	Collaborative Medicinal Development, LLC	Cu(II)ATSM	Amyotrophic Lateral Sclerosis	CMD-2019-001; In Australia	35	52

Source: Biomedtracker | Informa, 2019

Lilly's Pegilodecakin Fails Pancreatic Cancer Test

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Eli Lilly & Co.'s pegilodecakin, the lead immuno-oncology asset from its $1.6bn acquisition of Armo BioSciences Inc. last year, is the latest drug to fail as a potential therapy for notoriously difficult-to-treat pancreatic cancer.

The US major has announced top-line results from its Phase III SEQUOIA trial evaluating pegilodecakin, plus the widely-used FOLFOX (folinic acid, 5-fluorouracil and oxaliplatin) chemotherapy regimen compared to FOLFOX alone in patients with metastatic pancreatic cancer whose disease progressed following a first-line gemcitabine-containing regimen. Lilly gave few details other than noting that the study did not meet its primary endpoint of overall survival (OS).

The firm did note that the most common grade 3/4 adverse events occurring at a higher rate for the pegilodecakin plus FOLFOX arm were neutropenia, thrombocytopenia, fatigue and anemia. Detailed results will be submitted for presentation at a future medical meeting.

Maura Dickler, head of late phase development at Lilly Oncology, said, "Pancreatic cancer has proven to be one of the most difficult tumor types to treat and there have been very few recent treatment advancements in the later-line metastatic setting. While we are disappointed by the outcome of the SEQUOIA study, we look forward to the upcoming results in lung cancer, learning from those results and increasing our understanding of pegilodecakin's novel mechanism of action in cancer immunotherapy."

Showing OS benefit was always going to be tricky in metastatic pancreatic cancer and Lilly noted that just 3% of patients in the US are living five years after diagnosis. In the US, it is the third leading cause of cancer death and is expected to become the second in the next decade, ahead of colorectal cancer. Globally, pancreatic cancer is the seventh leading cause of cancer-related death.

The SEQUOIA fail is not the end of the road for pegilodecakin, however. Lilly pointed to two ongoing Phase II trials – CYPRESS 1 and 2 – looking at the combination of pegilodecakin with checkpoint inhibitors in non-small cell lung cancer, with results expected in 2020.

The CYPRESS studies will "inform future studies in NSCLC," Lilly said, adding that a focus will be on assessing biomarkers. Pegilodecakin is also being evaluated in renal cell carcinoma, "where the molecule has shown promising activity."

The SEQUOIA study is a setback for Lilly's ambitions in oncology, an area where it has slipped behind its peers. Its best-selling therapy in that area is the lung cancer chemotherapy drug Alimta (pemetrexed), which had first-half 2019 sales of $1.08bn, while in the same period sales of the VEGF receptor 2 antibody Cyramza (ramucirumab) were $440m, up 9.5% on the previous year. As well as the Armo purchase, Lilly also bought Loxo Oncology Inc. for $8bn earlier this year and that acquisition could soon bear significant fruit.

Published online 17 October 2019

APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
James Sapirstein	AzurRx BioPharma Inc	Chief Executive Officer and President	Hepion Pharmaceuticals	Chief Executive Officer and President	10-Oct-19
Merav Bassan	BiomX Ltd	Chief Development Officer	Teva Pharmaceutical Industries	Vice President, and Head, Translational Sciences	10-Oct-19
Amy C. Peterson	CytomX Therapeutics Inc	Chief Development Officer and Executive Vice President	BeiGene	Chief Medical Officer	14-Oct-19
Glenn Michelson	CytomX Therapeutics Inc	Vice President, Clinical Development	Portola Pharmaceuticals	Vice President, Clinical Development	14-Oct-19
Jason Braun	CytomX Therapeutics Inc	Vice President, Commercial Strategy	Optera Therapeutics	Vice President and Head, Commercial	14-Oct-19
Marella Thorell	Palladio Biosciences	Chief Financial Officer	Realm Therapeutics	Chief Financial Officer and Chief Operating Officer	11-Oct-19

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

Source: Medtrack | Informa, 2019

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