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Novarits looks to lead the pack

Novartis Counts On AS and PsA For Cosentyx Growth

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Novartis AG has presented yet more data on *Cosentyx* (secukinumab) at the European League Against Rheumatism (EULAR) congress in Amsterdam which it believes will help the drug achieve a leading position in ankylosing spondylitis (AS) and psoriatic arthritis (PsA), as well as psoriasis.

In an interview with *Scrip* on the sidelines of EULAR, Eric Hughes, global development head of immunology, hepatology and dermatology, noted that the Swiss major presented 26 abstracts at the meeting. "We have run over 100 studies with Cosentyx, generating a wealth of data we could be mining forever already," he added.

In particular, Hughes highlighted radiographic data from the nearly 10,000-patient FUTURE 5 study which show that after 24 weeks, Cosentyx inhibited progression of joint damage from PsA, while reducing the signs and symptoms of the disease. Also of note were data from two AS studies; in MEASURE 1, almost 80% of AS patients on Cosentyx had no radiographic progression of the spine at four years, while MEASURE 2 showed that the IL-17A inhibitor provided sustained improvement in the signs and symptoms of AS for up to four years with a consistent and favorable safety profile.

Hughes said that the data Novartis had been producing showed the benefit of early treatment which is needed to prevent the structural changes that lead to lack of mobility, rather than just treating the symptoms and reducing pain. He added that PsA and AS combined affect more patients than rheumatoid arthritis and there is a need for greater education of physicians to appreciate "the continuum of disease" that links psoriasis, PsA and AS.

The psoriasis market is "gigantic" and Cosentyx, which had first-quarter 2018 sales of $580m and has been prescribed to over 150,000 patients, will continue to grow in that space, Hughes said, but there is a lot of competition. However, IL-17 inhibition appears to be particularly important in PsA and AS, where the competition is less, and Cosentyx is growing faster in those two indications than psoriasis.

With regards to the IL-17 market, Cosentyx now has competition from **Eli Lilly & Co.**'s *Taltz* (ixekizumab), which is approved for psoriasis and PsA and to a lesser extent brodalumab, sold by **Valeant Pharmaceuticals International Inc.** as *Siliq* in the US and by **Leo Pharma AS** in Europe as *Kyntheum* for psoriasis only. However, Hughes believes that "the wealth of our data stands on its own" for Cosentyx, as does its mechanism of action, saying that "IL-17 has many different sources but targeting the cytokine as Cosentyx does, hitting the heart, is the best way."

Added to its profile of no anti-drug antibodies being observed and very few reported serious injection site reactions, he said Cosentyx was "the obvious IL-17 to use, a once-in-a-lifetime drug." He also cited real-world evidence presented at EULAR which showed that over 90% of AS patients who were treated with Cosentyx for three months or more were satisfied with their overall symptom improvement and 74% indicated overall symptom improvement to be better with the Novartis drug compared to their previous treatment.

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

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Eli Lilly stays committed to Alzheimer's R&D (p6-7)

To Lower Or Not To Lower
No big pharma volunteers for price reductions (p11)

Eye on IO
Specialists mull lung cancer treatment options (p14-15)

from the editor

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Conference season continues with the European League Against Rheumatism (EULAR) having just concluded in Amsterdam. Kevin Grogan was in attendance for *Scrip*, interviewing executives from a range of companies. This week get the inside track from Novartis on the prospects for Cosentyx beyond psoriasis in related conditions ankylosing spondylitis and psoriatic arthritis (see cover story), and read about Eli Lilly's rheumatoid arthritis drug *Olumiant*'s potential to treat lupus (p4).

One notable component of EULAR is discussion around biosimilars, particularly in the highly lucrative anti-TNF markets. Interestingly, Celltrion unveiled data on a subcutaneous version of infliximab. The originator product, Johnson & Johnson's *Remicade*, only comes as an intravenous injection, and Celltrion markets an approved intravenous biosimilar. However, its development of a potentially more convenient subcutaneous version of a drug whose originator has not developed and does not intend to develop such a product raises interesting questions.

For new biosimilars, FDA guidance says a product will not be licensed if it has a different route of administration from the originator. Similarly, the EMA guides that "both biosimilar and reference medicine must have the same posology and route of administration" (with some possible exceptions).

However, presumably Celltrion – which has confirmed to me that it is working with regulators in different countries and hopes subcutaneous infliximab will be made available to patients "in the near future" – would seek an extension to existing approvals of its intravenous biosimilar infliximab. Since Remicade would remain the reference product in this case, it is unclear how much clinical evidence it would need to marshal to win approval. Another biosimilar condundrum!

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Aim High And Keep Pushing: China Biotech Dealmakers Borrow Page From Trump
https://bit.ly/2MILxGb
Recent biotech investment deals involving WuXi, Oncologie and Siranomics show Chinese investors are becoming increasingly bold and savvy in betting on innovative assets both inside and outside the country.

Teva's CGRP Inhibitor Fails In Chronic Cluster Headaches, Continues In Episodic
https://bit.ly/2yrFV00
Unlike the migraine space, there is only one competitor for Teva's CGRP inhibitor in cluster headaches, but that opportunity narrowed with fremanezumab's failure in chronic cluster headaches, though a trial in episodic cluster headaches is ongoing.

Bluebird 'Turns A Corner' With Lentiglobin Gene Therapy, Tests Remain
https://bit.ly/2tcdiyW
Updated results of studies of its Lentiglobin gene therapy using bluebird's new manufacturing process presented at the EHA meeting are encouraging but the real test will be in the longevity of its effects and the strength of its surrogate marker.

IGEM Therapeutics: Pursuing Novel IgE Antibodies For Solid Tumors
https://bit.ly/2K6sozG
Emerging Company Profile: IGEM Therapeutics has been spun out of King's College London to evaluate the use of IgE-based monoclonal antibodies for the treatment of cancer, including difficult-to-reach solid tumors.

Finance Watch: Investors Go Nuts For NASH As Madrigal Raises $300m, Galmed Skyrockets
https://bit.ly/2tcfc2y
Madrigal and Galmed shares more than doubled after reporting what were viewed as positive results in mid-stage NASH studies, with Madrigal going on to raise $300m on the back of the data.

Deal Watch, Focus On Asia: Cipla Licenses India Rights To Lilly's Basalgar
https://bit.ly/2MHVMe0
Cipla expands on its in-licensing strategy in India with Lilly's insulin glargine product, while Aptose signs second agreement with CrystalGenomics to add Chinese rights for leukemia candidate CG-806, and Yakult gains Japanese rights to Verastem's duvelisib.

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CONTINUED FROM COVER

Competition to Cosentyx is of course not limited to IL-17 drugs and it is up against the anti-TNF blockbusters *Humira* (adalimumab), *Enbrel* (etanercept) and *Remicade* (infliximab) and, increasingly, cheaper biosimilars of the latter drugs, as well as **Johnson & Johnson**'s established IL-12 and IL-23 inhibitor *Stelara* (ustekinumab) for psoriasis and PsA and the US healthcare giant's freshly-approved IL-23 inhibitor *Tremfya* (guselkumab).

In response, Novartis is running a number of head-to-head trials, the most recent one being ARROW, to assess what it believes is the mechanistic superiority of the direct inhibition of IL-17A with Cosentyx over the inhibition of IL-23 with Tremfya, with results being expected in 2019. Hughes also mentioned EXCEED and SURPASS, where Novartis is aiming to challenge Humira's status as the preferred first-line biologic for AS and PsA, respectively.

He also spoke about the PREVENT study with Cosentyx for patients with non-radiographic axial spondyloarthritis (nr-axSpA), which has nearly completed enrolment. "We are doing a good job at stopping the progression of diseases," he said but with nr-axSpA, "we want to stop it earlier before it even manifests in radiographic changes. We think we can prevent a lot of this disease."

As well as Cosentyx, much of the focus at EULAR was on Novartis' *Ilaris* (canukinumab), thanks to positive data from a secondary analysis of the 10,000-patient CANTOS cardiovascular (CV) risk study which suggests that the interleukin-1 beta inhibitor could play a preventative role in atherosclerosis patients with gout.

In the analysis all participants were divided into three groups based on their serum urate level and the results showed that Ilaris significantly reduced the rate of flares of gout by more than half compared with placebo, across all of them. The hazard ratio was 0.40, 0.48 and 0.45 for the low, medium and high baseline serum urate groups, respectively.

Ilaris is already approved for a number of rare auto-inflammatory indications including periodic fever syndromes and juvenile rheumatoid arthritis and while it can also be used to treat flares in certain patients with gout who have contraindications to standard therapies, it is currently not approved for this indication.

Novartis has high hopes that Ilaris will become a blockbuster now that it has been filed in Europe and the US for the CV risk reduction based on the findings from CANTOS. Hughes told *Scrip* that Ilaris is growing very quickly in the smaller indications and the future looks bright in the bigger ones, including possibly lung cancer, saying "it is the little engine that could."

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Lilly's Olumiant Makes Big Leap In Lupus Trial

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Eli Lilly's bid to expand the label on its rheumatoid arthritis drug *Olumiant* (baricitinib) has been boosted by positive mid-stage data for the oral Janus kinase (JAK) 1 and 2 inhibitor as a treatment for lupus.

Top-line data from a Phase II study have been presented at the European League Against Rheumatism (EULAR) congress in Amsterdam, which showed that after 24 weeks of therapy for 314 patients with systemic lupus erythematosus (SLE) who were receiving standard background therapy, 67% on a once-daily 4 mg dose of Olumiant achieved significant resolution of arthritis or rash, compared with 53% on placebo. The proportion of patients on 4 mg who achieved flare reduction, plus improvement in lupus low disease activity state and tender joint count change was also significantly improved; the 2 mg dose did not achieve statistical significance.

There were no deaths, malignancies, major adverse cardiovascular events, tuberculosis or serious herpes zoster infections reported in the study. There was just one serious adverse event (SAE) of deep vein thrombosis reported in a patient with risk factors in the 4 mg arm, which is interesting given that thrombosis was one of multiple risks flagged in a boxed warning on the label for Olumiant by the FDA which approved the 2 mg dose of the drug but rejected the 4 mg dose for RA early this month.

Speaking at a press conference at the congress, Thomas Dörner of Charité University Hospitals in Berlin and chairperson of the EULAR abstract selection committee, said that novel therapeutic strategies were needed for SLE "and so we are delighted to see the positive results from the Phase II trial of baricitinib."

There has not been much in the way of innovation when it comes to lupus in the last 50 years, except the approval by the FDA in 2011 of **GlaxoSmithKline PLC**'s *Benlysta* (belimumab). The latter blocks B cell-activating factor but Dörner said that the interferon (IFN) pathway and other cytokines such as interleukin (IL)-23, IL-12 and IL-2 have recently emerged as a more promising target. By targeting common components of the signalling cascade, such as the JAK-STAT pathway, he said there may be therapeutic advantages by more complete suppression of IFN and other cytokines in disease-related processes.

James McGill, global development leader for Lilly Bio-Medicines, told *Scrip* that given the great deal of heterogeneity among lupus patients, with different factors triggering SLE in different organs – e.g. kidneys, lungs or heart – " it is gratifying to see these responses," as Olumiant appears to work across a variety of inflammatory pathways. He added that two Phase III trials would be starting later this year, saying that Olumiant may offer a convenient oral option for patients with SLE, "an area of deeply unmet medical need."

Analysts at Biomedtracker said that these positive results for Olumiant in SLE were tempered by the fact that statistical significance was seen for the 4 mg but not the 2 mg dose. They believe the data raises the likelihood of a lupus approval, even though the FDA highlighted safety issues about the 4 mg dose for RA when rejecting it, coupled with the one report of a deep vein thrombosis SAE in the 4 mg Olumiant arm of the SLE trial.

Nevertheless, the lupus data is good news for Lilly seeing that Olumiant is the first of the JAK class to have shown significant benefit. Coming up closely behind however is another JAK inhibitor, namely **Gilead Sciences Inc.** and **Galapagos NV**'s filgotinib - Biomedtracker noted that a Phase II trial had been initiated and has an estimated primary completion date of October 2018.

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Sanofi Takes On Infringing Look-Alike In India

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Sanofi hasn't taken kindly to seeming attempts by certain groups to near replicate its trademark and trade name along with almost-identical logos for business gains.

The French multinational, which has been pursuing legal action in the case, recently informed the Delhi High Court that the alleged infringers had gone ahead and established a company with a set of directors.

The case essentially entails the alleged infringer using the "nearly identical" trademark "Snofinn" and trade name "Snofinn Pharmaceuticals" on its website along with "identical" logos as that of Sanofi for its pharmaceutical products and services.

Even the tagline of the alleged infringer - "A universal healthcare provider focused on patients' needs" - is deceptively similar to that of the French multinational's own tagline - "A global healthcare leader focused on patients' needs." Sanofi claimed that the defendants had adopted a trademark, trading name, domain name, color combination and device in its logo, and a tag line which is "visually, phonetically, structurally and aurally deceptively similar" to that of the French firm.

Sanofi referred to the Snofinn "interactive and dynamic website" and expressed concern that the defendants may be making sales of their goods and services in Delhi. Snofinn is said to be engaged in developing active pharmaceutical ingredients and biosimilars and carrying out research services for new chemical entities and is promoting its products and services on Facebook.

CAUSING CONFUSION AMONG CONSUMERS

While trademark infringement issues are not particularly unusual in the pharmaceutical industry, several cases in India have seen imitators typically ride on well-established product/brand names. Snofinn appears to have taken things a notch higher - or rather lower - although some companies have found themselves in stranger situations. For example, **Gilead Sciences Inc.** found that there already existed another Gilead in India. Gilead moved court in India but last year the US firm and the local Gilead entered into a confidential settlement agreement resolving all disputes and claims amongst themselves.

Typically, infringers try and cash in on the deceptively or confusingly similar trademark and pass off their goods as coming from the more reputed player. Sanofi's concerns appear no different.

In the Snofinn case, Sanofi believes that the "bare" imitation, adoption and use of the nearly identical trademark, trade name logo and tagline by the alleged infringer had been done with the intent to "cause confusion and create an impression amongst consumers" that the defendants had a "direct nexus /affiliation" with the plaintiffs (Sanofi), had been granted a license by the plaintiffs in relation to its products and were doing business endorsed by the plaintiffs.

The Delhi High Court in December last year restrained Snofinn and all others acting on its behalf from "manufacturing, selling, offering for sale, advertising, directly and indirectly dealing in any manner" with products and services using the tag-line, trademark, trading name, the logos, the domain name www.snofinn.com that are similar with those of Sanofi or contained the French giant's trademark, tagline or any other trademark, trading name, artistic work, tag-line that is deceptively similar thereto.

'DRASTIC AMENDMENT OF PLAINT'

Things, however, don't seem to have ended there and Sanofi recently indicated that Snofinn had since been incorporated as a company and had certain directors on board.

The court, in turn, appears to have viewed this as a material development, and has permitted the French multinational to pursue the matter afresh.

"The recent developments would require a drastic amendment of the plaint and the matter is at the initial stage, the present petition is disposed of with liberty to the plaintiffs to file a fresh suit on the same cause of action," the Delhi High Court said in an order dated May 29.

On whether Sanofi has alerted its partners about the possible trademark deception and expects to file a fresh suit in case, Sanofi told *Scrip*: "We have been aware of the existence of trademark 'Snofinn' and trade name 'Snofinn Pharmaceuticals' that we consider infringement of our trademark rights on Sanofi. We will undertake any appropriate action to avoid any risk of confusion on the market place and to protect our own trademark and company name."

The Delhi High Court also held that the interim order of December will continue to hold for five weeks to facilitate filing of the fresh suit. Snofinn, whose website also includes a UK correspondence address, could not immediately be reached for a comment.

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Lilly Stays Committed To Alzheimer's

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Eli Lilly & Co. has not given up hope of finding a disease-modifying treatment for Alzheimer's disease, despite many failed attempts, including the recently discontinued Phase III program for the beta secretase cleaving enzyme (BACE) inhibitor lanabecestat.

In fact, Lilly Research Labs President Daniel Skovronsky said in an interview on June 13 – the day after the company and partner **AstraZeneca PLC** announced the lanabecestat failure – Lilly feels a commitment to keep investing in Alzheimer's disease (AD).

The ongoing investment in AD is fueled by the major unmet medical need, which is growing as the population ages, and the expertise that Lilly has developed during the past three decades.

Skovronsky was clear about Lilly's commitment in the lanabecestat announcement on June 12 that "Lilly remains dedicated to Alzheimer's disease research" and "we won't give up on finding a solution," which he told *Scrip* was by design.

"I think the patients need to know it – we're not going to give up on them," he said. "We hope they will continue to participate in trials, if not another Lilly trial, another industry trial."

Skovronsky noted that Alzheimer's is such as big problem that "if big companies like Lilly don't invest in it, no one will," and it's important for the company to keep going, because of the unique capabilities and technologies it's built through decades of research, including molecules, imaging and biomarkers.

MANY MOLECULES, ONE SUCCESS TO DATE

Lilly has just one approved product for Alzheimer's disease, but *Amyvid* (florbetapir F 18) is an imaging agent, not a treatment that reduces symptoms or slows disease progression.

In pursuit of a disease-modifying therapy, Lilly has invested heavily in the so-called "amyloid hypothesis," which assumes that reducing amyloid-beta (a-beta) in the brain or preventing amyloid plaques from forming will slow progression.

The company now has three high-profile Phase III failures to show that this hypothesis may not work – lanabecestat, solanezumab and semagacestat – but it has two remaining programs that may still demonstrate a role for amyloid-targeting therapies.

Development of solanezumab, which binds to soluble a-beta to clear it from the brain, was discontinued in November 2016 after one last Phase III attempt in mild Alzheimer's patients.

Development of lanabecestat, which as a BACE inhibitor is designed to prevent amyloid plaque formation, was shut down on the advice of a data monitoring committee that viewed ongoing Phase III trials as unlikely to succeed based on efficacy.

Semagacestat, which targeted amyloid via gamma secretase inhibition, failed on efficacy in Phase III in 2010.

"The emphasis here at Lilly, and that me and my colleagues share, is just disappointment on behalf of patients" that lanabecestat didn't work, Skovronsky said. However, the BACE inhibitor's failure, while disappointing, was not surprising based on the failure of **Merck & Co. Inc.**'s BACE inhibitor verubecestat, he admitted.

"We closely watched the data from Merck and even before that I think there was a growing understanding in the field that while it was worth exploring it was a mechanism that was risky," Skovronsky said, because BACE inhibitors designed to prevent amyloid formation were being tested as means for slowing disease progression in AD patients that already had amyloid plaques.

Lilly and AstraZeneca could have stopped their lanabecestat trials knowing that the Merck data and other Phase III BACE inhibitor failures didn't bode well for their drug, but the partners wanted patients eager to contribute to the greater good in AD to be able to continue in the lanabecestat studies, he explained.

But they eventually followed the data monitoring committee's recommendation to stop the studies based on interim data so that patients with progressive disease could seek other treatments.

"We had some time to think about it and knew this was likely to happen, but we wanted to get data that would be informative, yet not subject patients to something that was futile," Skovronsky said.

Eisai Co. Ltd. and partner **Biogen**, however, are continuing on with their Phase III BACE inhibitor elenbecestat based on a signal of efficacy seen in a small Phase II trial.

Even after solanezumab and lanabecestat failing in their respective studies, Lilly's thinking about its earlier clinical programs targeting amyloid and BACE is largely unchanged. With lanabecestat out of the picture, the company's most advanced AD programs are in Phase II, including the amyloid-targeting antibody LY3002813, which is being tested in combination with the BACE inhibitor LY3202626.

"This is the first time anyone has trialed two drugs that are disease-modifying – that, in itself is an important technical and regulatory and pragmatic step forward," Skovronsky said. "It's the right thing to do to advance the science."

The combo study is enrolling 375 patients with early symptomatic AD into three arms – placebo, the combination and LY3002813 alone.

"If this doesn't work, impacting amyloid in this population is not likely to work at all. We see that trial that's ongoing as the definitive test in this population," Skovronsky said.

"There's one other thing we want to try – to move into the prevention arena, because ultimately it's our goal to make Alzheimer's a preventable disease," he added, so Lilly is looking for opportunities to test both mechanisms in pre-symptomatic patients.

The company also has LY3303560 targeting the protein tau, which is downstream from the a-beta protein, in Phase I in healthy volunteers and AD patients. (*See table below for current and past AD programs in Lilly's pipeline.*)

"A-beta is mainly for prevention; tau is a little bit more effective later on," Skovronsky said.

The Lilly Research Lab head noted that "you won't see us move into Phase III without stronger Phase II evidence," but said the company is pushing forward with both programs that could be disease-modifying and others that could provide symptomatic relief.

LY3154207, a positive allosteric modulator of the dopamine receptor D1 (D1-PAM), is in Phase II to treat dementia associated with Parkinson's disease, but will be tested in Alzheimer's patients if that study is successful.

"The other frontier after amyloid and tau is neuro-inflammation," Skovronsky said. "We know that inflammation has consequences in the brain for Alzheimer's."

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Lilly's Alzheimer's Pipeline And Suspended Programs

DRUG	MECHANISM OF ACTION	STATUS
Amyvid (florbetapir F 18 injection)	Radioactive diagnostic agent	Approved in 2012 to identify amyloid-beta in the brain during a PET scan.
Flortaucipir F 18	Radioactive diagnostic agent	This is in Phase III to identify tau during a PET scan.
LY3002813	Targets amyloid-beta	A Phase II trial was initiated in December enrolling 375 patients with early symptomatic Alzheimer's in combination with LY3202626.
LY3202626	BACE inhibitor	The company is testing this in combination with LY3002813.
LY3303560	Binds to and neutralizes soluble aggregated tau	A 90-person Phase I study initiated in 2016 tested single, ascending doses of the antibody in healthy subjects and patients with mild cognitive impairment due to AD or mild-to-moderate AD. Another Phase I study was initiated in 2017 to test multiple ascending doses in 132 patients with mild cognitive impairment. due to AD or mild-to-moderate AD. Results are due next year.
LY3154207	Positive allosteric modulator of the dopamine receptor D1	This is in Phase II for dementia associated with Parkinson's disease, but if the study is successful when data are available in mid-2019 the drug will be tested in AD.
MEDI-1814	Anti-amyloid-beta antibody	Partnered with AstraZeneca, this drug showed evidence of dose-dependent and selective Aβ42 target engagement in the brain's central compartment in a Phase I study for which a final analysis was presented in July 2017. The companies are assessing the viability of this asset based on available data for MEDI-1814 and prior amyloid and BACE-targeting candidates.
Lanabecestat	BACE inhibitor	Lilly and partner AstraZeneca discontinued development on June 12, 2018 based on lack of efficacy that was likely to produce statistically significant results in Phase III studies.
Idalopirdine	5-HT6 receptor antagonist	Lilly licensed this to Saegis Pharmaceuticals in 2002, which was then acquired by Lundbeck in 2007. Lundbeck developed idalopirdine with Otsuka under a 2013 license agreement then discontinued development in 2017 after multiple Phase III trials failed.
LY2599666	Monoclonal antibody targeting amyloid-beta	Discontinued in Phase I in January 2017 as data showed lack of target engagement.
Solanezumab	Anti-amyloid antibody	After a second try at Phase III success, this drug failed in mild AD patients in November 2016 and a trial in prodromal AD was discontinued soon after. However, solanezumab is included in the investigator-sponsored Dominantly Inherited Alzheimer's Network Trials Unit (DIAN-TU) study and Anti-Amyloid Treatment in Asymptomatic Alzheimer's study (A4) study, both for asymptomatic patients who are at risk of developing AD.
Semagacestat	Gamma secretase inhibitor	Failed in Phase III in 2010, because it actually increased cognitive symptoms of AD and had other serious side effects, including a risk of skin cancer.
LY2886721	BACE inhibition	Development was suspended in Phase II in 2013 due to abnormal liver test results.
LY451395	AMPA receptor potentiator	Development was discontinued in 2011 after completion of a Phase II study in agitation and aggression associated with AD.
LY2811376	BACE-1 inhibition	A Phase I trial was completed in 2009, but the drug never advanced to Phase II.

Sources: Biomedtracker, Lilly

Opdivo Approval Opens China IO Doors But Pricing Key

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In a milestone for the treatment of cancer in the country, China has approved its first immuno-oncology therapy in the form of **Bristol-Myers Squibb Co.**'s *Opdivo* (nivolumab), but commercial prospects in the potentially huge market remain cloudy until the drug is priced and it becomes clearer if it may be reimbursed under major insurance schemes.

The PD-1-targeting therapy has been approved by the new China National Drug Administration for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) in adults previously treated with platinum-based chemotherapy, and with no EGFR or ALK tumor genetic aberrations.

In contrast to the first approvals in other major markets such as Japan (the first worldwide, in mid-2014) and the US, which were for the much smaller indication of malignant melanoma, Opdivo is moving into a large market opportunity off the bat. Based on patient numbers alone, the China NSCLC sector is potentially enormous, with around 781,000 new diagnoses of lung cancer annually in the country, a number expected to rise to 800,000 by 2020.

Survival rates are currently less than 5%, and the disease is the most prevalent cancer type and has the highest mortality rate among all cancers in China. There is an outstanding need for effective new therapies given that many cases are already at an advanced stage at the time of diagnosis.

The approval is a "significant therapeutic advance…offering for the first time an I-O treatment option that is proven to extend survival in [previously treated] predominantly Chinese patients," said Professor Yi-Long Wu, chair of the Chinese Thoracic Oncology Group, in a statement from BMS.

PRICING ISSUE

However, pricing and/or the provision of patient access support schemes, and the possible inclusion of Opdivo in key reimbursement schemes and official lists of essential drugs, will be key factors in its uptake.

BMS itself has so far given no indication yet on likely pricing, but the company's head of oncology development Dr. Fouad Namouni, did stress in a statement that the company is "committed to working with stakeholders to ensure patients [in China] can quickly access Opdivo".

China meanwhile has taken its own recent regulatory and policy steps to improve access to cancer drugs, including by cutting tariffs on selected imported products and designating certain rare diseases for special treatment.

CHECKMATE DATA

The Chinese clearance, which came following a filing last November and a priority review from the administration's Center for Drug Evaluation, was supported mostly by the 504-patient CheckMate-078 trial, in which 90% of the participants, who had Stage IIIb/IV NSCLC progressing after platinum-based doublet chemotherapy, were Chinese.

Those enrolled had no EGFR mutations and both squamous and non-squamous disease across PD-L1 expression status of <1% and ≥1%, and received Opdivo 3mg/kg intravenously every two weeks.

The drug reduced significantly the risk of death, by 32% versus chemotherapy (the primary endpoint), with a median overall survival of 12.0 months in the Opdivo arm versus 9.6 months in the chemotherapy arm (HR 0.68; 97.7% CI: 0.52-0.90; p=0.0006). OS improvements were seen across both forms of the disease and regardless of PD-L1 expression.

Overall response rate was 17% with Opdivo against 4% with docetaxel, and Opdivo decreased risk of disease progression by 23% versus docetaxel (p=0.0147). BMS said safety was consistent with the global CheckMate-017 and -057 studies, and in -078, Grade 3-4 treatment-related adverse events were less frequent with Opdivo than with docetaxel (10% vs. 48%).

The trial, presented at ASCO in April, was stopped early last November after the monitoring committee concluded Opdivo showed improved overall survival over chemotherapy, and it is the first study to confirm clearly the survival benefits in Chinese patients.

COMPETITION LOOMING

Opdivo, co-developed by Japan's **Ono Pharmaceutical Co. Ltd.** and then Medarex (now part of BMS), is unlikely to have the I-O market in China to itself for long however, given that arch rival **Merck & Co. Inc.**'s *Keytruda* (pembrolizumab) is also awaiting local approval and might receive a regulatory nod this year.

Among local firms, **Innovent Biologics Inc.** has resubmitted a Chinese NDA for its anti-PD-1 candidate IBI308 in Hodgkin lymphoma after voluntarily withdrawing this, and has been granted a priority review *(Also see "China Roundup: Innovent I/O Setback, Adagene, Hua Bag Millions, WuXi Relisting" - Scrip, 3 Apr, 2018.)*, while multiple other firms including Beigene are working in the I-O field. *(Also see "Interview: Beigene Bursts Onto World IO Scene With Celgene Onboard" - Scrip, 13 Jul, 2017.)*

Opdivo also being developed for a variety of other cancer types in China.

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From the editors of PharmAsia News.

Branded Advair Breathes Another Day

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GlaxoSmithKline PLC's blockbuster asthma treatment *Advair Diskus* (fluticasone/salmeterol) will have more time on the market alone now that a near-term headwind has been removed. **Mylan NV** was expecting US FDA action on its ANDA for a generic version of Advair by June 27, but the agency notified the company that it should expect a complete response letter rather than approval.

Mylan told investors after market close June 13 that it expects to receive a CRL from FDA on the June 27 action date, due to what FDA has deemed "minor deficiencies." The company said it would update investors on what to expect for the product after it receives the CRL, but kept an optimistic tone.

In its statement, Mylan said it still could receive an approval prior to the standard 90-day time-period after responding to the letter, because the application has a priority review designation. The company could still be the first to market with a generic version of Advair, but other rivals also are working to bring generics to patients.

Mylan has long talked about how encouraged it is by FDA's interaction on the application, but President Rajiv Malik sounded less confident about a June approval during an investor day in April. It is the second CRL Mylan has received for the generic product, which it plans to market as *Wixela Inhub*, coming more than a year after the first one in March 2017. **Sandoz International GMBH** and **Hikma Pharmaceuticals PLC** also have received CRL letters for their generics.

For GSK, the delay in a launch gives the company some breathing room in 2018, though the anticipation of an eventual generic has long been an overhang on the company's stock. The delay also is important to GSK's growing next-generation respiratory product *Breo* (fluticasone/vilanterol), as well as to **AstraZeneca PLC**'s competing *Symbicort* (budesonide/formoterol).

GSK has been providing financial guidance to investors, including and excluding a potential generic. Even if a generic doesn't launch in 2018, the company has guided investors to expect US sales to decline 20%-25% in 2018 due to ongoing pricing pressure and new competition. The hit would be much deeper if a interchangeable generic were to launch in July as had been expected. The company said US Advair sales would decline by more than half, to around £750m from £1.6bn in 2017.

The disappointing news for Mylan comes after a string of positive developments that have given the company some momentum. The company's biosimilar version of **Amgen Inc.**'s *Neulasta* (pegfilgrastim) was the first such biosimilar to be approved in the US earlier this month. The company is preparing to launch the product, *Fulphila* (pegfilgrastim-jmbd), shortly.

Mylan also has received clearance for a biosimilar version of *Herceptin* (trastuzumab) in the US and negotiated a timeline for launching the product with **Roche**, though it hasn't been disclosed. The company was the first to receive FDA approval of a generic version of **Teva Pharmaceutical Industries Ltd.**'s 40 mg dose of *Copaxone* (glatiramer) last year, a big win, though the launch has faced more commercial challenges than anticipated.

Advair launched in the US in April 2001 and enjoyed extended exclusivity on the market – post patent expiration – because it is a complex inhaled respiratory drug that is difficult to replicate. The composition of matter patents on fluticasone/salmeterol expired in 2010, though the Diskus inhaler was protected into 2016. Advair has generated £58.84bn in cumulative sales since GSK began breaking out sales of the product in 2003 through 2017.

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Dr. Reddy's Launches First Generic Suboxone Film

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Indivior PLC is looking to ward off the impact of FDA's approval of generic versions of its *Suboxone* sublingual film (buprenorphine/naltrexone).

The company said it is considering seeking an injunction to stop **Dr. Reddy's Laboratories Ltd.** "at-risk" launch of the treatment for opioid dependence. Immediately after FDA's June 15 approval of Dr. Reddy's and **Mylan NV** ANDAs, Dr. Reddy's announced its launch, opting not to wait for the outcome of Invidior's appeal of a district court ruling that Dr. Reddy's does not infringe three Suboxone patents.

Mylan did not respond to a query as to when it would launch. It settled patent litigation with Indivior in September 2017 under undisclosed terms. Jeffries said in an analyst note that the settlement went until 2023.

Individor settled patent litigation with **Par Pharmaceutical Inc.** last month and announced that the agreement permits Par to begin selling a generic version of Suboxone on Jan. 1, 2023, "or earlier under certain circumstances."

Jeffries said "an at-risk launch comes as a surprise; hence we expect a material initial adverse share price move." Indivior's stock price fell 27.5% at $24.36.

"We are surprised by Dr. Reddy's decision to launch 'at risk' given the ongoing litigation and associated significant risk to them of substantial economic damages if, as we believe, we eventually prevail in protecting the Suboxone Film patent estate," Indivior CEO Shaun Thaxter said in a release. "In the meantime, we will continue to pursue all legal avenues."

Indivior said it had developed contingency plans in the event of Dr. Reddy's market entry, including the potential launch of an authorized generic "as well as defined operational cost savings measures." It said an overriding principle of these plans is to continue to support and optimize the launch of Sublocade, a once-monthly injectable buprenorphine product.

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Eisai Refocuses AiM As It Builds US Immuno-Dementia Research

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Despite - or perhaps because of - multiple recent industry failures in the search for an effective drug against Alzheimer's disease (AD), **Eisai Co. Ltd.** is pushing ahead with a new research initiative in the US that will explore an immune approach to treating this and other forms of dementia.

The Japanese firm is establishing a Center for Genetics Guided Dementia Discovery (G2D2) in Cambridge, Massachusetts that plans to use human genetic data as a starting point for the discovery of innovative "immuno-dementia" therapeutics acting on neural inflammation targets. Along with the well elucidated roles of amyloid beta plaque and tau protein tangles in AD, chronic inflammation has long been put forward as another primary mechanism in Alzheimer's and other dementia disorders.

G2D2 will focus on the new approach in an effort "to succeed amyloid beta and tau", Eisai said, explaining that the new center will look mainly at functional genetic analysis and investigate the role of the immune system and neural inflammation in general as causative factors.

More specifically, multiple proteins expressed on microglia, a type of glial macrophage cell that accounts for around 15% of all brain cells and acts as the first line of CNS immune defense, will be investigated as potential therapeutic targets.

While brain microglia play a useful role in engulfing amyloid plaques and tangled neurons, it has long been thought that the immune inflammatory response they cause may exacerbate or even trigger Alzheimer's.

Eisai said the hope is to take the first of its candidates to emerge from this approach into the clinic by 2020.

The new facility is set to start operations within the Alewife Research Center in Cambridge in the first quarter of fiscal 2019 (beginning next April 1) and will be headed by Dr. Nadeem Sarwar, currently president of Eisai's Andover innovative Medicines Institute (AiM) in Massachusetts.

Once G2D2 opens, this facility - set up by the company as a multi-disciplinary discovery innovation unit in 2016 - will shut down. AiM employed around 90 researchers on opening, a number that will fall to around 70 in the new center as it hones its focus.

G2D2 will however build on a lot of the previous work at AiM, which conducted research into auto-immune disorders and immuno-oncology, as well as dementia, where it had been looking at neuro-immune mechanisms in dementia patients with immune-driven pathology and immune dysfunction.

Eisai said G2D2 will be positioned as part of a "multi-dimensional, comprehensive approach" to the immuno-dementia area within the company, which will also bring in its existing Tsukuba research labs in Japan and their expertise in small molecule organic chemical synthesis.

Eisai's UK-based European Knowledge Center (which works with several academic partners) and KAN Research Institute in Kobe, Japan, which focuses on the synapse microenvironment, will also feed in to the effort.

The G2D2 initiative will also include an open access space for use by external groups, to encourage collaboration with the biotech and academic expertise in the Cambridge area and potential open innovation projects. Such cooperation was a key part of AiM's approach, involving specific agreements in areas such as functional genomics and translational biomarkers and the participation of AiM researchers in precompetitive research consortia.

STRING OF CASUALTIES

Eisai has long been a major global player in AD through its one-time blockbuster but now genericized drug *Aricept* (donepezil), an acetylcholinesterase inhibitor.

The Japanese company and Alzheimer's alliance partner **Biogen Inc.** are also among the few survivors left in the race to develop an effective BACE (beta-site amyloid precursor protein cleaving enzyme) inhibitor for the disease, which has seen multiple casualties.

AstraZeneca and Lilly recently pulled the plug on Phase III trials of their candidate lanabecestat, while Johnson & Johnson's same class molecule atebecestat was earlier discontinued due to liver safety issues. Merck & Co meanwhile stopped work on verubecestat earlier this year.

Others still working in the field include Novartis and Amgen with CNP520, and Lilly with another BACE candidate, LY3202626 in Phase II.

ACE OF BACE?

Eisai/Biogen's elenbecestat (E2609) meanwhile is moving forward with enrollment for a Phase III trial, following positive top-line Phase II results in Alzheimer's patients with mild-to-moderate dementia or mild cognitive impairment.

Eisai in the US recently told *Scrip* that it still sees a future for BACE inhibitors, alongside its other approaches, despite the other recent failures, and is confident that the "amyloid hypothesis" will eventually bear fruit.

The Eisai/Biogen alliance, signed in 2014, is also progressing several other candidates, including the US's firm's aducanumab in Phase III.

Eisai meanwhile already has some experience in the immunotherapy approach to amyloid through the monoclonal antibody BAN2401 (originated by Swedish venture BioArctic), which is in a large Phase II study for prodromal or mild Alzheimer's for which results are due in the second half.

The antibody targets amyloid beta protofibrils by selectively binding to and neutralizing soluble amyloid beta aggregates.

Meanwhile in Japan, Eisai's KAN institute has entered into a consortium with six industry, academic and government groups for joint platform research into general nucleic acid drug discovery, focusing on novel nucleic acid synthesis and delivery technology.

The project is supported by Japan's Agency for Medical R&D, and will investigate potential gene-targeting nucleic acid therapeutics for multiple potential therapeutic areas in collaboration with Osaka University, Japanese venture GeneDesign, and The National Cancer Center.

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From the editors of PharmAsia News.

Big Pharma Voluntary List Price Reductions Doubtful

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None of the 10 large biopharmaceutical manufacturers contacted at the end of May by US Democratic senators said they have voluntarily lowered list prices since President Trump announced his drug pricing blueprint, Sen. Elizabeth Warren, D-Mass., said at a June 12 hearing.

"Zero out of 10 gave any indication that they plan to do so and in fact, one out of 10 said prices are going to go up later this year," Warren added. Warren and Sen. Tina Smith, D-Minn., wrote to companies in late May after President Trump said publicly that some firms would be announcing "massive" price reductions in response to the Administration's drug pricing blueprint.

Warren disclosed the companies' responses during a Senate Health, Education, Labor and Pensions hearing on the Administration's drug pricing blueprint. She and Smith also discussed the responses they got in a June 11 letter to HHS Secretary Alex Azar, which they have posted to their websites. "Nearly all replied with a series of non-committal responses," Warren and Smith wrote. (*See excerpts below.*)

"They told us that they 'seek to align pricing to value to reduce costs,' that they are 'dedicated to working with policymakers to enhance the private marketplace,' and that they 'are committed to ensuring our products are accessible and affordable for patients,' and, in a variety of other ways, refused to make any commitments about pricing."

Novartis AG was the only one to give a clear answer, the senators noted. The company "indicated that 'we do have some planned price increases later this year,'" they wrote.

Relying on drug companies "to take the lead in reducing drug prices is a poor excuse for a meaningful proposal to tackle the nation's drug pricing problem," Warren and Smith asserted.

Drug manufacturers are concerned that price reductions will generate a backlash from pharmacy benefit managers and distributors, Azar told Warren at the hearing. Several drug companies "who want to execute substantial, material reductions" in prices have expressed this concern in recent meetings, he said.

"They are finding hurdles from PBMs and distributors … who might say, 'Well, if you decrease your list price, I will take you off formulary compared to your competitor, who has a higher list price, where I will make more money'" because rebates and fees are based on list price.

Congress could help deter PBMs from discouraging list price decreases by ensuring there is "transparency" to payers about when their PBMs "receive offers to lower list prices and actually act against that," Azar suggested.

"I would hope that if we were to find ourselves in that situation, that the CEOs of those companies would find themselves sitting in this chair rather quickly to explain themselves," he told the committee.

He also suggested that employers and payers should be asking their PBMs right now whether they have received any commitments of any lower prices. They should be asking, "What have you done? Why have you not passed them on to us? And have you pushed back on drug companies, saying you would actually like higher prices?"

However, the HHS secretary and former Lilly exec also expressed confidence that manufacturers and PBMs will "figure it out. … Somebody's going to do it and if I was a drug company executive, I wouldn't want to be beaten by a competitor over that line because the first companies to do this are going to win."

Nevertheless, Azar also reiterated that prohibiting rebates as a way of reducing incentives for higher list prices remains under consideration at the department. He did not discuss the idea of passing through rebates at the point-of-sale, a policy that has been strongly supported by biopharma.

"We believe that discussing the removal of rebates within Medicare Part D is something that is and should be on the table. We for the first time ever have provoked that discussion as a regulatory matter," Azar said.

HHS has the regulatory authority to prohibit rebates by removing the safe harbor from the Anti-Kickback Statute, which currently allows them, he explained.

Rebates are "an exception we believe by regulation we could modify. But of course, if Congress were to take action, that would obviously shore up our authority and allow thoughtful consideration by Congress about what would be fairly far-reaching impacts of moving to a different system, of using instead, fixed-price discounts."

HAVE YOU LOWERED PRICES?

AbbVie: "We share concerns regarding patient access to affordable prescription drugs in both commercial and government health plans."

Amgen: "We believe our pricing is consistent with the value delivered to patients, providers and society, and we continue to invest heavily in research and development of new medicines and treatments for grievous diseases."

GlaxoSmithKline: "GSK's goal is to ensure that we are working in the interest of both our patients and shareholders, and the prices of our medicines reflect this approach."

Johnson & Johnson: "Last year, we provided discounts and rebates to payers and providers that outweighed increase in list price, resulting in negative average aggregate net price."

Merck: "We acknowledge the health care system faces a number of challenges, and we are committed to working with the Administration and Congress to develop policies that will ensure patients continue to have access to affordable, life-saving medicines."

Novartis: "No, there have been no WAC price reductions across our pharmaceutical portfolio since the President's announcement…we do have some planned price increases later this year."

Pfizer: "Pfizer is committed to pricing our medicines in a way that reflects the benefit they bring to patients and society; ensuring patients have reasonable access and enabling us to continue to invest in new medicines."

Roche/Genentech: "We take decisions related to the prices of our medicines very seriously, and our commitment to patient access and investment in future breakthroughs are reflected in our actions."

Sanofi: "It is our belief that the declining net prices for our medicines should result in improved access and lower prescription drug costs for patients. Unfortunately, it does not appear that payers consistently pass through the growing savings from increased negotiated rebates and discounts to patients."

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Externally Developed Products Mean Bigger Revenues, But Not In Diabetes

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Product revenue for externally developed products is growing at a compound annual growth rate (CAGR) of 10% between 2002 and 2026 in the therapeutic areas of diabetes, neurology (including pain), immunology/inflammation, and oncology. Conversely, revenue for internally developed products is only growing at 4%.

"During this particular time period, there happened to be a large volume of blockbusters in the dataset – *Humira*, *Remicade*, *Lantus*, for instance – that came in through acquisitions, as opposed to in-house research," explained report author Amanda Micklus.

"As for why they have been successful, it could be that because many of them had been fully developed, or even on the market at the time of sale, and significantly more efforts could be put toward commercialization, as opposed to R&D and having to advance them through the pipeline," she told *Scrip*. "However, it's important to keep in mind that this isn't always going to be the case, and acquisitions that include early-stage assets can also turn out to be blockbusters, with *Opdivo* being a good example."

This doesn't mean that big pharma's internal R&D engine is ready to be written off just yet, said Micklus, as many companies are balancing both kinds of efforts by supplementing internal R&D with business development transactions such as in-licensing and acquisition.

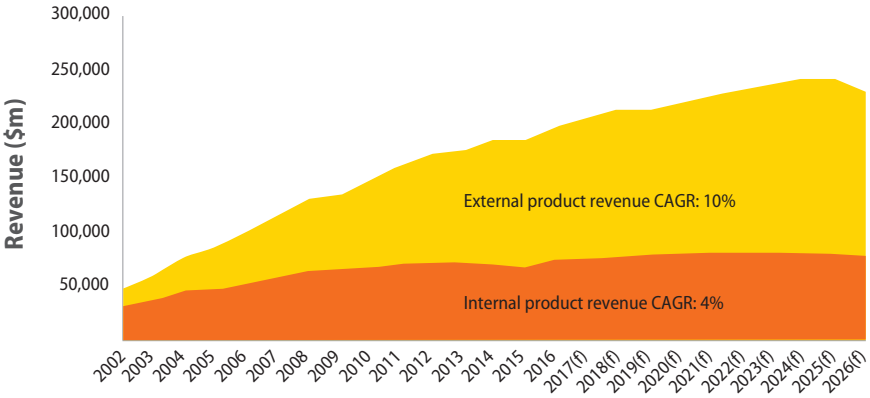
The report, *Innovation in Deal-Making*, also shows that externalized products are expected to have a higher average per-drug revenue. During three five-year time periods; 2002–06, 2012–16, and the forecasted time of 2022–26, average sales of externalized drugs surpass those of internally developed products.

DIABETES THE OUTLIER

This trend, of external products equaling commercial success, is true of the major therapy areas looked at by the report; neurology, autoimmune disease, and oncology. However, in diabetes, internally developed medicines are growing at a CAGR of 12%, with external products growing at just 7%. Key diabetes players such as **Sanofi**, **Eli Lilly & Co.**, **Novo Nordisk AS** and **Merck & Co. Inc.** have all produced commercially successful drugs such as *Humalog* (insulin lispro), *Trulicity* (dulaglutide), *Januvia* (sitagliptin) and *Victoza* (liraglutide). Datamonitor Healthcare is also forecasting a higher per-drug revenue from internally developed therapies.

"While internally developed diabetes drugs have done very well, it doesn't mean that companies won't seek innovation elsewhere," explained Micklus. "There are plenty of opportunities to improve diabetes treatment, including not

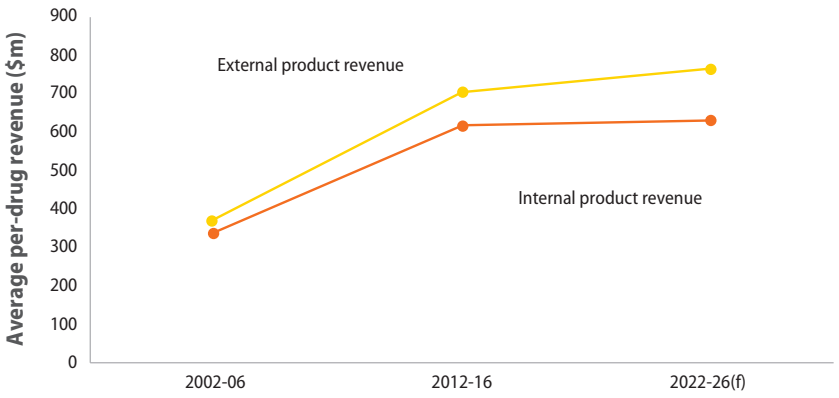
External versus internal product revenue for top 20 pharma peer set: all therapy areas, 2002–26



Notes: Includes revenue for top 20 pharma peer set and key therapy areas of diabetes, neurology (including pain), immunology/inflammation, and oncology. External products include those in-licensed, co-developed, or CAGR = compound annual growth rate

Source: Datamonitor Healthcare, PharmaVitae: Company Analytics, January 2018

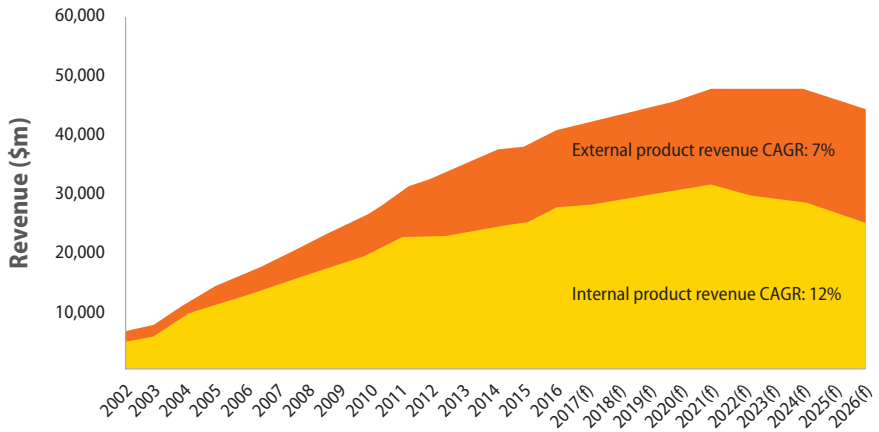
Average per-drug revenue is higher for externalized products, 2002–26



Notes: Includes revenue for top 20 pharma peer set and key therapy areas of diabetes, neurology (including pain), immunology/inflammation, and oncology. External products include those in-licensed, co-developed, acquired. Internal products are those developed through internal R&D.

Source: Datamonitor Healthcare, PharmaVitae: Company Analytics, January 2018

Diabetes therapies: external versus internal product revenue for top 20 pharma peer set, 2002–26



Notes: Includes revenue for top 20 pharma peer set, diabetes only. External products include those in-licensed, co-developed, or acquired. Internal produts are those developed through internal R&D. CAGR = compound annual growth rate

Source: Datamonitor Healthcare, PharmaVitae: Company Analytics, January 2018

> 'While internally developed diabetes drugs have done very well, it doesn't mean that companies won't seek innovation elsewhere'

only evaluating new mechanisms to address the disease."

Eli Lilly & Co., for instance, brought in multiple molecules from its $55m partnership with KeyBiosciences focusing on dual amylin- and calcitonin-receptor agonists. *(Also see "Lilly Pays KeyBioscience $55m Up Front to Expand Its Early Diabetes Pipeline" - Scrip, 9 Jun, 2017.)* There have also been tech and digital health deals which show that companies such as Sanofi and Novo Nordisk are seeking to innovate from the outside.

As for future innovative deal-making, Micklus believes that oncology will remain a major focus for most big pharma companies, along with niche areas, such as NASH and neurodegenerative diseases.

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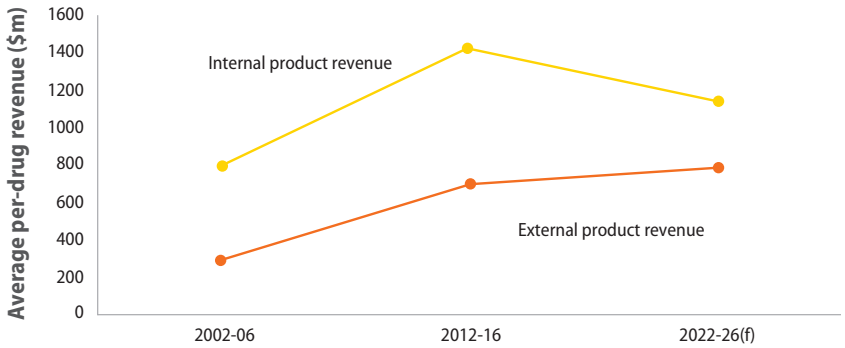
Diabetes therapies: higher average per-drug revenue for internally developed products, 2002–26



Notes: Includes revenue for top 20 pharma peer set, diabetes only. External products include those in-licensed, co-developed, or acquired. Internal products are those developed through internal R&D.

Source: Datamonitor Healthcare, PharmaVitae: Company Analytics, January 2018

Roche In $2.4bn Foundation Buy-Out

Roche's strategy of pursuing a personalized healthcare approach for its oncology drug development has moved on apace with the decision to spend $2.4bn to buy the remainder of molecular information company Foundation Medicine.

The Swiss major acquired a 56% stake in Foundation at the beginning of 2015 for $50 per share, or around $1bn, which at the time represented a whopping premium of around 109%. Three and a half years later, it is paying $137 per share, which is a premium of 29% to the US firm's closing price on July 18, valuing the latter at $5.3bn.

The deal fits with Roche's M&A strategy of bolt-on acquisitions but the cash being spent on the Cambridge, Massachusetts-based company is considerable. It claims to offer a full suite of comprehensive genomic profiling (CGP) assays to identify the molecular alterations in a patient's cancer and match them with relevant targeted therapies, immunotherapies and clinical trials.

In May, Foundation expanded a pact with Merck & Co. to include the development of companion diagnostic tests for use with the latter's anti-PD-1 blockbuster Keytruda (pembrolizumab). Other partners include Pfizer Inc. and AstraZeneca PLC.

Amanda Micklus, principal analyst at Datamonitor Healthcare, told *Scrip* that the deal followed "a recent pattern by Roche to build up capabilities in precision medicine and focus on the diagnostics part of its business, which over the past five years has represented an average 24% proportion of total revenue."

Some observers have picked up on Roche's stance of preserving Foundation's autonomy within the wider group and compared it to the semi-independent approach it adopted with Genentech.

This deal is different, however, with Roche getting hold of diagnostics rather than drugs, as was the case with Genentech.

kevin.grogan@informa.com, 20 June 2018

Specialists Rethink Lung Cancer Treatment Plans, With Eye On IO Biomarkers

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The huge load of data for immunotherapies in first-line non-small cell lung cancer presented at the recent American Society of Clinical Oncology meeting left specialists with the task of refining their treatment strategies and sorting out which immunotherapies to use when, in which patients.

Based on data presented at ASCO, held June 1-5 in Chicago, Morningstar Research increased its immuno-oncology (IO) projections overall by 10%, with the change largely coming from non-small cell lung cancer (NSCLC) sales based on strong data from **Merck & Co. Inc.** and **Roche**, analyst Damien Conover explained to *Scrip*. The investment research group projects the overall market for PD-1/L1 inhibitors will reach $33bn in 2022, ahead of consensus expectations of $29bn, Conover said in a June 7 note.

> 'Lung cancer is no longer a one size fits all therapy and it cannot all be lumped together'

Morningstar projects that NSCLC will drive the majority of the overall market, accounting for $17bn of the $33bn in 2022. Merck's PD-1 inhibitor *Keytruda* (pembroliziumab) is taking the lead in this indication, with a projected share of 44%, followed by **Bristol-Myers Squibb Co.**'s *Opdivo* (nivolumab) with 27%, Roche's *Tecentriq* (atezolizumab) with 18% and **AstraZeneca PLC**'s *Imfinzi* (durvalumab) with 8% in 2022.

"The strong efficacy and pricing power of immuno-oncology drugs should lead to one of the largest markets in the drug industry and add an important pillar of strength to the wide moats of these firms," Conover said.

TUMOR MUTATION BURDEN

One of the biggest IO events at this year's ASCO meeting was the presentation of results for Keytruda as a monotherapy vs. chemotherapy in first-line advanced NSCLC in the KEYNOTE-042 study during the plenary session on June 3.

Other first-line NSCLC immuno-oncology trial highlights at the meeting included Merck's KEYNOTE-407 (squamous), Roche's IMpower150 (nonsquamous) and IMpower131 (squamous), and Bristol's CheckMate 227 (squamous and nonsquamous), the last of which studied Opdivo with the CTLA-4 inhibitor *Yervoy* (ipilimumab) in patients with low PD-L1 levels and high levels of tumor mutational burden (TMB), an emerging biomarker.

TMB refers to the number of mutations in tumor cells; a high mutation burden is thought to be associated with better response to treatment.

Morningstar estimates about 18% of the NSCLC market is low PD-L1/high TMB.

In an interview at the meeting, David Graham, an oncologist at the Carolinas HealthCare System in Cornelius, North Carolina, commented: "We never had so many options… never had this type of conversation."

Just 10 years ago doctors were arguing about which chemotherapy doublet was best to use, he added.

DEFINING AN IO PIE

Further advances are eagerly anticipated. During a plenary discussion on June 3 at the ASCO meeting, NYU Langone Health specialist Leena Gandhi told oncologists that she believes that "we are going to see immune biomarkers define a pie for patients with immunotherapy, especially because we have biomarkers that really are not completely overlapping and really are going to selectively carve out different portions of patients who should get different therapies."

She added that the field should use what we have learned in the last 20 years from the targeted therapy world. "Lung cancer is no longer a one size fits all therapy and it cannot all be lumped together. Let's use biomarkers to select the best individual option for every individual," Gandhi said.

PUTTING PD-L1 IN PERSPECTIVE

The presentation of Merck's Keytruda monotherapy data at the ASCO meeting provided an opportunity to rethink the role of PD-L1 expression as a biomarker and compare results to competing data for Bristol's Opdivo.

Keytruda is already approved as a monotherapy for first-line NSCLC, including squamous and nonsquamous types, in patients with at least 50% PD-L1 expression and the study promised to expand labeling and a chemo-less option to include all patients with at least 1% PD-L1 expression. Keytruda is approved for second-line use in patients with at least 1% PD-L1 expression.

Merck's drug is currently the only PD-1/L1 drug cleared as a monotherapy in first-line metastatic NSCLC. Bristol was lining up its competing Opdivo as a monotherapy but that drug spectacularly failed in the CheckMate 026 trial – though Bristol has shown performance was betterin patients who were TMB-high, so there could theoretically be a route forward in this segment of the population.

KEYTRUDA AND OPDIVO MONO TRIALS ALIKE

Like Bristol before it, Merck was looking for a wide range of PD-L1 expression, with multiple cutoffs. The KEYNOTE-042 study showed Keytruda to be superior to chemo when using PD-L1 cutoff points of over 50%, over 20% and over 1%. But although the overall results in KEYNOTE-042 suggest that Keytruda monotherapy offers improved OS in patients with over 1% PD-L1 expression, this benefit was driven by those with at least 50% PD-L1 expression.

During her plenary discussion, Gandhi noted that there was a crossing of survival curves at the beginning of the trial, which shows that some patients on Keytruda monotherapy were truly not getting

a benefit. In those with 1% to 49% expression, the benefit was not as clear-cut compared with those who had at least 50% expression, Gandhi said during the June 3 plenary session.

Gandhi, who is director of thoracic medical oncology at the Perlmutter Cancer Center at NYU Langone Health, also said it was very important to note that Merck's study did not allow crossover from the chemo control arm.

In Bristol's CheckMate 026 study of Opdivo in patients with at least 1% PD-L1 expression, crossover was allowed, which may explain some of the survival differences that were reported, she said.

In CheckMate 026, 60.4% crossed over from chemotherapy to immunotherapy, whereas only 19.8% crossed over in KEYNOTE-042, maybe because one-third of patients in the latter trial were treated in East Asia, where second-line immunotherapy is not readily available, Gandhi suggested.

Looking at the survival curves from Merck's KEYNOTE-042 and Bristol's CheckMate 026, the results were actually very similar, though Bristol's study was negative, she said. In both studies, some patients initially did not benefit, but then curves crossed and there was a tail at the end in both trials, where there were durable responders who do better long term.

Many emerging biomarkers could add value in terms of complementing PD-L1 expression. TMB, for example, has shown clear predictive value for nivolumab and nivolumab with ipilimumab in multiple studies, though it is a dynamic biomarker and doesn't select out all the patients who won't benefit, Gandhi said.

OTHER BIOMARKERS

There are a lot more other potential biomarkers to come, and the focus of the whole field of oncology is on what are the other predictive markers, which include many things in the tumor microenvironment, such as tumor infiltrating lymphocytes, Gandhi said.

As for the challenges of testing for TMB, getting biopsy tissue was difficult in the past but that has changed with the introduction of targeted therapies, and "patients have been more than willing to do what it takes to get the best treatment for their individual care," she said.

In their investor briefings at the meeting, PD-1/L1 sponsors expressed their commitment to studying TMB and other biomarkers.

Commenting on her choices now for first-line metastatic NSCLC therapy, Gandhi offered a number of possible scenarios, considering PD-L1 status, tumor burden, TMB and mutation status:

- Patients with high PD-L1 and a relatively low level of tumor burden could get pembrolizumab monotherapy.
- Some with EGFR mutations and liver metastases may be candidates for a combination of Roche's *Avastin* (atezolizumab) and Tecentriq with paclitaxel/carboplatin. Roche's Phase III IMpower studies included patients with EGFR and ALK mutations, whereas the other pivotal trials did not.
- In patients with no PD-L1 expression and high TMB there is a rationale for giving the Opdivo/Yervoy combination, Gandhi maintained, as data presented from the CheckMate 227 study indicated a PFS improvement, though no OS benefit as yet.
- Patients with low or no PD-L1 expression should mostly get some kind of combination therapy, either Keytruda/chemo or combination immunotherapy, she suggested.

One thing is clear, though – chemotherapy alone is no longer a first-line standard of care in non-small cell lung cancer, Gandhi concluded.

DEMAND FOR OS BENEFIT

Other discussants at the meeting were not ready to accept TMB.

Discussing trial results during another session, Duke University oncologist Tom Stinchcombe summarized first-line trial results, highlighting those where an overall survival benefit was shown and arguing that OS is needed for adoption of any combination as part of the standard of care.

Stinchcombe said that his choice in first-line squamous and nonsquamous NSCLC with PD-L1 expression over 50% is pembrolizumab monotherapy.

"I like the thought of avoiding chemotherapy toxicities," he explained.

Stinchcombe does not think the combination of Yervoy and Opdivo and the TMB biomarker, per CheckMate 227, are ready for adoption, as an overall survival has not been shown yet. Bristol's Phase III CheckMate 9LA study examining TMB prospectively in first-line NSCLC is ongoing.

HOW THIS AFFECTS MARKET SHARE

Including the latest releases, Merck believes that its broad dataset supports the use of Keytruda across the spectrum, with the exception of ALK/EGFR expressers, and that it will be used in combination with chemotherapy for most patients, Deutsche Bank's Gregg Gilbert commented in a June 5 note.

Roche holds "relatively uncontested NSCLC potential in nonsquamous patients with ALK/EGFR mutations or liver metastases," close to 30% of the nonsquamous market combined, with its combination of Tecentriq, Avastin and chemotherapy, which should gain FDA approval by September, Morningstar's Conover concluded.

However, Conover added that Roche needs strong results for its Tecentriq/chemo combination studies IMpower132 and IMpower130 to access the broader nonsquamous NSCLC market. Both studies will report this year.

BMO Capital Markets Alex Arfaei said in a June 5 note that Bristol's CheckMate 227 update incorporating tumor mutation burden "doesn't really change anything" given that it was a descriptive analysis, but the results "do further strengthen the adoption of TMB as well as PD-L1 for patient selection."

Opdivo and Keytruda are more similar than different, Arfaei suggested, and observed differences are more likely due to trial design; for example, CheckMate 026 allowed crossover and KEYNOTE-042 did not.

The presentations at the ASCO meeting are likely to further reshape the standard of care, with Merck's Keytruda/chemotherapy combination garnering the most attention from physicians and investors, but "we continue to believe the Opdivo plus Yervoy regimen can play a role in a subset of first-line patients and the presentation of additional results from CheckMate 227 reinforces the benefit of Opdivo plus Yervoy in patients with low PD-L1 expression but high [TMB]," William Blair analyst Matt Phipps said in a June 5 note.

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Levin Calls Takeda/Shire Merger 'Inspired'

JOSEPH HAAS joseph.haas@informa.com

When asked to sit back and reflect on the state of the biopharmaceutical industry, **Ovid Therapeutics Inc.** CEO Jeremy Levin didn't hold back. During an interview at the Biotechnology Innovation Organization 2018 International Convention, the industry veteran criticized how biopharma deployed the savings realized under US tax reform, critiqued its M&A priorities and discussed how biopharma needs to work with other stakeholders to provide clarity on the value and pricing of new products.

Speaking with *Scrip* at BIO's 2018 International Convention in Boston on June 5, Levin charged that large pharma companies had used their windfalls from the US tax reform enacted in late 2017 to fund share buybacks and executive compensation, instead of M&A activity that would have replenished their pipelines as well as the industry's larger R&D ecosystem.

"I fear that [rather than] what was a very good move to strengthen the capital base that would allow for M&A to take place, you have instead a simple way of rewarding short-term compensation for the management teams who are doing this, short-term [consideration] for the shareholders and not long-term [benefit] for the industry," he said.

Levin pointed to the pending merger of **Takeda Pharmaceutical Co. Ltd.** and **Shire PLC** as exemplifying the kind of transformative M&A that is seen rarely in biopharma. Reports surfaced recently that an anti-internationalist segment of Takeda's shareholder base is opposing the merger because it would undermine the pharma's more than two-century Japanese heritage; Levin called the planned transaction "an extraordinary strategic step" and said he hoped the deal would close.

"On the face of it, a Japanese company with good but relatively small capabilities acquires a larger European/American company with different capabilities," said Levin. "And that's the point – different. Immediately gaining access to areas it didn't have, understanding orphan disorders and at the same time expanding its footprint outside of what was essentially Japanese governance into a European governance."

TAKEDA/SHIRE STANDS OUT

Levin, who served as CEO at **Teva Pharmaceutical Industries Ltd.** for about 18 months in 2012-2013, said the only comparable situation he can think of is the string of deals involving **Watson Laboratories Inc.**, **Warner Chilcott PLC**, **Forest Laboratories Inc.** and **Actavis Group** that yielded today's **Allergan PLC**, a company now focused more on R&D and new products than its prior emphasis on generics. "That perhaps is the most insightful, remarkable industrial transformation through acquisition that we've seen," he asserted.

A key part of that process was the divestiture of Actavis' generics business to Teva for $40.5bn in July 2015, after the Israeli pharma gave up on a hostile bid to acquire peer company **Mylan NV**. The transaction took place about two years after Levin stepped down as Teva's CEO, and at this year's BIO, he said that, unlike Takeda/Shire, the Teva/Actavis deal provided "no good strategic rationale."

Levin added: If you don't buy into the strategic rationale, walk away. I'll give you an example of where that never occurred, one which I am very familiar with. There was no good strategic rationale for spending $40bn to buy **Actavis Generics**. The marketplace for generics was deteriorating, Teva hadn't fixed itself and they had just emerged from a fight with Mylan. Now, if you asked yourself the question 'what were the things they needed to fix?' – [which was] their pipeline, their cost structure, how could an acquisition like that fix those? It couldn't."

To overcome whatever opposition exists to the Takeda/Shire merger, Levin said Takeda will need to offer a clear strategic rationale for the transaction, adding that CEO Christophe Weber is off to a solid start on that effort.

"If you ask the question, can one articulate the strategic reason, well, I think [Weber's team] has. I think they were solid, I think they were convincing at least from a strategic perspective," he said. "Now, it's all about execution. It's very difficult to execute [a large merger]. So it's not a question of [who will] prevail one way or another. There's a dialogue between the shareholders and the company and it's about whether the shareholders have trust in the vision of the company."

More generally, relatively small acquisitions will drive the R&D revitalization he thinks the industry needs, Levin added. "Small acquisitions are where you can make a huge difference," he said. "It's those types of acquisition where you have inspired R&D leaders who understand their base, understand what they need to do to build that base and are willing to take the risk."

Levin predicts such deals will occur consistently over the next three-to-five years in areas such as immuno-oncology, gene therapy and neurology. "The idea that a pharmaceutical company would buy a genetic therapy company was anathema for years, and yet they are now looking at it as a serious opportunity," he said.

As the biotechnology sector brings novel modalities like gene therapy to the market, pricing becomes more of an issue – but Levin said it is the responsibility of the entire pharmaceutical value chain, not just the drug makers, to ensure reasonable pricing as well as fair access to these new medicines.

Levin noted that more than a decade ago, former **Merck & Co. Inc.** CEO Roy Vagelos predicted that the benefits of new life-saving and/or curative therapies would change the debate on pricing. Vagelos had the right idea, Levin said, but what he predicted didn't happen, partly because of how much more complex the prescription drug value chain has become in just a decade, with the emergence of pharmacy benefit managers and with insurers increasingly emphasizing profit.

"In order to address the topic of pricing, you really need, given these new therapies, to start with a very different premise – to ask the question to what extent are the payers the partner in the patient journey," he said. Levin indicated that the answer to that question clearly should be affirmative.

"It is the industry's obligation to ensure that every patient who has a disorder is treated. No patient is left behind," he said. "When I say the industry, I do mean the insurers, the PBMs, the distributors and the producers. I didn't say the biotech or the pharma industry; I said the industry because that's the value chain. And if you disassemble that and say 'it's the pharma guys who charge this' you are fundamentally missing the point today."

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Scrip Asks... What Is The Future Of Biotech?

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Five years ago, concepts like digital pills and being able to precisely edit genes and manipulate cells for personalized therapy were on the far end of the spectrum, still in the realm of science fiction. At the BIO 2018 International Convention June 4-7 in Boston, *Scrip* asked some of the attendees how they anticipate biotechnology will change over the next five years.

Many of the biotech executives we spoke with said they expect advances in digital health care, personalized medicine and patient-centric drug development. But Ovid Therapeutics CEO Jeremy Levin offered a far-reaching look at several issues facing biotech now and in the near-term future, and a look back at past upheaval.

"Remember, there was a moment in time when an antibiotic was unimaginable," he said. "So, every time you have a change in medicine which results in lives being saved, people's diseases being ameliorated, there is a change fundamentally in the mentality of everybody looking at medicines."

Levin talked about previous waves of innovation in biopharmaceuticals, starting with antibiotics and then advancing to cardiac medications, anti-inflammatories, antibody therapeutics and direct-acting antivirals to address the HIV/AIDS crisis.

"If you ask about the next five years, well, it's very difficult to look into the future, but if history is a teacher and a predictor, we can learn from each one of those cycles about what precipitated them and then ask the question 'What is being precipitated now that might result in massive change in the future?'" he said.

JEREMY LEVIN, CEO, OVID THERAPEUTICS

Change takes time, Levin noted. In both immuno-oncology and virology, the recent waves of innovative new drugs had their roots in discoveries made a decade ago or more, he said, and similar groundwork is being done today in several therapeutic areas.

"The first is different types of genomic therapy – these include the [antisense oligonucleotides], genetic therapy per se, there's a hint that the CRISPR technology will emerge as a powerful technology for clinical treatment, and then I think you should not dismiss the fact that cellular modification and re-introduction ... of cells genetically and reinsertion into the body – not just for cancer, but for other disorders – will become reality," he said. "I think those are very exciting."

"Another broad area is I think we are facing a revolution in neurology," Levin continued. "I think all of the tools, the understanding, the animal models, the cell-based models, the ways of determining where a drug binds in the brain, the different ligands that allow you to measure what's going on in the brain, all of these have changed fundamentally in the last five to six years. That plus the focus on the importance of understanding neurologic disorders better so that you can address the large disorders like Alzheimer's, schizophrenia and depression eventually, the ability to segregate populations genetically, all of that is going to revolutionize [care in that space]. I think you'll see fundamental changes in epilepsy, in neurodevelopment, in many of what are considered rare, but very important disorders for learning about other bigger disorders."

"Microbiome is a total revolution – it's the understanding that we are not alone on this planet, but that in fact we largely are a conglomerate of bugs and human cells," Levin said.

"And then, I think one of the most remarkable changes that we've seen is the ability to measure things in human beings and to assemble the data around it," he concluded. The ability to measure movement, temperature, brain waves, the ability to understand how your body moves and reacts from the outside, without ever touching the individual is a revolution because [we have] the tools not just to measure but actually the ability to integrate data, so you'll be able to dissect out patterns the way they've never before been seen. I would envision being able to detect changes in rhythms of bodies inside homes, to say to you 'are you taking your medicine?' I think there's a whole revolution on the medical application side, which is coming down the path, which is driven by artificial intelligence and big data, our ability to measure and most importantly synthesize genomic data. That will tease out human variability and allow us to see patterns. It's a really exciting five years."

BASSIL DAHIYAT, CEO, XENCOR

"We're going to be facing the challenge of making technologies work to make drugs that are really groundbreaking and high-risk, because I think the economic challenges that we face in the case of pricing and also the emerging wave of patient empowerment is going to drive that. We're going to have to rethink who our market is in a sense – for a long time as drug developers, our market has been the FDA. I think the FDA and our industry are going to have to change that mindset, so I think patient-reported outcomes and patient-centric drug development are going to change a lot about how we make drugs. I don't know exactly how that's going to play out."

CHRIS GIBSON, CO-FOUNDER AND CEO, RECURSION

"I suspect the biopharma world won't look entirely different in five years. I think we'll start to see things that feel a little bit different, like changes even in the highly regulated area of clinical trials with Flatiron and other sorts of similar advances. But I see us as an industry sort of right at the bottom of this exponential hockey stick-looking curve. I think this is true of probably most industries right now, in terms of what technology is likely to bring. I suspect given the inertia and mass of this industry that five years won't be enough to feel the huge changes, but over 10 years we'll really start to see the big, big shifts. I think those are changes in the way that regulatory bodies are working with biopharma to try and bring the right treatment to the right patient more quickly, and I would say [this entails] leveraging technology to drive insights into biology, rather than just sort of bringing efficiency into the space, is kind of what is happening. So, we'll be doing new medicine that we didn't expect, we'll be driving new insights that probably humans will have come up with, leveraging technology to get us there."

RICHARD POPS, CEO, ALKERMES

"The most interesting thing right now is related to the brain, because the central nervous system probably has been the last frontier in biotechnology. We've been doing a tremendous amount work in neurology, oncology, inflammation, but the CNS is still largely im-

penetrable, because it doesn't yield to simple genetics. There aren't single genetic defects that are driving major diseases in the brain, things like schizophrenia, depression, OCD, PTSD, all of which really are the diseases of our age, but haven't yielded yet to biotechnology."

DAVE JOHNSON, CEO AND CO-FOUNDER, GIGAGEN

"All of the antibodies that are in the news right now are monoclonal antibodies; they're targeting single antigens, single epitopes. We're actually making the first recombinant polyclonals with Grifols, which makes plasma-derived polyclonals. … The problem is that from batch to batch there is some variation, and you can't really engineer plasma-derived polyclonals, so we're doing the very first ones which are engineer-able, allowing us to target specific kinds of epitopes, but yet cover a broad range of different specificities. So basically, envision a future 10 years from now where instead of targeting just one epitope on OX40 or PD-1, you're actually covering an entire cell's worth of different cancer epitopes, which enables an entirely different class of drugs."

AJAY VERMA, CHIEF MEDICAL OFFICER, UNITED NEUROSCIENCE

"I think it'll be a kind of back-to-the-future kind of moment in appreciating the healing powers of the body itself. I call it back to the future, because it sounds old school, but the body has incredible reparative properties. Not only when you're young, but also into old age. Most people who live [long] don't get Alzheimer's – people lose track of that. It's still a minority of people around the world. What can the healthy teach us about the not so fortunate? I think we're just stumbling onto the fact that there are stem cells in the brain and that the antibodies you get when you receive a monoclonal [therapeutic], some people can make them on their own. Now, can we help that along with a vaccination, with drugs to tweak the stem cells to get going? I think that's going to be a new revolution. Because as amazing as these drugs are – antisense, gene therapy, all kinds of devices and interfaces with computers and stuff – I'm not sure they're practical for a huge problem like Alzheimer's disease. We've got tens of millions of people around the world, 200m people at risk probably. Those medicines may never even touch the people who need them, just because they're so expensive. They're hard to reach for most people, some of the delivery mechanisms are real cumbersome and not practical for people.

CAMERON TURTLE, PORTFOLIO MANAGER, BRIDGEBIO

"I think the trend that both BridgeBio is built on and that I believe will continue over the next five years is that the success of genetically targeted therapies is going to be broadened from where it's been successful in precision oncology with companies like **Loxo Oncology Inc.**. That success will be translated into a variety of other therapeutic areas as well. For example, companies like **MyoKardia Inc.** in heart failure and carving out small subsets of that population. *(Also see "MyoKardia Shares Skyrocket On Promising Phase II Data In HCM" - Scrip, 7 Aug, 2017.)* Most of our companies are also aiming for genetically specified diseases and then genetically specified subsets of larger diseases. That's a trend that I think will continue; it's a way to be much more practical about targeting therapies."

PAUL WOTTON, CEO, SIGILON

"There are two elements that I'm familiar with which relate to Sigilon in particular. We have a technology that hides implants from the immune system so that the immune system won't attack those implants. That means for the first time now we can manufacture cellular implants so you can do things like the artificial pancreas, which is what we did with **Eli Lilly & Co.**. Or you can manufacture implants that become cell factories, which can do things like treat hemophilia by manufacturing Factor VIII or Factor IX."

NICLAS STIERNHOLM, CEO, TRILLIUM

"I belong to the camp that thinks technology is always outpacing human social thinking. I think in some areas, you'll see quite a substantial change – personalized medicine, diagnostics – but in other areas of biotechnology, there's still going to be the preferred way of treating cancer … [surgery], radiation and chemotherapy aren't going anywhere … particularly … when there are proven ways of doing things, but gene therapy, gene editing, when you have no other options, I think that's going to advance much faster. Over the next five years, I think you are going to see more and more stories about embryonic gene editing – correcting some of these often deadly and very morbid conditions *in utero*. And of course, personalized medicine – it's already changing treatment. This is your tumor, you're going to get this drug. That's just going to take off."

NANCY SIMONIAN, CEO, SYROS

"I think that in five years, we're going to have much more understanding of which drugs to use for the right patient, the precision medicine angle. I think we're just at the cusp of that and for a lot of diseases, such as cancer, really understanding what are all the alterations in the multiple pathways that are important that you need to target and understanding the right patients, I think that's going to be more and more prominent in terms of how we think about treating patients. But not just cancer. I think cancer will be at the forefront, but other diseases are behind, but will come along. For most complex diseases, it's unlikely that any single targeted agent will take care of all different pathways that are important in that disease. I think the ability to understand how to put drugs together, which drugs should be put together, is also going to be incredibly important so that we're not throwing darts, that we actually have a rationale for doing that."

IOANNIS SAPOUNTZIS, HEAD OF BD AND LICENSING, US AND SPECIALTY CARE, BOEHRINGER INGELHEIM

"We've seen a lot of things happening the digital health sphere – with data integration – and I think it will change the way we are doing drug discovery and development in the future. It's a priority for our company – it's fair to say that we want to continue to understand how we can be not only a part of it, but actively drive those insights that we can generate from big data, AI and how can we drive it. I think it's not yet clear how this will happen, but we are definitely following this and it's a large theme here. It's a big trend and I think what it ultimately will do is cut down development timelines for the benefit of patients in need, because our industry has rather long development timelines. And it may also help us to identify more specifically patients that benefit from treatments. So, if it can do those two things, it will be wonderful.

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Takeda and AllianceBernstein Moves Contain A Message For Pharma

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Three examples capture the pace of change all around us: the largest car company today does not own any cars, the largest hotel company does not own any rooms or hotels, and the largest marketing company does not take title to many goods. And rapid growth at these three pioneers, Uber, AirB&B and Amazon, reminds us how this pace of change is only accelerating.

Underpinned by similarly accelerating change, money manager AllianceBernstein's relocation from New York City to Nashville, Tennessee has something of a parallel in **Takeda Pharmaceutical Co. Ltd.**'s proposed "acquisition" of **Shire PLC** - which also is at least partly to "relocate" beyond Japan.

To be sure, both of these moves are only a partial relocation, but the symbolic importance cannot be overemphasized. The growing IT bandwidth now makes all of us a part of a small village, just as a particular domicile is losing its significance. But digital disruption goes much deeper in dismantling cost structures at every step, including offering the opportunity to lower the tax burden while searching out appealing locales to help attract and retain scarce talent.

TAX BENEFITS BECKON

Both Takeda and Shire have already pruned their tax rates with their globalization strategies – especially the latter with its tax-inversion-focused switch to Ireland as its headquarters. Shire's workforce has grown five-fold, and income three-fold, while taxes have shrunk by two thirds—all while it has grown its US footprint with high-priced "rare disease" therapies that enable Shire to report operating margins close to 50%.

Takeda has some distance to go in achieving such a global footprint, or such profit margins, which goes a long way to explaining the appeal of Shire. Though this move is not primarily driven by the so called "tax inversion" just to reduce its tax obligations, efficient integration of its future combined operations still can bring Takeda's tax rates down from high-teens to low-teens.

Yes, Takeda would accept a heavy debt load at five times EBITDA, the same as what Shire ended up with after its **Baxalta Inc.** acquisition. The new Takeda leadership aims to bring this burden down to two times EBITDA within its planning horizon, hoping that the need to feed this newly created top-10 biopharma giant would not face the same fate that Shire just did. *(Also see "Takeda To Unlock More Cash As It Preps For Shire" - Scrip, 14 May, 2018.)* Shire reduced its 2020 sales target by 13% last January, as many readers would know.

Shire's Baxalta brings another valuable and "rare" franchise, in the oligopolistic blood plasma therapies market, which is shared largely by three dominant players. This sector faces innovation-driven competitive threats, especially from **Roche**. Shire also has lost some of the talent at this lucrative business unit. Still, Takeda has an opportunity to build a worthy rival to **CSL Ltd.** of Australia, which dominates this space, and sports over $60bn in market value. If appropriately strengthened, this blood plasma business alone could justify a good majority of what Takeda is paying for Shire – unless of course it chooses to divest it so as to reduce the debt burden.

So it all comes down to execution, as always, starting with the shareholders of both companies accepting the risk of heavy debt and approving the merger. Retaining and strengthening the talent across the ranks, and above all, building an efficient global operation that is not addicted to the high margin "rare disease" cash flow, offer the real challenge. Such high margins may provide rich cash flow in the short term, but gathering storm clouds around such franchises justify caution about their long-term sustainability, and call for careful preparation for broadening of the management horizons.

NEW PARADIGMS

AllianceBernstein faces a financial industry that my generation can hardly recognize, hence its relocation of a substantial portion of its people costs to a locale that perhaps offers a better quality of life, even if it is in the financial backwaters. This move may not be entirely surprising. An analyst can do her analysis almost anywhere with near-universal access to data as well as to the managements and experts through audio and video chats. So why not in Nashville, a town a tenth of the size of New York that is often rated as one of the more desirable places to live in the US? Why not, indeed! Whether AllianceBernstein can retain its superior ranking in asset management after this out-of-the-box move remains to be seen. No amount of cost savings would save AllianceBernstein unless it in fact adapts to the transformed financial industry, and improves its performance ranking to continue to attract talent as well as capital.

The biopharma industry seems a decade behind the financial industry, not to mention Uber, AirBnB, and Amazon—primarily due to the regulatory barriers. But such barriers are thinning at the edges around the world. A new paradigm where the patient in her rightful position is guided by her advisors (regulators, payers, and providers to name the three key ones) to choose appropriate treatment at the right price can align the role as well as incentives of all stakeholders, including biopharma.

Regulations already are adapting to this reality with a focus on real world data, among a growing list of initiatives, just as patients are taking charge of their disease, learning about their options, and walking into doctors' offices with a folder-full of

insights. Payers are ever-eager to explore such a paradigm for a more rational cost framework. Providers, as usual, will need time to change.

"Biopharma leaders need to recognize the shift they must undertake from imbalanced innovation and marketing infrastructures that limit their flexibility points"

Microsoft faces a similar shift, where open source software developers are increasingly shaping the future of IT, and doing so much more time- and cost-effectively. After its own efforts in this space failed to gain traction, Microsoft made a major about-face and bought GitHub so as to be able to put the software developer in the center. GitHub has become the leader in this space with 28 million developers working on 90 million software projects around the world—all of this in less than 10 years! Regulatory barriers notwithstanding, someone is going to actualize open-source biopharma innovation, not to mention open-source marketing (as selling is relegated with the advent of precision medicine) - possibly in less than 10 years. The questions is: would it be biopharma innovating and benefiting, or will a whole new frontier need to emerge to awaken the giants?

TIME FOR BIG SHIFT

The Microsoft purchase of GitHub deserves a column of its own, but suffice it to say that its pivot from calling the open-source developer platform a cancer just a few years ago, to paying $7.5bn, shows Microsoft is going all-in. This shift by Microsoft offers a mirror for biopharma leaders to recognize the shift they must undertake from imbalanced innovation and marketing infrastructures that limit their flexibility points, and broadening their horizons to adapt to this imminent future.

Takeda-Shire are taking a tradition-worn step to buy time, but unlike earlier mega-mergers in our industry, the newly globalized team of the combined Takeda-Shire can see the writing on the wall, and has an opportunity (and now the resources) to evolve its business model for this patient-centric future.

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Viren Mehta founded and is managing member of Mehta Partners, LLC, a globally integrated boutique providing strategic insights to senior management teams in the biopharmaceutical sector for nearly 30 years.

More Change At GSK's Top, With Vaccines Chief Luc Debruyne To Go

STEN STOVALL sten.stovall@informa.com

Luc Debruyne, who has been with **GlaxoSmithKline PLC** for 27 years and its president for global vaccines since 2013, is leaving at the end of 2018.

He will be replaced by Roger Connor, currently GSK's president of global manufacturing and supply, who will take up his role in September.

Luc Debruyne, President, GSK Vaccines

Roger Connor, President-Designate, GSK Vaccines

Debruyne has held a number of roles at the UK's biggest drug maker, including general manager for the Netherlands and Italy and senior vice president for pharmaceuticals in Europe.

> Debruyne's decision to leave is the latest departure from GSK's senior ranks

For the past five years, he has led the group's vaccines division, a role that included overseeing the integration of the **Novartis AG** vaccine division.

As head of GSK's market-leading vaccines business, Debruyne also shaped the division's research and development portfolio, while aligning resources to priority projects. There, he worked closely with Moncef Slaoui, GSK's former head of R&D and vaccines chief until he retired a year ago.

Debruyne also helped prepare for the launch of *Shingrix*, its hugely successful shingles vaccine. *(Also see "Shingrix Seen Replacing Zostavax In EU & US as Shingles Standard Of Care" - Scrip, 31 Jan, 2018.)*

Taking Debruyne's slot as president of the vaccine division is Roger Connor, the current head of GSK's global manufacturing and supply. He will assume his new role on Sept. 1 and receive help with the transition from Debruyne, a company spokesman said.

LATEST TOP CHANGE

Debruyne's decision to leave is the latest departure from GSK's senior ranks since Emma Walmsley became chief executive 14 months ago. *(Also see "GSK Management Shake Up Ahead Of New CEO Sees Hussain Out, AZ's Miels In" - Scrip, 19 Jan, 2017.)*

In May Simon Dingemans, the company's CFO, announced his intention to retire in May 2019. In November last year GSK announced that Hal Barron, **Genentech Inc.**'s former research chief, would become president of R&D, replacing Patrick Vallance, who left GSK to become the UK government's chief scientific adviser.

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

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

Selected clinical trial developments for the week 8–14 June 2018

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
PHASE III SUSPENDED			
Eli Lilly Eli Lilly & Co./ AstraZeneca PLC	lanabecestat	Alzheimer's disease	AMARANTH, DAYBREAK-ALZ; trials discontinued, not likely to meet primary endpoints.
PHASE III RESULTS PUBLISHED			
AbbVie Inc.	upadacitinib	rheumatoid arthritis	SELECT-NEXT, -BEYOND; *The Lancet*, June 13, 2018.
PHASE III INTERIM/TOP-LINE RESULTS			
Takeda Pharmaceutical Co. Ltd./ Lundbeck Inc.	*Trintellix* (vortioxetine)	major depressive disorder	Positive results in trial in Japan.
Allergan PLC	bimatoprost SR, sustained release implant	glaucoma	Positive clinical results.
GlaxoSmithKline PLC	*Tivicay/Epivir* (dolutegravir/ lamivudine)	HIV / AIDS	GEMINI 1 and 2 studies met the primary endpoint.
AIT Therapeutics Inc.	nitric oxide (AIT)	bronchiectasis	NO-BRO pilot study. A pivotal study is expected Q4 2019.
Presidio Pharmaceuticals Inc./ Ascletis Pharma Inc.	ravidasvir	hepatitis C (HCV)	Positive results in in genotype 1 non-cirrhotic patients.
UPDATED PHASE III RESULTS			
Zealand Pharma AS	dasiglucagon (ZP4207)	hypoglycemia	Study 16136; confirmed safety and efficacy profile.
Esperion Therapeutics Inc.	bempedoic acid	dyslipidemia	CLEAR Tranquility; reduced cholesterol levels.
GenSight Biologics SA	GS010	Leber's hereditary optic neuropathy	REVERSE; positive data.
Nektar Therapeutics	NKTR-181	chronic low back pain	NKTR-181 demonstrated consistently low abuse potential in SUMMIT-07.
Roche	*Ocrevus* (ocrelizumab)	multiple sclerosis (MS)	Phase III ORATORIO study. May provide meaningful disability benefits in primary progressive MS.
Novartis AG	*Cosentyx* (secukinumab)	psoriatic arthritis (PsA)	FUTURE 2 study. Sustained improvements in signs and symptoms of active PsA through 3 years.
Eli Lilly	*Taltz* (ixekizumab)	psoriatic arthritis (PsA)	SPIRIT-P1. improvements in the signs and symptoms of PsA persisted up to 3 years.
PHASE III INITIATED			
Roche/MorphoSys AG	gantenerumab	Alzheimer's disease, early	GRADUATE-1, -2; global studies.
Roche	*Ocrevus* (ocrelizumab)	multiple sclerosis (MS)	Phase IIIb CONSONANCE in the complete spectrum of progressive MS (PPMS and secondary progressive MS (SPMS).
Idorsia Pharmaceuticals Ltd.	nemorexant	insomnia	Adult and elderly patients.
Grunenthal GMBH/ Abiogen Pharma SPA	*Nerixia* (neridronate)	complex regional pain syndrome	Confirmatory trials.

Source: Biomedtracker

Vortioxetine Set For Japan Filing But Prospects Limited?

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Takeda Pharmaceutical Co. Ltd. has reported "positive results" from a Japanese Phase III study with vortioxetine in major depressive disorder (MDD), clearing the path for an approval submission in the country.

Based on the results of the placebo-controlled trial (NCT02389816), initiated in 2015 in around 490 adults with recurrent MDD, "both companies intend to move forward with regulatory filing…later this year," the Japanese firm and Danish co-development partner Lundbeck Inc. said.

Typical standard review times in Japan are around one year, which – depending on exact timings and the reimbursement price listing process – could potentially result in a launch sometime by the end of 2019 at the earliest. The multi-modal drug was commercialized for MDD in early 2014 in the US, its biggest market.

Neither company gave further details of the results of the study, which compared vortioxetine 10mg or 20mg a day with placebo, against the primary endpoint of change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score after eight weeks of treatment. Secondary endpoints in the trial included MADRS response and remission, and change from baseline in Hamilton Rating Scale.

The molecule is known to act as a serotonin 5-HT reuptake inhibitor, thought to be its main mode of efficacy in MDD, but is also an agonist of 5-HT1A, a 5-HT1B partial agonist, and a 5-HT3, 5-HT1D and 5-HT7 antagonist, but its exact mechanism in the disorder is not clearly understood.

LIMITED MARKET?

Originally discovered by Lundbeck, the two companies will co-promote the drug in Japan, where the prevalence of diagnosed clinical depression is around 4%. Depression in general however remains relatively under-diagnosed in the country, as many patients do not present for diagnosis or treatment.

The antidepressant has already been launched in more than 60 countries as *Brintellix* and is enjoying generally strong growth in the US, where the two companies also co-promote it, as *Trintellix*. Takeda reported sales in this market of JPY48.4bn ($438m) in the fiscal year to March 31, and like the US will pay royalties to Lundbeck on its Japanese sales.

However, the product is a relative latecomer to the market, and Datamonitor Healthcare predicts Japanese sales of a modest $52m in 2024. Vortioxetine is usually approved and positioned as a later line depression therapy following initial treatment with SSRIs or SNRIs - some of which are now available generically in the country - and then tricyclic or tetracyclic drugs, which is likely to limit its potential commercial market.

However, Datamonitor Healthcare's patient-based forecast predicts that the overall depression market in Japan will decline over the coming years, from an estimated $1.25bn this year to $930m in 2024, in large part due to the continued genericization of mainstay therapies.

Vortioxetine was also submitted in the US last December for treatment-emergent sexual dysfunction. Elsewhere in Asia, the drug was approved in China late last year, as part of Takeda's push to introduce its global innovative products there.

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Sanofi has appointed ***Jean-Baptiste Chasseloup de Chatillon*** as executive vice president, chief financial officer (CFO) and a member of its executive committee, effective October 1. He will join Sanofi on September 1 to ensure a smooth transition with ***Jérôme Contamine*** who will retire on September 30, after more than nine years at the company. Chasseloup de Chatillon was most recently SFO and EVP for PSA Group. He was also chairman of the board of Banque PSA Finance from 2012 to June 2016, and has been a member of the Peugeot S.A. Managing Board since 2012.

Celgene has appointed ***Jonathan Biller*** executive vice president and general counsel, effective July 3. Biller will succeed ***Gerald F. Masoudi***, who has been in the position since 2015. Masoudi is leaving Celgene to return to Washington, D.C. to be chief legal officer with a private company outside the biopharmaceutical industry. Biller joined Celgene in 2011 and was most recently senior vice president, tax and treasury and served as Celgene's treasurer. He joined from agriculture and food company Bunge Limited, and previously worked at Alcon.

Eduardo Bravo has left his role as CEO of **TiGenix** effective June 15, 2018. Following the first acceptance period of the takeover bid by Takeda, Bravo will be succeeded immediately on the board of directors by ***Sebastian Wehle***, who will be in charge of the daily management of TiGenix together with ***Claudia D'Augusta***, CFO of TiGenix. Wehle is senior director at Takeda, and was previously at Nycomed and Altana. Meanwhile, Vivet Therapeutics, a biotechnology company developing novel gene therapies for metabolic diseases, has announced the appointment of Bravo as chairman of the board. He takes over from Florent Gros who has served as chairman since the Vivet's creation.

Allogeneic CAR-T company **Allogene Therapeutics Inc.** has appointed ***Eric Schmidt*** as chief financial officer. He joins from Cowen and Company, where he served as managing director and senior biotechnology analyst. Before joining Cowen in 1998, Schmidt was a vice president and research analyst covering the biotechnology sector for UBS Securities, and prior to that he co-founded Cambridge Biological Consultants, a scientific consulting and research firm.

Food allergy company **Aimmune Therapeutics Inc.** has appointed ***Jayson Dallas*** as president and CEO, effective June 19. He will also become a member of the board. Dallas joins Aimmune from Ultragenyx, where he was the company's first chief commercial officer. Before that, he spent five years with Roche, following positions at Novartis and Pfizer. Dallas succeeds Stephen Dilly who announced his planned retirement late last year.

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