

## China Changes

Fresh measures to streamline development and approvals of foreign drugs (p4)

## Slow Start

Newly launched US drugs are taking their sweet time to rack up sales (p14)

## Class Effect?

Real-world evidence that the SGLT2 inhibitors are game changers (p7)

# Scrip

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## The Decline And Fall Of The Pharma Pipeline

2016 saw a drop in the growth rates for both number of products in active development and in the number of companies in active R&D. The data from a new report from Pharmaprojects seem to point to an end to recent years of accelerated growth in the pipeline that followed five years of stagnation.

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The number of products in active development by the pharma and biotech industries rose to an all-time high in January 2017, but this headline figure flattered what were actual drops in the rates of growth not just of this key metric, but also of the number of companies active in R&D. When added to an actual decline in the number of new active substances launched in 2016 (down by 11%), it paints

a picture of an industry whose footing has become slightly less secure.

New data from Informa Pharma's Pharma R&D Annual Review 2017 from Pharmaprojects show that there were 14,872 pipeline projects in development in January 2017, and increase of 8.4% on the corresponding figure from 2016. The growth rates for the previous two years were higher at 11.5% and 8.8%. Citeline's annual review takes a

snapshot of the Pharmaprojects database in early January, allowing comparisons to be made across the years.

*Editor's note: "Pipeline" in the context of this article and the Citeline white paper means all drugs in development by pharmaceutical/biotech companies, from those at the preclinical stage, through the various stages of clinical testing and regulatory approval, and up to and including launch. Launched drugs are still counted, but only if they are in still in development for additional indications or markets.*

What is reassuring is that the growth is again spread throughout the pipeline. The chart on page 8 compares the number of drugs at each stage of development with the equivalent data for last year. The greatest growth occurred at the preclinical stage, with an extra 632 early drug candidates, a rise of 9.2%, but there are increases across the board throughout the clinical and later regulatory phases.

### Key Facts

- Largest number of products in R&D ever recorded
- Growth rate of the pharma pipeline declined
- Growth rates declined at each clinical phase
- Growth rate of the number of companies with active R&D fell
- Number of New Active Substance first launches dropped by 11%

Stripping out the preclinical projects, for which it is notoriously difficult to gain a truly accurate picture, the data from the past decade or so show an upward trend for each of the broad clinical phases.

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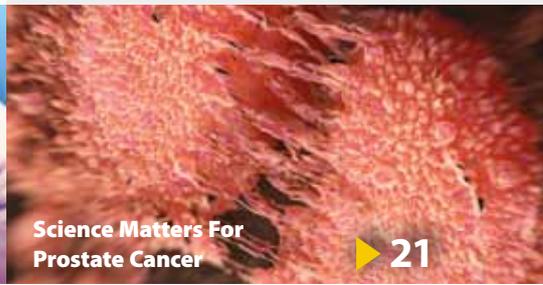
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## from the editor

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While transparency of one sort was brought to light in recent company pricing reports (see p3), transparency of another sort was spotlighted in the UK this week.

The Association of the British Pharmaceutical Industry revealed that only 55% of healthcare professionals receiving payments from pharma in 2015 had consented to their details being disclosed in its database of industry payments to HCPs, not 70% as it had estimated last year. The vast majority of pharma companies operating in the UK have signed the ABPI code of practice, which obliges them to reveal how much they pay to healthcare professionals and organizations, but individual recipients can use data protection law to conceal their identities.

In fact, payments whose recipients are named in Disclosure UK make up only one fifth of the \$363m industry reported paying out. Despite industry having been more open than the individuals it pays, it is pharma's reputation on the line. Selective disclosure highlights the missing information, and opens the door to accusations that doctors have something to hide in their relationships with drug makers. Companies should refuse to work with HCPs who won't disclose.



## exclusive online content

### A New Business Model For Deprioritized Clinical Trials

While the pharmaceutical industry faces many issues, a lack of potential assets is not one of them. A structured approach to developing those products, which may have been deprioritized because of company resources or do not promise the ROI needed by external investors, is being explored to the benefit of all parties.

<http://bit.ly/2n8JJZ5>

### Deal Watch: BioLineRx, Ono, Vedantra Ink Separate Cancer Immunotherapy Pacts

BioLineRx buys Agalimmune and its alpha Gal candidate for melanoma and possibly other oncology indications. Japan's Ono signs an R&D agreement with Switzerland's Numab, while Boston biotech Vedantra and Neon will collaborate on potential cancer vaccines.

<http://bit.ly/2ngwfl1>

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# Which Pharma Firm Increases US Prices The Most?

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*Transparency reports from companies aim to change conversation from prices to discounts, but also invite comparisons. Lilly, for example, saw a higher average list price increase in 2016 than Merck and Janssen, but its net prices grew by less than the others.*

Are pharma company efforts to disclose their pricing activities having an impact on public or political perception of their practices in the US? Nothing dramatic yet, it seems, but the flow of reports does invite some interesting comparisons between the firms themselves.

Eli Lilly & Co. is the latest major pharma company to issue a pricing transparency report revealing its average price increases over the past five years. While its 2016 list price (wholesale acquisition cost) increase of 14% is below that of the previous year, it is higher than the average increases reported by Merck & Co. Inc. and Janssen Pharmaceutical Cos. However, its average net price increase is lower than the other firms.

Lilly included the pricing information in its 2016 Integrated Summary Report. In a March 20 blog post announcing its availability, Lilly President & CEO Dave Ricks stated that with rebates and discounts Lilly cut the average U.S. list price of its medicines by 50%, which is nearly twice as much as the 28% average discount it provided five years ago.

"Because of these growing discounts, the average U.S. net price of Lilly medicines – the actual amount we recoup from selling our products – rose 2.4% last year. That's lower than overall medical inflation," Ricks said.

Lilly's net price increase has fluctuated over the years, going from 1.6% in 2014 to 9.4% in 2015 and then 2.4% in 2016. By comparison, Merck's net price increase rose 5.5% and Janssen's rose 3.5% last year.

Drug makers are releasing the pricing reports as they continue to face criticism over the costs of their medicines and President Trump calls for some form of price negotiation to drive down "astronomical" prices. The reports do not include price increases for specific products, and many of the differences in approach to pricing and discounting are likely due to the particular market dynamics each company's product portfolio faces.

## FACTORS BEHIND UPTICK IN DISCOUNTS

Companies are emphasizing the price savings they are providing through discounts and rebates. Janssen reported that its discounts and rebates to insurers, pharmacy benefit managers and others totaled approximately \$11bn in the US in 2016, or a discount rate of 35.2%.

Lilly noted in its report that several factors are driving this trend.

"Along with changes to the Lilly portfolio, increases in competition among pharmaceutical manufacturers, as well as increased negotiation leverage by pharmacy-benefit managers (PBMs), have resulted in deeper discretionary discounting over the last several years," Lilly said. "Additionally, mandatory government discounts have significantly increased since passage of the Affordable Care Act in 2010."

Lilly announced in December that it would launch a new discount program for its insulins, including *Humalog* (insulin lispro), that could save people who pay full price up to 40%.

Several companies, including Allergan PLC, Novo Nordisk AS and AbbVie Inc. have pledged that they will keep annual price increases throughout their portfolio below 10%. AbbVie noted at the J.P. Morgan Healthcare conference in January that it expects one price increase in the calendar year for all of its brands with no increase to exceed single digits for any product.



Asked about the pricing reports, Roche's Genentech Inc. unit said that "while many companies are making public pledges to limit their annual price increases to below 10%, our annual average has been below that benchmark for many years." Genentech noted that over the past four years, its annual average list price increase across all of its medicines was between approximately 5.5% and 7%, adding that it doesn't see this approach changing in the future.

Sanofi said it is finalizing a corporate pricing policy which will state its average list and net price increases. It noted that from 2015 to 2016 its wholesale acquisition cost price increased by 2.3% on average and its net price decreased by 0.5%. In addition, its 2016 average annual discount was 50.2%.

Sanofi noted that it recently introduced a new copay offer for eligible diabetes patients to pay no more than \$10 per prescription for its insulin glargine products *Lantus* and *Toujeo* for up to 12 months regardless of insurance coverage. Eligible U.S. patients with commercial insurance also pay no co-pay for Sanofi's *Soliqua* 100/33 (insulin glargine/lixisenatide), which launched earlier this year.

Companies are also touting the availability of medicines through charitable organizations. Lilly noted that over the past three years, it has donated more than \$378m in diabetes medicines to charitable organizations for further distribution to qualifying individuals.

The US government is scrutinizing the relationships companies have with these organizations. Several companies have reported receiving requests from US attorney offices for documents related to their support of 501(c)(3) organizations that provide financial assistance to patients. Drug makers have also received requests for information about their contracts with

pharmacy benefit managers. ▶  
Published online  
21 March 2017



View charts comparing  
company price rises here:  
<http://bit.ly/2n0uvN8>

# Now Is The Time! Rule Changes To Open Up China To Foreign New Drugs?

*The China FDA has outlined a raft of new measures to streamline the development and approval process for foreign new drugs, in changes that are likely to bolster multinationals' interest and activity in China, and to quicken the pace of launches to potentially overcome the country's "drug lag."*

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Spring may finally be here for multinationals looking for a smoother development path for their new drugs in China.

Just days after the head of the country's drug review and approval agency expressed publicly a willingness to welcome more foreign drugs into China, a new draft regulation that promises just that has been released by the China FDA.

The document, dated March 17, proposes revising a burdensome requirement relating to the conduct of multi-regional clinical trials (MRCTs) at sites in China and potentially allowing the more simultaneous conduct of early-stage studies in the country.

The purpose of the revision, per the CFDA, is "to encourage novel new drugs that have not yet been approved overseas to conduct parallel studies in China upon [study] approval, to shorten the new product [approval time and] launch lag between inside and outside China, and to meet the public demand for new drugs."

## FOUR MAIN POINTS

There are four main points mentioned by the CFDA in its draft document, all of which look positive for the foreign pharma industry and the commercialization of new drugs in China.

The first concerns the elimination of the current requirement that a new drug for which an MRCT is planned in China must have been approved – or at least have entered Phase II or III trials – in another country overseas. Vaccine products are the exception.

Additionally, the draft proposes that upon completion of the MRCT in China, a new drug application can be filed with the CFDA directly using the data obtained from the study (rather than any other additional Chinese studies), although the NDA will need to comply with the requirements of China's Drug Registration Administration and other rules.

A third planned change is to eliminate a requirement for a certificate of pharmaceutical product for imported chemical drugs and biologic products. This has had to be issued by the competent authorities of the country where the manufacturer is located and should comply with World Health Organization format, and has been used as an additional way to ensure safety and quality,

delayed new product launches by an average of around 30 months, or 2.5 years.

The new revisions, if implemented, could therefore be significant for companies eager to launch their novel products in China, noted one veteran clinical study manager working for a multinational pharma firm in China.

"There are two aspects to the issue. One is that a clinical trial approval would be

Industry observers said the draft rule could potentially spur earlier-stage Phase I work in China, which bodes well drug approval standards

Finally, for MRCT applications that have previously been filed and accepted, the CFDA will grant a waiver for any additional local trials on condition the filings meet the other new requirements. (Applicants have usually had to apply separately for this waiver.)

## TWO TO THREE YEAR SAVING?

The new moves are a direct departure from the CFDA's previous "Sanbaosanpi", the so-called three filings, three approvals procedure for new imported drugs due to the different levels of requirements, which has been in place since 2014 but is generally considered burdensome by applicants.

This system usually requires an MRCT application, plus a filing to conduct local trials, and then the final NDA to secure approval. Pre-2014, applicants conducting completing MRCTs could apply for a waiver for local-only trials, but the Sanbaosanpi system effectively did away with this, added an extra procedural requirement for a local clinical trial approval.

Multinationals have complained that the additional requirements for the conduct of clinical trials with new drugs in China have

accelerated, allowing study sponsors to include a China study in a parallel global study. And secondly, the data obtained from the study will be able to be used towards a NDA filing; both are important," he told *Scrip*, adding there could be a two-year shortening in the current delay for new product launches in China.

One legal expert agreed. Katherine Wang, a partner at law firm Rope & Gray's Shanghai office, said the changes would benefit obtaining both clinical trial approvals and NDAs for imported drugs in China.

"It appears to revise the course [back to prior to 2014] when data from MRCTs could be used directly towards a product approval filing, and on top of that, the rule further relaxes requirements for imported drugs applying for clinical trials approvals, which would be a good news if implemented," said Wang.

## INNOVATION, ACCESS

Both the industry observers said the draft rule could potentially spur earlier-stage Phase I work in China, which bodes well for the government's plans to switch to an innovation-driven economy and encourage original research.

In a note on the changes, Jefferies analyst Eugene Huang said the changes could cause MNCs to refocus on China, and might bring new work and pricing opportunities to contract research firms as sponsors look to more local studies to access large patient pools, save costs, and build links with local researchers.

On the other hand, domestic generics firms might be hit by a closing of the drug lag, and perhaps by a lowering in local development costs that might enable more price reductions by foreign firms.

Interestingly, the new move came after China's recent annual plenary Two Sessions meetings (of the People's Congress and Political Consultative Meetings), during which CFDA Commissioner Bi Jinqian said the country welcomes more foreign drugs.

It also came ahead of a high-level discussion forum in which several global pharma CEOs were due to discuss their ideas with Chinese leaders on topics ranging from regulatory reforms to innovation ecosystem building.

## RECENT APPROVALS

There have been other positive signs over new drug access as well. Just two days ahead of the release of the new CFDA draft proposals, the regulator approved Pfizer Inc.'s JAK inhibitor *Xeljanz* (tofacitinib) for rheumatoid arthritis, along with several other new drugs from multinationals granted recent nods. These included AstraZeneca PLC's *Forxiga* (dapagliflozin) for type 2 diabetes and afatinib from Boehringer Ingelheim GMBH for non-small cell lung cancer.

"We applaud the efforts of the Chinese government and the CFDA to bring new medicines to the Chinese healthcare system," Pfizer China country manager Wu Xiaobin said in a statement. The *Xeljanz* approval was based on efficacy and safety data obtained from a global study with a subgroup in China, the company noted.

Public comments on the draft CFDA proposals are being collected until April 20 via [www.chinalaw.gov.cn](http://www.chinalaw.gov.cn) and email submissions can be made to: [hxypc@cfda.gov.cn](mailto:hxypc@cfda.gov.cn) with the subject "Adjustment to Imported Drugs Opinions." ▶

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From the editors of *PharmAsia News*.

# Heartache For Novartis As Serelaxin Failure Ups Pressure On Entresto

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*Novartis's latest Phase III study of serelaxin has failed, deleting a significant chunk of forecasted revenue that analysts had attributed to the heart failure drug candidate.*

Novartis AG's relaxin receptor agonist serelaxin (RLX030; recombinant relaxin) – touted as a potential blockbuster by some analysts – has failed in the RELAX-AHF-2 Phase III clinical trial for acute heart failure (AHF). The drug missed both co-primary endpoints of worsening of heart failure and cardiovascular death in the RELAX-AHF-2 study, which had been required by regulators to confirm serelaxin's potential benefits following mixed results from an earlier trial.

"We had included the product in our pipeline forecasts at \$500m in 2021 and \$750m in 2025," admitted Bernstein's Tim Anderson in a March 22 note. "Removing those revenues represents a loss of \$0.10 (1.5%) from 2021 [earnings per share (EPS)]."

But Deutsche Bank's Tim Race suggested in a same-day report that investors were prepared for bad news from the serelaxin program.

"The trial was always high-risk and investors appeared well aware of this in our view," Race wrote on March 22. However, "due to the scale of the opportunity, [it] carried near blockbuster expectations." The failure of serelaxin will shine an even broader spotlight on revenue from Novartis's approved heart failure drug *Entresto* (sacubitril/valsartan), which missed a 2016 sales target of \$200m, "as well as the importance for management to bolster its pipeline," the Deutsche Bank analyst pointed out.

Few would disagree that Novartis is going through a difficult patch. "Coming after the *Entresto* misfire, the Alcon [sell-off] delays, the on-again/off-again Roche stake divestiture – we understand why some investors express frustration," Bernstein's Anderson said.

Novartis presented heart failure as one of its areas of focus together with oncology, dermatology and respiratory back in



2014. But with RELAX-AHF-2 missing its endpoints, Bryan, Garnier & Co. analyst Eric Le Berrigaud wrote in a March 22 report that *Entresto* has "full responsibility to build Novartis's expertise in heart failure." In the meantime, "Respiratory was relegated to a secondary role and with recent mixed feedbacks about [*Kisqali* (ribociclib; LEE0110)] (questionable label in the US) and [*BAF312* (siponimod)] (second study required, unlikely to be conducted by the company), we see poor momentum for the stock."

Novartis chief medical officer and global head of Drug Development Vas Narasimhan said in regard to the latest serelaxin data that the company is "disappointed" the efficacy of the drug was not confirmed in acute heart failure, "especially given the urgent need for effective new treatments for this condition." The Swiss firm "will continue to further analyze the data to better understand and learn from these results as well as evaluate next steps for the overall program," Narasimhan said.

RELAX-AHF-2 was an event-driven, multicenter, randomized, double-blind, placebo-controlled, Phase III trial of serelaxin added to standard of care in patients with acute heart failure (AHF). It included 6,600 patients hospitalized for AHF and was initiated in October 2013. ▶

Published online 23 March 2017

# Gilead Cites 'More Sophisticated' Process As Pressure Increases

*CEO John Milligan offered few details about Gilead's deal strategy during an investor conference last week, but analysts think internal pressure for a major deal is beginning to equal the external sentiment, including an analyst who sees Incyte as a likely target, but not a quick fix for Gilead's declining HCV drug sales.*

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The ongoing decline of its hepatitis C revenues has put additional pressure on Gilead Sciences Inc. to make a significant purchase that might boost its forward momentum – something that apparently is as clear inside the virology powerhouse as outside – but recent commentary by CEO John Milligan leaves doubt as to whether the firm is willing to greatly change the parameters of what it seeks in a transaction.

Milligan spoke on March 14 at the Barclay's Global Healthcare Conference, during which analyst Geoff Meacham tried to draw him into a discussion of a "Dear Management and Board" letter that Meacham circulated the day before, urging Gilead to look outside its core therapeutic areas and perhaps loosen its expectations for return-on-investment in evaluating available merger-and-acquisition possibilities. Milligan didn't delve deep into Gilead's deal strategy, but acknowledged the recent hire of former Novartis AG exec Alessandro Riva to lead the company's oncology unit as an indication of how its M&A thinking has evolved.

Riva is undertaking a two-part remit at Gilead, Milligan noted, reviewing the current oncology pipeline for potential unrealized opportunities in hematology and assessing external programs that might make ideal additions to the pipeline.

"He's working on various aspects of looking at what might fit within Gilead," the CEO said. "At the same time, we've had some turnover in our business development group and decided to bring in brand new leadership and revamp our processes so that we now have a much more sophisticated machine looking all across the spectrum from early licensing deals to sort of new technology, new things that will take some time, as well as ... more mature programs."

"This is a long-term business; we think 10 years out in almost everything we do," Milligan continued. "So, we have to invest across that spectrum to make sure that we have

a more consistent flow of products going into the future than we have currently."

An obvious answer, to some external observers, would be to bolster the cancer business with a buyout of Incyte Corp. Credit Suisse analyst Alethia Young pointed out in a March 13 note that Novartis partnered with Incyte on hematology drug *Jakafi* (ruxolitinib) outside the US during Riva's tenure with the Swiss pharma. In addition to the commercial product approved for myelofibrosis and polycythemia vera, acquiring Incyte also would bring Gilead the Phase III IDO inhibitor epacadostat, which is being tested in immuno-oncology combination regimens, and a pipeline covering a wide range of oncology targets.

## INCYTE A POTENTIAL TARGET

Young estimates that Gilead might need to pay around \$35bn to land Incyte – roughly a 15% premium over current valuation – which would require some degree of financing despite Gilead's strong cash position. The Foster City, Calif.-based firm has more than \$32bn in cash, with another \$27bn held offshore, which could leverage financing.

Still, she wonders whether an Incyte takeout would bring the near-term infusion of value Gilead is thought to need. Young projects a deal would not be accretive to earnings until 2021, when ramp up would begin for regimens including epacadostat. Meanwhile, in the shorter term, Gilead might incur expenses in building on its current *Zydelig* (idelalisib) sales force to make an apparatus big enough to also support *Jakafi*, she said.

Barclay's analyst Meacham attempted to crystallize Gilead's thinking on M&A in a March 10 note that urged the company to cast a broader net for a "transformational or even incremental" deal that would shift investor focus away from quickly decreasing revenue from hepatitis C drugs and serious doubts as to whether a revitalized HIV fran-

chise can take up the slack. The company surprised some of its investors during its Feb. 7 earnings call by sharply reducing its 2017 guidance for hepatitis C virus (HCV) sales.

Meacham said the ROI from the 2011 acquisition of Pharmasset Inc. that brought Gilead the HCV blockbusters *Sovaldi* (sofosbuvir), *Harvoni* (sofosbuvir/ledipasvir) and *Epclusa* (sofosbuvir/velpatasvir) combo pills set "clearly an impossible benchmark" for future M&A. But going forward, Meacham continued, Gilead may need to think outside its current therapeutic focus areas of virology, oncology and inflammation.

"Our fear is that as quarterly operating cash flow declines ... so does the capacity to do any meaningful transaction," he wrote.

The need for Gilead to make a substantial deal has been the focus of roughly 90% of his conversations about Gilead over the past three years, Meacham noted.

Adding an orphan drug specialist that would bring franchises in cystic fibrosis, paroxysmal nocturnal hemoglobinuria (PNH) or atypical hemolytic-uremic syndrome (aHUS) would fit well with Gilead's cost structure, Meacham suggested, and "could provide a long-term, durable business with 2020 revenues north of \$4bn." Although Meacham did not mention any potential buyout targets for Gilead by name, Alexion Pharmaceuticals Inc.'s *Soliris* is approved for both PHN and aHUS. *Soliris* (eculizumab) posted sales of \$2.84bn in 2016.

Gilead also should think beyond deals that would add on-market products or near-to-market Phase III candidates, the analyst said, noting that the company would be best served by deal structures that would ameliorate the clinical risk of such an acquisition. He proposed a focus on deals structured to account for value-creating clinical events with multiple mid-to-late-stage opportunities and an underlying business beyond the R&D pipeline that could benefit from Gilead's scale. ▶

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# Cardiovascular Benefits of SGLT2 Inhibitors: A Class Effect?

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*A large real-world evidence study has found SGLT2 inhibitors cut the rate of hospitalizations for heart failure and all-cause mortality in patients at low risk of cardiovascular events, but the results of CV outcomes studies are awaited to confirm the findings.*

Preliminary evidence that the cardiovascular benefits ascribed to Boehringer Ingelheim GmbH/Eli Lilly & Co.'s *Jardiance* (empagliflozin) may be a feature of all SGLT2 inhibitors has come from a recent real-world data analysis supported by AstraZeneca PLC, but definitive evidence still awaits a series of cardiovascular outcomes studies with individual antidiabetic agents.

The analysis of AstraZeneca's CVD-REAL study, presented last weekend at the American College of Cardiology meeting, did not break out patient outcomes for individual sodium-glucose cotransporter 2 (SGLT2) inhibitors, but did present compelling evidence that the rates of hospitalizations for heart failure, and death, were cut by half by use of the three currently marketed SGLT2 inhibitors in diabetes type 2 patients, compared with other types of diabetes therapies.

## DATA SCRAMBLE

Empagliflozin became the first diabetes therapy to have a cardiovascular mortality risk reduction claim approved by the US FDA at the end of the year, based on the results of the EMPA-REG CV OUTCOME trial. But even before that date, companies were scrambling to gain similar data on their diabetes therapies, and there are a number of CV outcomes studies underway with DPP-4 inhibitors, GLP-1 agonists and SGLT-2 inhibitors.

Novo Nordisk AS already has data from the LEADER trial that its GLP-1 agonist *Victoza* (liraglutide) may be associated with a cardiovascular mortality benefit, as does its investigational GLP-1 agonist, semaglutide. KOLs like the Cleveland Clinic's Steve Nissen believe therapies for type 2 diabetes will be dominated in the future by cardioprotective agents rather than blood sugar reducers, and suggests that companies will need to adjust their commercialization strategies.

Datamonitor Healthcare analyst Kevin Shannon said the AstraZeneca study supported the current sentiment among physicians that there is a class benefit associated with SGLT2 inhibitors, and that Janssen Pharmaceuticals Inc.'s *Invokana* (canagliflozin) and AstraZeneca's *Farxiga* (dapagliflozin, named *Forxiga* outside the US) will be found to have positive effects on major adverse cardiovascular events (MACE) when data from their cardiovascular outcome studies are announced. The AZ study may also protect *Farxiga*'s and *Invokana*'s share of the market by reducing the number of patients switching to *Jardiance*, Shannon commented.

The results of the AZ study also support the use of SGLT2 inhibitors in early lines of therapy across all patient populations, not just those at increased risk of cardiovascular events, Shannon noted. The *Jardiance* EMPA-REG-CV study involved type 2 diabetes patients at

high risk of cardiovascular events, while in the AZ study almost 90% of patients had no history of cardiovascular disease. There has been some debate about what patient population would benefit most from SGLT2 inhibitors, but the study suggests that SGLT2 inhibitors should be used as first- or second-line treatment across all patient populations, he suggested.

CVD-REAL collected anonymized data from more than 300,000 diabetic patients from six countries (Denmark, Germany, Norway, Sweden, the UK and the US), and found that treatment with an SGLT2 inhibitor, either dapagliflozin, canagliflozin or empagliflozin, significantly reduced the rate of hospitalization for heart failure by 39% ( $p < 0.001$ ), and deaths from any cause by 51% ( $p < 0.001$ ), compared with other diabetes therapies. For the composite endpoint of hospitalization for heart failure and death from any cause, the reduction was 46% ( $p < 0.001$ ).

The CVD-REAL study is the first to observe the beneficial effects of SGLT2 inhibitors in a broad group of patients – 87% of patients in the study did not have a history of cardiovascular disease. And only a small percentage of patients were being treated with empagliflozin that has already been associated with cardiovascular benefits. For the analyses of hospitalizations for heart failure, 52.7% of patients were being treated with canagliflozin, 41.8% of patients were on dapagliflozin, and only 5.5% were on empagliflozin.

It's possible that further real-world evidence may become available in the future on the potential benefits of individual SGLT2 inhibitors; AstraZeneca said the data presented were the first of several comparative analyses, and future analyses will add datasets from additional countries.

## DECLARE OUTCOME IN 2019

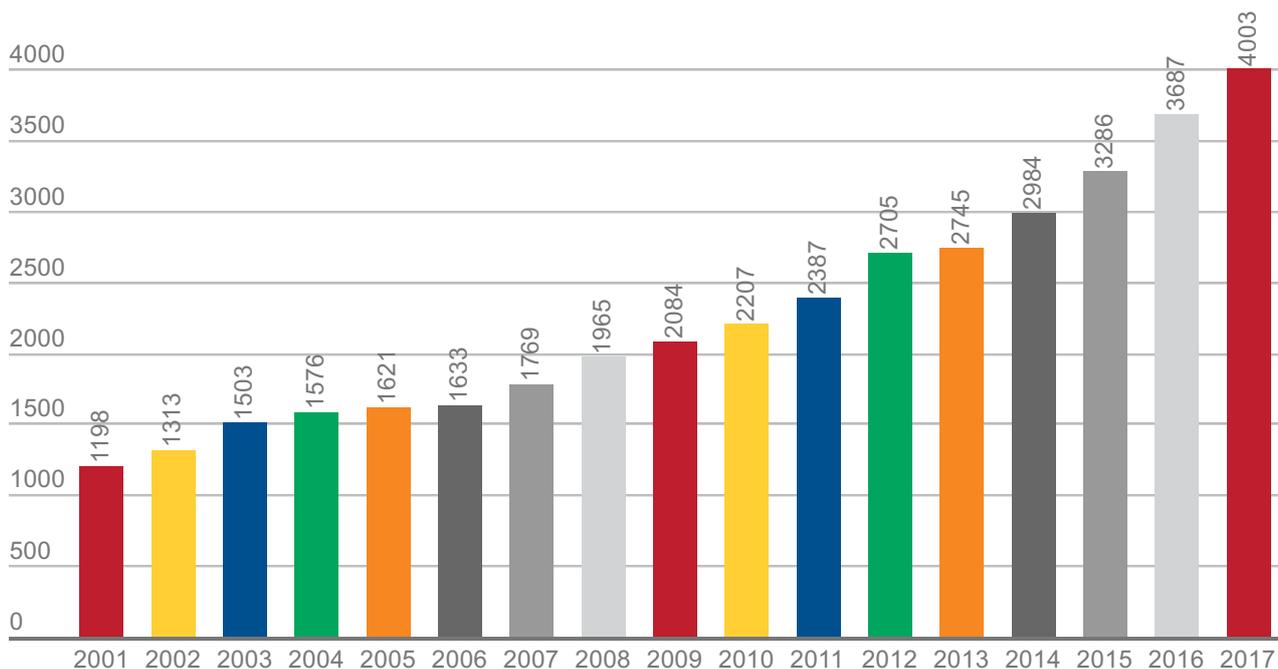
The first direct evidence of the effect of dapagliflozin on cardiovascular outcomes is expected to come at the latest in 2019 from the DECLARE study, which is enrolling more than 17,000 patients treated with either dapagliflozin or placebo in addition to standard of care in adults with type 2 diabetes and a high risk of cardiovascular disease. The company has also started two outcomes studies, DAP-HF and DAPA-CKD, to define the possible role of dapagliflozin in patients with chronic heart failure and chronic kidney disease.

Datamonitor Healthcare issued a report March 17 on type 2 diabetes forecasting that the SGLT2 inhibitor class of antidiabetic agents will experience significant growth over the 2016-2025 period, owing to the anticipated effect on cardiovascular outcomes. Such benefits are expected to drive more than \$3bn in sales growth over the decade. Overall, the type 2 diabetes market could be worth more than \$38bn in 2025, driven by an increasing patient population, the use of more expensive second and third line therapies, and the effect of SGLT2 inhibitors and GLP-1 agonists on body weight and cardiovascular benefits. SGLT2 inhibitors will become the largest oral antidiabetes class by value, the report forecasts. ▶

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CONTINUED FROM COVER

Total R&D Pipeline By Year 2001-2017



Source: Pharmaprojects®, January 2017

The increase at Phase I was the greatest, with the number of candidates rising by 11.2%, to reach a figure almost twice the number of that seen 10 years ago. The corresponding values for Phase II and Phase III were 4.2% and 7.4%, respectively. All of these increased rates are lower than those seen a year ago – the Phase III figure considerably so (last year it rose by 18.1%).

COMPANY RISERS AND FALLERS

Table 1 lists the Top 25 biggest companies by size of R&D pipeline. While the names on the top 10 companies did not change, there was some jockeying for position among the big players. GlaxoSmithKline PLC lost its top position last year, being squeezed out by a single project by Novartis AG. What's more, the Swiss conglomerate's ascendancy to pole R&D position is strengthened by the fact that it originated a greater proportion of its pipeline itself.

At least GSK extended its lead over UK rival AstraZeneca PLC, which fell back this year both in terms of position and hard numbers. Johnson & Johnson, Roche and Sanofi also showed declines in the numbers of drugs in their pipelines.

Even without the help of Allergan's contribution, the US giant Pfizer Inc. started to claw its way back up the Top 10 – it last held the top spot in 2011 following its acquisition of Wyeth but subsequent consolidation

meant its pipeline ranking had consistently slipped since. Similarly, it is already clear that one company set to rise next year will be Johnson & Johnson once its acquisition of Actelion completes (slated for the end of the second quarter). Actelion Pharmaceuticals Ltd. currently has 24 drugs in its pipeline, but this deal is complicated by the fact that its Phase II and below pipeline will be spun off into a separate company under the direction of the Swiss biotech's current R&D hierarchy, in which J&J will have a minority stake.

Outside the top 10, Shire PLC moved up the charts to 18 thanks to its acquisition of

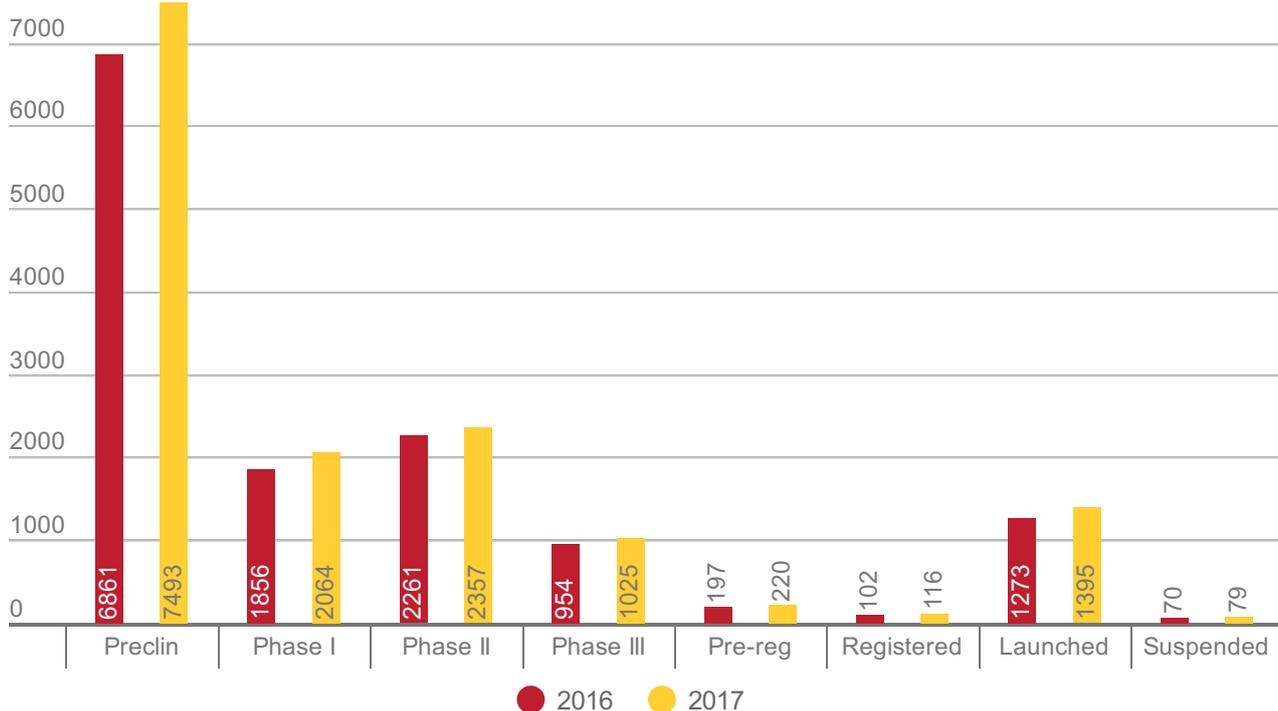
Baxalta Inc., and big riser Ligand scraped into the top 25 by virtue of a raft of licensing deals – its tally of 66 (up from 38 the previous year) was notable for having the highest proportion of drugs that did not start their lives in the company's own labs.

But crashing out of the top 25 were Gilead Sciences Inc., which entered at 25 last year only to slip back to 27th position despite a slight growth in its pipeline, plus the Japanese companies Mitsubishi Tanabe Pharma Corp. and Sumitomo Dainippon Pharma Co. Ltd., which fell back to 28 and 31 spots, respectively.

Table 1: Top 10 Pharma Companies by Size of Pipeline

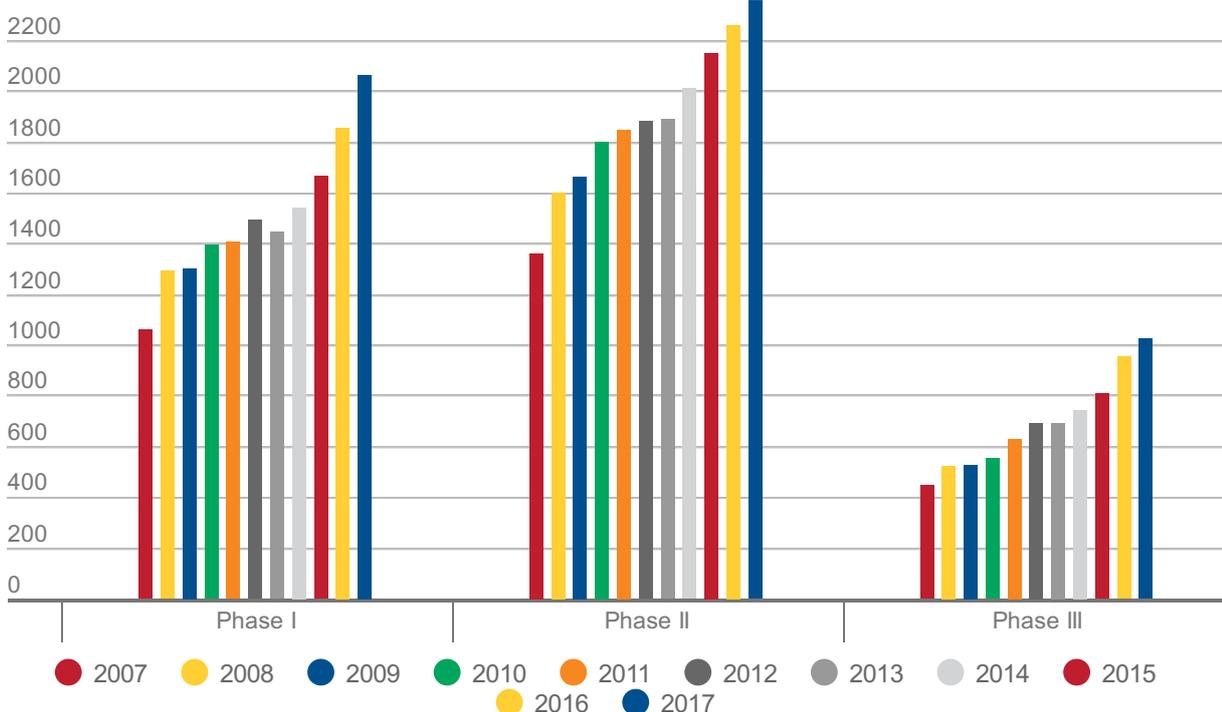
POSITION 2017 (2016)	COMPANY	NO OF DRUGS IN PIPELINE 2017 (2016)	NO OF ORIGINATED DRUGS 2017
1 (2)	Novartis AG	251 (240)	161
2 (1)	GlaxoSmithKline PLC	250 (242)	149
3 (6)	Pfizer Inc.	232 (217)	148
4 (5)	Merck & Co. Inc.	229 (223)	141
5 (4)	Johnson & Johnson	214 (227)	111
6 (3)	AstraZeneca PLC	213 (231)	119
7 (7)	Roche	206 (211)	129
8 (8)	Sanofi	193 (199)	80
9 (10)	Bristol-Myers Squibb Co.	144 (136)	105
10 (9)	Takeda Pharmaceutical Co. Ltd.	141 (137)	80

Pipeline By Development Phase 2017 vs 2016



Source: Pharmaprojects®, January 2017

Clinical Phase Trends 2007-2017



Source: Pharmaprojects®, January 2017

**EXPANSION CONTRACTION**

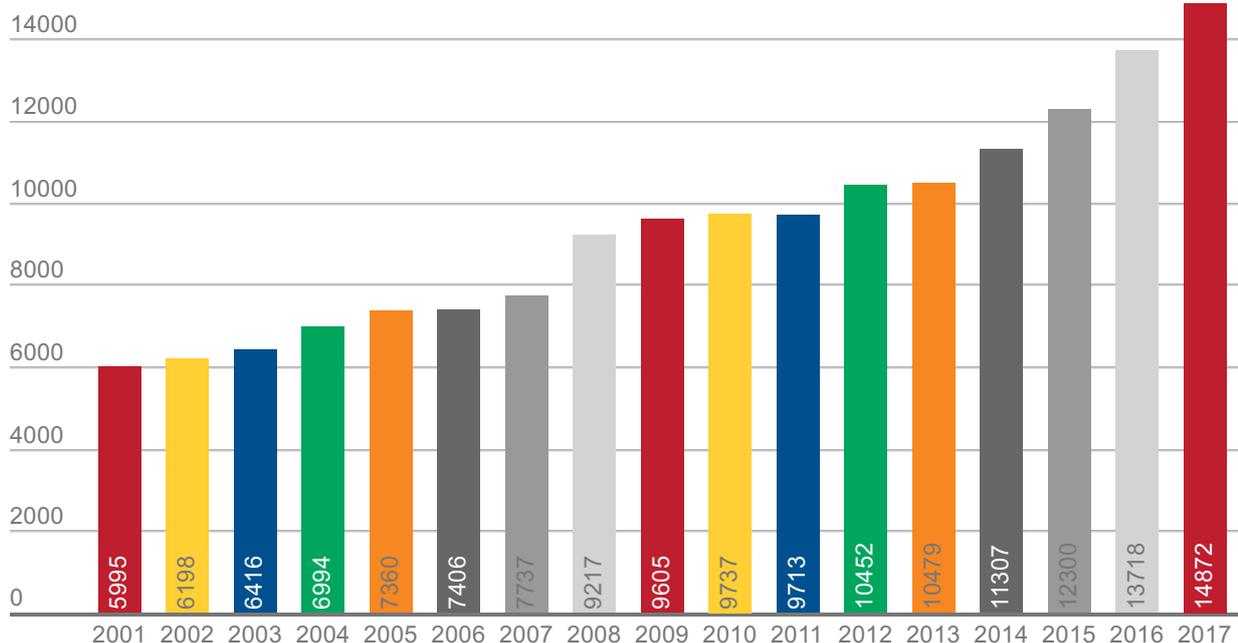
The pharma universe once again expanded last year – although its growth rate contracted. “Almost 750 new companies were identified and added to the Pharmaprojects database over the past 12 months – a stag-

gering birth rate, and a significant uptick from the 618 seen in both preceding years,” said the report’s author Ian Lloyd, senior director at Pharmaprojects. “However, company acquisitions, and more pointedly, company deaths or hibernations, meant that the

total number of active companies grew by less than half this figure.” As of January 2017, 4,003 pharma firms were reporting active pipelines, an increase of 8.6%. Once again, this growth rate is lower than the 2015-16

CONTINUED ON PAGE 10

Total Number Of Companies With Active Pipelines 2001-2017



Source: Pharmaprojects®, January 2017

number (12.2%). Of these, 1,578 companies have just a single product in their pipelines, and 679 have two. Together they contribute more than half (56.4%) of the total – a proportion virtually unchanged this year.

Also notable was the eastward migration of pharma’s base. Asian firms now account for 19% of companies, up from 16% last year, and driven not only by further expansion in China, but also by general growth throughout the region.

This has come at the expense of Europe and the US, which both fall back by 1%, although the latter still accounts for almost

half of all R&D companies worldwide. “Keen Brexiteers will no doubt be heartened by the UK taking its share up from 5% to 6%, and it will be interesting to track this metric over the coming years,” said Lloyd.

**CANCER DOMINANCE WIDENS**

What’s not changed is cancer’s dominance of the pipeline. The Oncology therapy area keeps bucking the trend, with a rise in its rate of growth this year.

The number of Oncological therapeutics in the pipeline increased by 669 candidates, a growth rate of 16.0%, just surpassing last

year’s record-breaking 15.9% rise. This puts it in 2017 growing at almost twice the rate of the pipeline as a whole, and taking a 32.6% share of the pie – almost a third.

“For the first time, there is perhaps a hint that others are being squeezed out by this unchecked expansion – the Respiratory group actually posts a decline this year. Elsewhere, some other expansion rates are pegged back, with Neurologicals only up by 1.2% and Musculoskeletal by 5.0%,” commented Lloyd.

Alimentary/Metabolic drugs increased by a percentage close to the average, and Anti-infectives actually also beat the mean with an 11.1% rise.

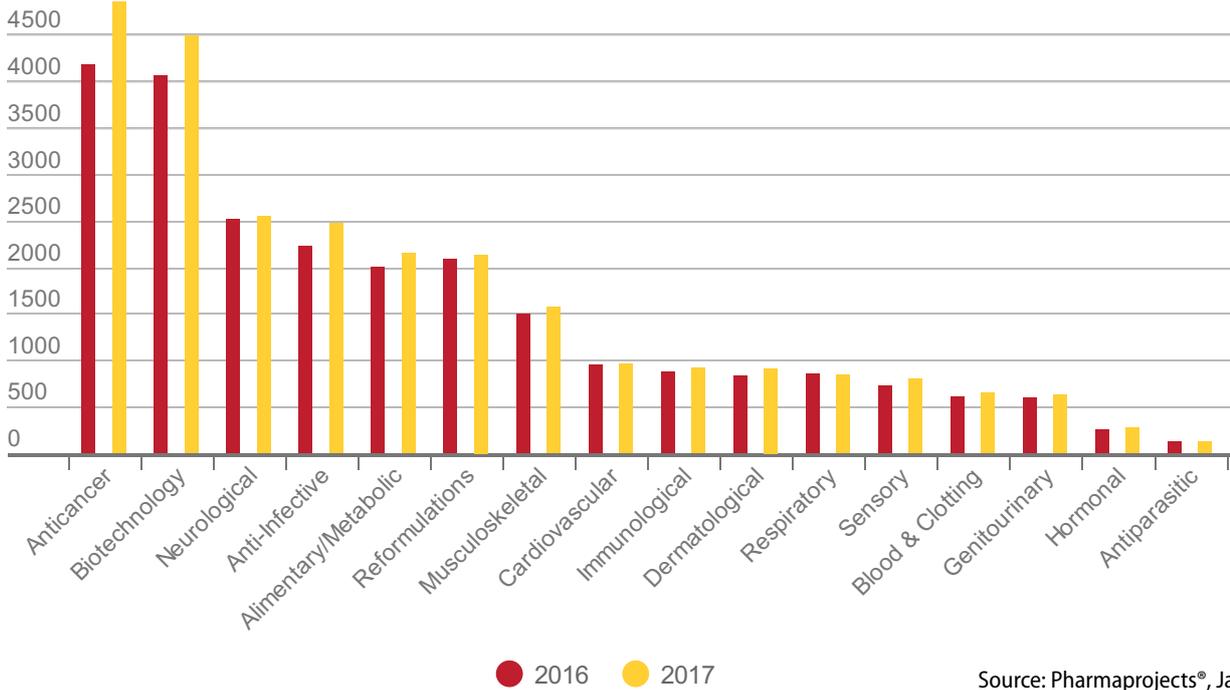
Breaking down the therapeutic categories further, what becomes quickly apparent is the continued expansion of the immune-oncology pipeline. The table of the top 10 Therapeutic categories listed by Pharmaprojects (see left) shows that while the general cancer category stayed top with a 7.7% increase, there was a 25.3% growth in numbers of immunological anti-cancers, driven by IO products, narrowing the gap.

Elsewhere, the once out-of-favor Gene Therapy category continued its renaissance with a second straight year of growth, increasing by 31.2% on the back of a 41.8% expansion last year. Both pro-

Table 2: Top 10 Therapeutic Categories

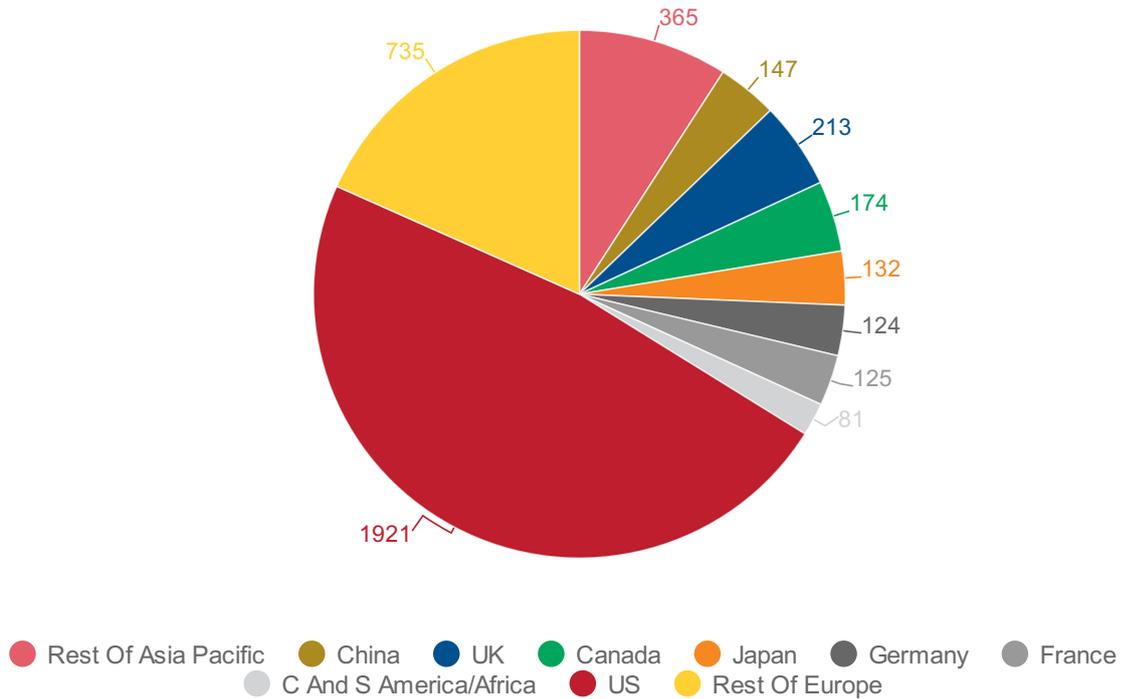
POSITION 2017 (2016)	THERAPEUTIC CATEGORY	NO. OF R&D PRODUCTS 2017 (2016)
1 (1)	Anticancer, other	2231 (2071)
2 (2)	Anticancer, immunological	2001 (1597)
3 (3)	Prophylactic vaccine, anti-infective	848 (729)
4 (4)	Antidiabetic	624 (592)
5 (5)	Ophthalmological, other	615 (546)
6 (10)	Monoclonal antibody, other	589 (432)
7 (14)	Gene therapy	547 (417)
8 (6)	Anti-inflammatory	513 (475)
9 (11)	Antiviral, other	488 (424)
10 (9)	Immunosuppressant	478 (437)

The R&D Pipeline By Therapy Group



Source: Pharmaprojects®, January 2017

Distribution of R&D Companies By HQ Region/Country



Source: Pharmaprojects®, January 2017

phylactic vaccines and antivirals contributed to the anti-infective rise but general cell therapy category dropped out of the Top 25, being replaced by anticancer vaccines.

The drop in growth rates follows two successive declines in the number of novel drugs reaching the market for the first time – these will be discussed in a com-

panion piece to be published shortly, but the headline data is that they fell by 11%.

**WANT TO READ MORE?**

The full [Pharma R&D Annual Review 2017](#) white paper is available from Pharmaprojects and also contains analysis of the R&D pipeline by:

- Disease/indication
- Origin of Material
- Delivery Route
- Mechanisms of Action
- Drug Protein Targets
- Orphan Drug and Expedited Review Status ▶

Published online 20 March 2017

## MS Space Awaits Ocrevus: MedDay Sees Opportunity

Medicines for progressive multiple sclerosis (MS) are a bit like London buses; nothing for ages and then two appear almost simultaneously. “The MS market is becoming saturated with treatment options for relapsing-remitting MS patients, so a major commercial opportunity now lies in the development of therapies for progressive MS subtypes,” Datamonitor Healthcare analyst Ines Guerra told *Scrip*. “Primary progressive MS patients, in particular, have no single therapy approved at the moment – although this might soon change with the expected approval of Roche’s *Ocrevus* (ocrelizumab).” But *Ocrevus* is not the only new MS product under review by regulators [*Editor’s note: The US FDA approved Ocrevus on March 29.*]. MedDay Pharmaceuticals filed its highly concentrated pharmaceutical-grade biotin (vitamin H) with the European Medicines Agency last year and a decision on whether the drug, known as MD-1003, will be approved for sale in Europe is expected by the end of this year. In the meantime, almost 6,500 patients are taking the drug under the ATU early access program in France, MedDay’s CEO Frédéric Sedel told *Scrip*. Earlier this year MedDay launched a new study, called SPI2, “a confirmatory Phase III in the US population,” said Sedel. “This is required for FDA approval. We are currently in the recruitment phase and plan to enroll 600 progressive MS patients only by the end of this year.”

*sukaina.virji@informa.com, 22 March 2017*

## Positive EU Opinions For Keytruda And Opdivo

The EU’s CHMP has given the green light to expanded approvals of the two leading anti-PD1 products at its latest meeting. The move signals impending licensing for use of MSD (Merck & Co. Inc.)’s *Keytruda* (pembrolizumab) in Hodgkin’s lymphoma and Bristol-Myers Squibb Co.’s *Opdivo* (nivolumab) in squamous

## Lilly’s Abemaciclib In CDK4/6 Race

Eli Lilly & Co.’s abemaciclib has passed its first Phase III breast cancer test and a US FDA submission is anticipated shortly, but more detailed results are needed to understand whether the CDK4/6 inhibitor can overcome its third-to-market position behind Pfizer Inc.’s *Ibrance* and Novartis AG’s *Kisqali*. It’s hard to know whether abemaciclib can overcome its third place position, but the company will seek FDA approval in the second quarter of 2017 based on its prior Phase II MONARCH 1 monotherapy clinical trial with plans for a supplemental filing in the third quarter based on combination therapy with fulvestrant in MONARCH 2. The first indication would give Lilly the only CDK4/6 inhibitor approved as a monotherapy and the second indication would cover a different population than the labels for palbociclib and ribociclib. But with *Ibrance* on the market for three years and *Kisqali* marketed for a year by the time abemaciclib is launched, Lilly may need to show a significant safety or efficacy advantage in its the detailed MONARCH 2 data to win over prescribers. The company reported only top-line results from the 669-patient MONARCH 2 trial on March 20, but said abemaciclib plus fulvestrant met the primary endpoint of an improvement in progression-free survival (PFS) versus fulvestrant alone in women with hormone receptor (HR)-positive/human epidermal growth factor 2 (HER2)-negative advanced breast cancer who relapsed or progressed after endocrine (or hormone-based) therapy. More detailed results will be presented at a future medical meeting, and they should shed some light on whether Lilly’s drug can speed past the two approved CDK4/6 inhibitors.

*mandy.jackson@informausa.com, 20 March 2017*

cell cancer of the head and neck. *Opdivo* is set to be the first anti-PD1 product to gain an indication for use in head and neck cancer in adults progressing on or after platinum-based therapy, following a positive opinion from the CHMP at its March meeting. Once approved, the indication will add to *Opdivo*’s label which already includes six indications in four different cancers: melanoma, non-small cell lung cancer, renal cell carcinoma and classical Hodgkin’s lymphoma.

*alex.shimmings@informa.com, 24 Mar 2017*

## CSL Behring Nears Market With HAE Prophylactic

The results of the CSL Behring-sponsored Phase III COMPACT (clinical study for optimal management of preventing angioedema with low volume subcutaneous C1-inhibitor replacement therapy) trial showed that twice-weekly, self-administered subcutaneous injections of CSL830 were as-

sociated with a significant reduction in the frequency of acute HAI attacks, compared with placebo, with only mild and transient adverse effects. “More than 50% of patients had no moderate-to-severe attacks while they were receiving CSL830,” noted UK clinical researcher Hilary Longhurst and colleagues in a paper presenting the final COMPACT results, published in the *New England Journal of Medicine* (March 23, p 1,131). CSL Behring has considerable experience in the HAE market, having marketed an intravenous formulation of C1-esterase inhibitor, *Beriner*, for the treatment of HAI for a number of years. A US BLA was submitted for the subcutaneous version, CSL830, in Aug. 2016, and analysts at Morningstar expect the new product to be approved and launched in 2017. They value the market at around \$1.4bn, and expect CSL830’s commercial role to be focused on defending CSL’s 20% share of the HAE market.

*john.davis@informa.com, 23 March 2017*

# Pfizer's Avelumab Makes Its Debut, In Rare Form Of Skin Cancer

MICHAEL CIPRIANO michael.cipriano@informa.com

*Pfizer got Bavencio to market by focusing on an unmet need, but the PD-L1 inhibitor is still a few years behind, competing with other checkpoint inhibitors over more valuable indications.*

Despite the recent news of a setback for Pfizer Inc.'s development of *Bavencio* (avelumab) in lung cancer, the drug giant's strategy of focusing on an unmet need allowed it to get to market in some capacity and will give it a test run with physicians and payers before moving into the larger markets.

The US FDA granted accelerated approval of avelumab March 23 for the lead indication of Merkel cell carcinoma, based on overall response rate and duration of response. The second PD-L1 inhibitor to be approved, *Bavencio* is the first FDA-approved treatment for the rare form of skin cancer. It had a breakthrough therapy designation and received a priority review.



Shutterstock - Mandav

Roche took a similar tack with its *Tecentriq* (atezolizumab), the first PD-L1 inhibitor to reach the market, which first received approval for bladder cancer in May 2016. It was cleared for non-small cell lung cancer in October and brought in \$158m last year. Roche, however, has a deep development program for the drug alone and in combination.

*Bavencio*, which is partnered with Merck KGAA, also beat AstraZeneca PLC's *durvalumab* to market, which was expected to be the next approved PD-L1 inhibitor. *Durvalumab* is under review for the treatment of metastatic urothelial cell carcinoma with a decision expected in June or earlier.

*Bavencio* also is being reviewed for metastatic urothelial carcinoma; the user fee date for the bladder cancer indication is Aug. 27.

## STILL LAGGING BEHIND

Despite the approval, *Bavencio* is still far behind the other PD-1/L1 inhibitors on the market: Bristol-Myers Squibb Co.'s *Opdivo* (nivolumab), Merck & Co. Inc.'s *Keytruda* (pembrolizumab) and *Tecentriq*. All of these treatments are approved for more valuable indications.

Pfizer recently faced a delay in competing with *Opdivo* and *Keytruda* in non-small cell lung cancer (NSCLC), the most valuable indication for immuno-oncology, after making major protocol changes

to the JAVELIN Lung 100 study. Adjustments to the Phase III study, which tests avelumab as a single agent against chemotherapy, include a large increase in the number of trial participants and a nearly two-year delay in the primary completion date for the study, from August 2017 to April 2019.

Robert Jeng, a Biomedtracker analyst, told *Scrip* he believes the current approval for *Bavencio* is not significant in the long run.

"Of course, getting a first approval is satisfying, but we already have several examples among the PD-1s where efficacy in one tumor type is not predictive of general efficacy across tumors," Jeng said. "Furthermore, Merkel cell is a fairly small target population," with only about 1,500 cases diagnosed in the US each year.

Jeng touted the drug's broad development program, but added that "the space is getting more and more crowded with little differentiation thus far other than final clinical outcomes."

"Thus, if *Bavencio* can gain some additional approvals, it should compete reasonably with other PD-1s, although with a strong lag to market in an ever-shrinking pie to split," he said.

Pfizer/Merck KGAA are also studying avelumab in Phase III trials in NSCLC, gastric cancer, ovarian cancer, renal cell carcinoma and squamous cell carcinoma of the head and neck.

## POTENTIAL FOR DIFFERENTIATION

Pfizer has maintained that late-comer avelumab, which marks the company's entrance into the immuno-oncology market, has the potential to stand out compared to the other programmed-death checkpoint inhibitors.

"The antibody has an intact IgG1 Fc domain, which means its effector function is retained, leading to greater cell-based killing (antibody-dependent cell-mediated cytotoxicity, or ADCC)," Bernstein analyst Tim Anderson said in March 23 note.

So far it has not manifested in an efficacy benefit, the analyst observed, but he thinks it might be the cause of a higher rate of infusion-related reactions (IRRs) compared to the other PD-1/L1s. Labeling for *Bavencio* reports IRRs in about 25% of patients, mostly low-grade. "We recently analyzed the data with competitor products on this metric, and IRRs for them tend to be in the single digit percent range," Anderson said.

Also, *Bavencio* labeling recommends pretreatment for the first four infusions with acetaminophen and an antihistamine. "Competitor labels lack this," the analyst pointed out. "All labels, however, have some mention of IRRs."

Anderson does not see the IRRs as a major issue, "because the frequency of severe IRRs is still quite low, and all of the other anti-PD[-1/L1] therapies do cause occasional severe IRRs. Where avelumab stands out is the higher frequency of mild IRRs. However, in the tight race among the different PD[-1/L1] companies who are jockeying for mind- and market-share, this may provide at least a bit of ammunition to competitors." ▶

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# Quick Commercial Standouts Lacking Among 2016 US Launches

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*The number of novel drugs approved by FDA in 2016 was down versus prior years, and many of the drugs that did launch are off to a slow start. The expectation is increasingly for drugs to build sales over time.*

The novel drugs that launched in the US in 2016 were fewer than in recent prior years and those that did reach the market got off to a relatively lackluster start. The two outliers are in hepatitis C, which despite the quick successes is a challenging therapy area commercially over the long term because sales have already started to decline as patients are treated and cured.

There were 22 new molecular entities and novel therapeutic biologics approved by the FDA's Center for Drug Evaluation and Research and six novel biologics from the Center for Biologics Evaluation and Research in 2016, about half the number approved in 2015.

None of the launches, outside of Gilead Sciences Inc.'s *Epclusa* (sofosbuvir/velpatasvir) and Merck & Co. Inc.'s *Zepatier* (grazoprevir/elbasvir), both for hepatitis C, generated particularly notable sales in the first months of launch.

But ZS Associates Managing Principal Maria Whitman said that trend reflects the changing launch trajectory for pharmaceuticals in which blockbusters are built over time through indication expansion.

"We are moving from a world of single product/single indication...to more of this concept of asset value over time," she said in an interview.

"The first launch may not be the richest launch in terms of commercial opportunity, in fact the first five years might not be the richest opportunity for the asset," she said. "It might be a longer-term play."

Whitman pointed to new drugs like Roche's *Tecentriq* (atezolizumab) and AbbVie Inc./Roche's *Venclexta* (venetoclax) as two examples of drugs that have enormous R&D investment behind them that are expected to grow substantially with time.

Eight out of 10 NMEs had 44 unique indications they are going after, Whitman said.

The challenge for industry now is executing repeatedly on the launch of a drug in each new indication.

"We used to think about launch excellence, so how do I launch this product really well one time across the global landscape," Whitman said. "What we now have is how do I do an excellent launch over and over again."

## SHORTER LIFE SPAN

Gilead's *Epclusa* was an early commercial standout, generating \$1.75bn in just two quarters on the market. The launch of the first all-oral, pan-genotypic single tablet regimen for HCV helped to energize the company's maturing HCV franchise following the FDA approval June 28. It's also the first single-tablet regimen for patients with genotypes 2 or 3 of the virus. The challenge is that some of the sales will come at the expense of the sofosbuvir franchise more broadly, which also includes *Sovaldi* and *Harvoni*.

Merck's *Zepatier*, a protease inhibitor/NS5A inhibitor combination pill approved by FDA in January, generated \$555m in sales following its debut. The challenge in hepatitis C, however, is sustaining the value of a cure long-term when patients move through treatment. Experience has already shown with Gilead's *Sovaldi* (sofosbuvir), the first breakthrough treatment for hepatitis C that launched in late 2013, that success can be fast and furious and quickly wane.

The class of 2016 drug launches included some products that were second- or third-in-class to market. Roche's *Tecentriq* is one, approved in May for advanced bladder cancer.

*Tecentriq* is the first PD-L1 inhibitor to reach the market but follows already available PD-1 inhibitors, Merck's *Keytruda* (pembrolizumab) and Bristol-Myers Squibb Co.'s *Opdivo* (nivolumab), which launched in 2015 and 2014, respectively; differences between the two approaches are not well known. *Tecentriq* is the first immuno-oncology drug approved for bladder cancer,

however, and it gained a second indication for patients with metastatic non-small cell lung cancer who have progressed following chemotherapy later in the year. *Tecentriq* generated CHF157m (\$158.1m) in the seven months following its launch – whereas *Opdivo* and *Keytruda* generated \$3.77bn and \$1.4bn, respectively.

Eli Lilly & Co.'s *Taltz* (ixekizumab), an interleukin-17A blocker for moderate-to-severe psoriasis, was second to market, following rival Novartis AG's *Cosentyx* (secukinumab) by about a year. *Taltz* was approved by FDA in March as a new entrant in a burgeoning blockbuster class. *Taltz* generated \$113.1m in sales following its debut. *Cosentyx*, meanwhile, generated \$1.1bn in 2016 revenues, its first full year on the market.

There were other important new drugs that reached the market, notably the first drug approved by FDA for Duchenne muscular dystrophy, Sarepta Therapeutics Inc.'s *Exondys 51* (eteplirsen), which cleared FDA in September with some controversy. The drug has efficacy limitations and costs \$300,000 per year; Sarepta reported revenues of \$5.5m related to *Exondys 51* in the short time it was on the market.

AbbVie/Roche's BCL-2 inhibitor *Venclexta* was approved for the treatment of patients with chronic lymphocytic leukemia (CLL) who have a particular chromosomal abnormality, 17p deletion, and who have been treated with at least one prior therapy. The FDA approval came in April, but the companies did not provide revenues from sales in year-end financials, generally a sign the sales were not material. To Whitman's point, AbbVie is studying *Venclexta* in relapsed/refractory and first-line CLL as well.

The class of 2015 drugs included some clear winners on the road to blockbuster status, including *Opdivo*, *Cosentyx* and Pfizer Inc.'s breast cancer drug *Ibrance* (palbociclib). ▶

*Published online 23 March 2017*

A Table Of Drug Launches In The First 10 Months Of 2016 here: <http://bit.ly/2nZZDdp>

# Intercept Hopes Statin Trial Will Lessen Ocaliva's Perceived CV Risk

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*After an otherwise successful Phase II NASH trial showed Ocaliva can increase a patient's LDL cholesterol levels, Intercept hopes a study in NASH patients who use atorvastatin will show this effect is manageable.*

Intercept Pharmaceuticals Inc. is hoping that its ongoing Phase II CONTROL study will ameliorate a lingering concern about Ocaliva's prospects in non-alcoholic steatohepatitis (NASH) by showing that co-administration of a statin can manage the LDL-elevating effect seen in some patients receiving the drug.

Ocaliva (obeticholic acid/OCA), a farnesoid X receptor (FXR) agonist already approved in the US and Europe to treat primary biliary cholangitis (PBC), is one of three drug candidates to reach Phase III in NASH. Intercept was the first to start a Phase III trial and industry consensus has the company in the lead to introduce the first approved therapy for NASH, but concerns about the compound's effects on lipid levels caused concern that a long-term cardiovascular outcomes study might be needed to gain approval.

## PHASE II TRIAL IN PROGRESS

Intercept executives addressing the Oppenheimer Healthcare Conference March 21 outlined the Phase II trial that is intended to demonstrate what happens to NASH patients who are treated with Ocaliva and then are given a statin to manage rising LDL cholesterol.

"In regards to the primary objectives of this trial, they are two-fold," Intercept Head of Investor Relations Mark Vignola said. "We're looking to evaluate the impact of various doses of OCA on LDL, lipid metabolism, and we're asking the question what is the ability of the statin to mitigate those changes?"

The 80-patient, placebo-controlled study is enrolling patients with biopsy-confirmed NASH who already are on statin therapy. It uses a four-week washout period to eliminate the benefits of statin therapy and determine baseline lipid levels before adminis-

tering one of three testing doses of Ocaliva – 5 mg, 10 mg or 25 mg.

Ocaliva reduced non-alcoholic fatty liver disease score (NAS) by at least two points in the Phase II FLINT study without worsening of fibrosis in 45% of patients, compared to 21% in a placebo arm. However, Intercept drew controversy in 2014 for withholding information about the LDL increases seen with the drug in that same trial, even though the company had disclosed in 2009 that elevated LDL levels were seen in another 64-patient Phase II trial testing Ocaliva in patients with NASH and type 2 diabetes.

No LDL effect is mentioned in Ocaliva's labeling for the PBC indication.

"We expect to see a lipid profile [in CONTROL] probably similar to what we saw in the FLINT trial, and we expect to see OCA recapitulate the same thing, which was about a 20% increase in LDL," Vignola told the Oppenheimer crowd.

After the statin washout period, patients will begin receiving 10 mg of atorvastatin (Pfizer Inc.'s *Lipitor* and generics) after four weeks on one of the three doses of Ocaliva, and then be titrated up to 20 mg of atorvastatin after four weeks, and then a final titration in which the patient will receive the amount of atorvastatin recommended by the treating physician. The study will measure the patients' LDL levels from baseline over a 16-week treatment period.

"You'll have a sense how this compares to baseline LDL, and we'll be looking at all the lipid parameters that one might expect," Vignola said. "And we expect to, hopefully, recapitulate what we saw retrospectively in FLINT, which is that the addition of a statin is able to mitigate the LDL increase that we saw."

Intercept says enrollment is completed and it expects to report data from CONTROL this year. Biomedtracker – which gives Ocaliva an 85% likelihood of approval for NASH, 20% above average for a Phase III NASH candidate – estimates top-line data from the study by the end of 2017.

Morningstar analyst Kelsey Tsai, in a Feb. 17 note, calls Ocaliva well positioned in NASH based on the FLINT efficacy data, but adds that the drug's "less than ideal" safety profile, which also includes pruritus, leaves an opportunity for competitors. Two of those are Genfit SA and Gilead Sciences Inc., which have advanced elafibranor, a dual PPAR alpha/delta agonist, and selonsertib, an ASK1 inhibitor, respectively, into Phase III development for NASH.

"Gilead, which has an earlier-stage portfolio targeting various mechanisms of the disease, and potentially other players such as Novo Nordisk AS, Allergan PLC and Genfit, have potential products that could be longer-term winners in this emerging therapeutic area," Tsai wrote, adding that Ocaliva and elafibranor appear to be most likely to reach the market first. Morningstar projects peak sales potential of \$3.5bn for Ocaliva in NASH.

## PROTOCOL CHANGES

Intercept increased its chances for success in its Phase III REGENERATE study last month when, after consultation with the US FDA, it revised the trial protocol so that if either of two co-primary endpoints is met, the study will be deemed successful. Originally, REGENERATE was designed to require Ocaliva to show the ability to both improve fibrosis score with no worsening of NASH and resolve NASH without worsening of fibrosis.

The study also was revised to employ a more "objective" definition of NASH resolution adopted by the Liver Forum at 2016's meeting of the American Association for the Study of Liver Diseases.

Vignola disagreed with Oppenheimer analyst Jay Olson that the revised protocol, while easier to achieve, might reduce Ocaliva's market potential in NASH.

"We preserve the best of both worlds, so we haven't held ourselves to a higher bar versus our competitors, but we have this upside [if] we hit both fibrosis improvement and NASH resolution, and these will be in the label," Vignola said. ▶

*Published online 22 March 2017*

# Parkinson's Niche To Expand With New Drugs, More Patients

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*Newron's new Parkinson's disease therapy, Xadago, approved in the US after a regulatory delay, is expected to be the first of several new products to be introduced in this long-neglected therapeutic sector.*

The US approval of Newron Pharmaceuticals SPA's add-on Parkinson's disease therapy, *Xadago* (safinamide), announced March 21, may have been welcomed by that company's investors, but after nearly a decade with few if any new products, the therapeutic niche is rapidly becoming more competitive, with several new products nearing the market.

Italy's Newron, headquartered near Milan but listed on Switzerland's SIX stock exchange, has seen its share price increase by 22% in the past month to CHF27.5 (\$27.8) per share, more than likely in anticipation of the FDA approval of *Xadago* on or near the PDUFA date of March 21, 2017, a date achieved by the regulator.

*Xadago* is the first new chemical entity approved for Parkinson's disease in the US for more than 10 years, and the US sublicensee, US WorldMeds LLC, said it would accelerate its US launch preparations to make the product available to patients. US WorldMeds is a Kentucky-based specialty pharmaceutical company that sublicensed US marketing rights for *Xadago* from Newron's development partner, the fellow Italian specialty company, Zambon SPA.

But the US approval of *Xadago* comes two years after its European approval, and a year later than originally anticipated in the US, and competing products are nearing the market. These include Acorda Therapeutics Inc.'s CVT-301, an inhalable formulation of levodopa, for which a US NDA submission is planned for the second quarter of 2017, and a European filing by the end of 2017. The drug has shown a statistically significant improvement in motor function in patients have off periods.

**Xadago was approved in the US for the treatment of Parkinson's disease as add-on therapy to levodopa/carbidopa**

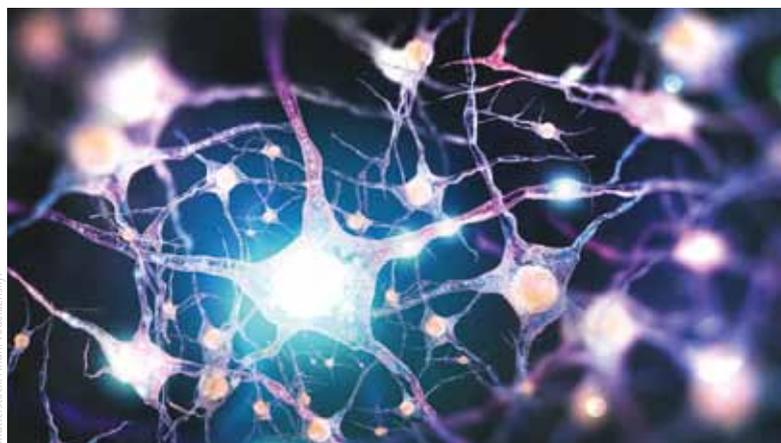
And in 2016, Acordia acquired Biotie Therapies Corp. and with it that company's adenosine 2A receptor inhibitor tozadenant, currently being evaluated in a Phase III study for improving motor function and activities of daily living in people with Parkinson's disease; the study should be completed by the end of 2017.

Analysts at Jefferies estimated that peak sales of *Xadago* could reach \$700m worldwide, around \$430m of which are expected to be in the US. It should be used in around 15% of moderate-to-severe Parkinson's disease patients on L-dopa in the US, 20% in Europe and 2.5% in the rest of the world, the analysts estimate.

## FDA CONCERNS ABOUT ABUSE POTENTIAL

Although introduced in Germany in 2015 and in Italy, Spain, the UK, Belgium, Denmark, Sweden, Luxembourg, the Netherlands, Norway and Switzerland in 2016, progress in the key US market for *Xadago* has previously been thwarted by FDA concerns, the most recent being about its risk of abuse and the development of dependence, outlined in a complete response letter in March 2016.

Newron convinced the FDA that new clinical studies were not necessary, and that data from preclinical abuse liability studies and clinical data analyses were sufficient. The company then resubmitted the NDA in Oct. 2016, with a PDUFA date of March 21, 2017.



The US is the largest market for Parkinson's therapies, with around one million patients with the disease, and that number is expected to grow in the future in line with the aging of the susceptible elderly population. Although there are effective therapies for Parkinson's disease, many of which are generic, there is still an unmet need to shorten the "off" time – the time when levodopa therapy is ineffective – during which patients experience motor fluctuations such as tremor.

*Xadago*, a dual MAO B-inhibitor and glutamate release inhibitor, was approved in the US for the treatment of Parkinson's disease as add-on therapy to levodopa/carbidopa.

According to analysts at Datamonitor Healthcare, the Parkinson's disease market was worth around \$2.8bn in the US, Japan, and the five major US markets in 2014, but is expected to increase to \$3.4bn by 2023, driven by products such as *Xadago* that decrease patients' off-time on levodopa.

In a statement issued March 21, Newron's chief medical officer, Ravi Anand, pointed out that *Xadago* significantly improves on time, off time and parkinsonism compared with standard of care without increasing time spent with dyskinesia in patients experiencing motor fluctuations while on optimized levodopa/carbidopa therapy. ➡

*Published online 22 March 2017*

## Cerulean Shifts From Ovarian Cancer To Contraceptives

Cerulean Pharma Inc. has sold the last of its assets and will flip its empty shell to Daré Bioscience Inc. during the second quarter of 2017, now that the company has given up all hope that a partner would come to the rescue after a devastating Phase II clinical trial failure last year. Waltham, Mass.-based Cerulean will execute a reverse merger that will give shareholders of the privately held women's health firm Daré, headquartered in San Diego, Calif., a majority stake in the combined company. The stock purchase agreement will give Cerulean shareholders 30% to 49% ownership and Daré shareholders will have a 51% to 70% stake. Cerulean also will sell its Dynamic Tumor Targeting (DTT) platform for developing nanoparticle-drug conjugates (NDCs) to its partner Novartis AG while a subsidiary of NewLink Genetics Corp. will buy its two clinical NDC candidates. Cerulean revealed on Feb. 1 that a strategic review was under way with the company considering all options from a sale of the company or its assets to a winding down of operations, but a partnership for ongoing development programs was the preferred alternative. Cerulean had \$38.1m in cash at the end of the third quarter on Sept. 30 and does not intend to report fourth quarter 2016 earnings, but the company will file a form 10-K with the US Securities and Exchange Commission (SEC) by March 31.

*mandy.jackson@informausa.com, 23 March 2017*

## Array BioPharma's Business Strategy Stymied

The US biotech Array BioPharma Inc. says its withdrawal of the US NDA for the MEK inhibitor binimetinib for the treatment of NRAS-mutant melanoma will not affect the filing of the combination, binimetinib plus the BRAF inhibitor encorafenib, in

## C4 And Google's Calico Enter Mysterious Alliance In Aging

Two of the more mystery-shrouded new players in the biopharmaceutical sector – C4 Therapeutics Inc. and Calico Life Sciences LLC – are teaming up to join the former's targeted protein degradation approach with the latter's focus on treating "diseases of aging." Presumably, big bucks are part of the five-year collaboration between the two privately held firms, but no one is saying. Announced March 23, C4, whose backers in a \$73.5m Series A last year included Roche and Novartis AG, and Calico, a Google-financed startup, will collaborate to discover, develop and commercialize therapies that treat diseases associated with aging. Calico lists cancer among aging-related diseases, but C4 President and Chief Scientific Officer Andrew Phillips told *Scrip* not to assume cancer will be a focus of this partnership, under which C4 will perform the preclinical work, while Calico will be responsible for clinical development and commercialization of whatever emerges from what he termed "a highly collaborative partnership." Is Calico reimbursing C4 for R&D expenses or taking an equity position in the Cambridge, Mass.-based biotech? What targets or indications will the collaboration focus on? No one is saying yet, which is par for the course for Calico. C4, which unveiled itself in January 2016 with the Series A announcement and a collaboration with Roche, has been a bit more forthcoming. Its technology derives from intellectual property licensed from the Dana-Farber Cancer Institute around the concept of naturally degrading targeted proteins via a cell's ubiquitin/proteasome system.

*joseph.baas@informa.com, 24 March 2017*

the larger indication, BRAF-mutant melanoma, but the stock market was still disappointed with the withdrawal, with the company's share price knocked down by 34% in pre-market trading on March 20. The decision will likely disrupt Array BioPharma's overall business strategy based on using the approval and introduction of lead product binimetinib in a small indication as a launch pad for its commercialization plans in larger indications, and for introducing its pipeline of other anticancer products. The company was planning to build up its commercial infrastructure with binimetinib in preparation for the potential launch in 2018 of a binimetinib plus encorafenib combination in the more competitive but larger BRAF-positive melanoma. Around 15-25% of patients with melanoma have the NRAS-mutation form of the condition. The NDA withdrawal has

doubtless also disconcerted its ex-US marketing partner, Pierre Fabre Group, a seasoned marketer of oncology products but one that needs to replenish its aging marketed products with newer agents.

*john.davis@informa.com, 20 March 2017*

## Newron's Xadago Priced At \$600-700/Month

Newron Pharmaceuticals SPA's Xadago (safinamide) once daily Parkinson's disease drug will launch in the US at a list price ranging from \$600-700 for a 30-day supply of the 50 mg or 100 mg tablet. It is on par with Teva Pharmaceutical Industries Ltd.'s competing product *Azilect* (rasagiline), which has a list price (wholesale acquisition cost) of \$694.40 for a 30-day supply.

*brenda.sandburg@informa.com, 23 Mar 2017*

# Novartis Pursues Disease-Modifying Differentiator For Cosentyx In Psoriasis

*New extension data suggesting that Novartis's IL-17A inhibitor Cosentyx could alter the course of disease in its lead indication of psoriasis could position the drug earlier in the treatment paradigm and please payers; the company has launched a new prospective study to see if the results hold true.*

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Novartis AG's first-in-class IL-17A inhibitor *Cosentyx* (secukinumab) may be able to modify the progression of moderate to severe psoriasis, the company claims based on extension data from two Phase III studies. It is now starting a new trial – STEPIn – which it hopes will back up the findings and make the case for earlier use of the drug.



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Novartis claims that the A2302E1 extension study provides the first robust data on psoriasis following treatment discontinuation. The study followed 120 patients who achieved a 75% or greater improvement in skin affected by the disease in the pivotal Phase III ERASURE and FIXTURE studies. Data presented at the 13th Annual Maui Derm for Dermatologists 2017 conference in Maui, Hawaii, show low scores on the Psoriasis Area Severity Index (PASI) were maintained a year after stopping treatment with *Cosentyx* (PASI score of 2.9 after one year and 1.7 after two years off-drug versus 20.5 and 19.2 at baseline).

Also, 21% of patients who discontinued *Cosentyx* therapy were able to maintain their treatment response for a year, and 10% for two years, the data show. Moreover, the extension study results hint that

patients who had a longer disease duration before *Cosentyx* treatment were more likely to relapse, highlighting the potential importance of early intervention.

"These results suggest that *Cosentyx* may go beyond simply treating symptoms and could actually modify the course of psoriasis, and highlights the need for further investigation into early intervention," said Vas Narasimhan, Novartis's global head of drug development and chief medical officer in a statement. "Being able to change the course of disease is the ultimate goal of treatment, which is why we are investing in the STEPIn trial to further understand the disease modifying ability of *Cosentyx* in psoriasis."

*Cosentyx* has already reached blockbuster status since its first launch in early 2015 for moderate to severe psoriasis with 2016 sales that topped \$1.1bn. The monoclonal antibody is now available in more than 75 markets and has since received additional approvals in most regions for ankylosing spondylitis and psoriatic arthritis. Its success is attributed to excellent skin clearing effect or almost clear skin (PASI 90 to PASI 100) in up to 80% of patients out to four years. It also boasts superiority versus the older anti-TNF product and Amgen Inc. blockbuster *Enbrel* (etanercept) as well as its closest rival, Johnson & Johnson's anti-IL-12/IL-23 antibody *Stelara* (ustekinumab).

Analysts at Datamonitor Healthcare say the new results could give *Cosentyx* another edge in the competitive psoriasis market. "These data could allow *Cosentyx* to be positioned earlier in the treatment algorithm and become a market leader in psoriasis," Datamonitor's Ines Mihel said.

The hint of an earlier-is-better effect is of particular importance since achieving disease remission in psoriasis is one of the top three treatment challenges encountered according to Datamonitor

Healthcare's 2016 primary research survey with dermatologists. "There are currently no therapies that have demonstrated the ability to achieve disease remission after discontinuation of therapy, giving a competitive edge for *Cosentyx* in the psoriasis market and further boosting its clinical attractiveness," the report said.

## STEPIN

Novartis has begun the STEPIn trial to further investigate the disease modification potential of *Cosentyx* and to assess early intervention with *Cosentyx* in new-onset disease. Its ambition, it says, is to identify a novel strategy of treating patients with new-onset moderate-to-severe psoriasis, with the ultimate goal of altering the natural course psoriasis to reduce the disease burden and need for treatment.

**'Being able to change the course of disease is the ultimate goal'**

The study will evaluate a 300mg subcutaneously administered dose of *Cosentyx* given for 52 weeks to patients with new-onset moderate-to-severe plaque psoriasis as an early intervention compared with the standard of care – narrow-band UVB therapy. The trial will enroll 205 patients and is due to complete in early 2022, according to [clinicaltrials.gov](http://clinicaltrials.gov).

"Should *Cosentyx* demonstrate the ability to reverse the disease with early treatment, this could convince payers to prescribe *Cosentyx* at first-line before using phototherapy or the cheaper anti-TNF biosimilars, since patients could benefit from real long-term improvements in their disease," Datamonitor's Mihel said. ▶

*Published online 22 March 2017*

# Microbiome Market Value To Reach \$500m by 2022

*The microbiome market will see its value rise to \$500m by 2022, and higher during the next decade. The key driver will be the increase in biotech and pharma firms looking at the emerging research space for new therapeutic options to treat chronic conditions such as Crohn's disease.*

LUCIE ELLIS [lucie.ellis@informa.com](mailto:lucie.ellis@informa.com)

Investment in microbiome research, specifically in the gut, is expected to increase substantially over the next 10 years – alongside the launch of several new firms dedicated to this science – as interest in bacterial treatments grows with the accumulation of data from active players. Venture capital group Seventure Partners has already launched a new €160m fund, HealthForLife Capital, focusing solely on microbiome investments, to ride this wave of enthusiasm.

In 2016, the global microbiome market was estimated to be worth around \$184m, and is expected to grow at a compound annual growth rate (CAGR) of +19%, leading to a market worth \$500m by 2022.

To date, the gut microbiome is the most closely studied niche and abnormalities of the gut microbiome (collectively known as dysbiosis) have been linked to various diseases – especially the difficult-to-treat infections

associated with *Clostridium difficile* and inflammatory bowel diseases (IBDs) like Crohn's disease, Seventure notes in a new report.

The report, titled *The human microbiome: A new protagonist in managing human health*, which is available on request from Seventure, noted that while experts are divided when choosing the most promising drug modality in microbiome treatment in gut conditions, consensus is that there are numerous paths that reveal potential options.

"The spectrum reaches from 'bugs as drugs,' where the gut microbiome is supplemented with living microbes, all the way to more classical small-molecule drug candidates," the report authors noted. Probiotics and nutritional solutions have the majority market share when it comes to current microbiome products, while drugs and others account for less than a quarter.

"Over the course of the next decade, this market will gradually be overtaken by next generation probiotics, medical foods and drugs such as live biotherapeutic products, small-molecule compounds and biologics targeting the microbiome-host interaction," Seventure highlighted.

Near-term challenges for microbiome therapy developers will be the transfer of scientific know-how of the gut microbiome into reliable and efficacious treatments for specific indications. Looking further ahead, regulatory pathways may prove tricky for microbiome products until a rationale for this novel technology is established in the pharmaceutical arena. Microbiome technology is already used in the cosmetic and nutrition sectors. ▶

*Published online 20 March 2017*

*To access the report email [info@seventure.fr](mailto:info@seventure.fr).*

## Scrip Awards Winner » 2016 Licensing Deal of the Year

Galapagos NV received an upfront payment of \$725m consisting of a license fee of \$300m and a \$425m equity investment from its deal with Gilead Sciences Inc. to develop the JAK1-selective product filgotinib for the treatment of rheumatoid arthritis and other inflammatory diseases, in a boost to Gilead's inflammation R&D portfolio.

*"Hugely valuable strategically to Galapagos given that the asset had been returned only a few months previously, yet within three months it had found another big partner in Gilead and at much better financial terms. For Gilead, it's a decent addition to their portfolio in an important market."*

**The Scrip Awards Judges**

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WORLDWIDE CLINICAL TRIALS



**Winner: Galapagos and Gilead Sciences for filgotinib in inflammatory diseases**

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## AstraZeneca's ZS-9 Delay In US Gives Veltassa An Edge

AstraZeneca PLC received a second complete response letter from FDA on the NDA for ZS-9 (sodium zirconium cyclosilicate) for the treatment of hyperkalaemia, a potential blockbuster drug it paid handsomely to acquire. The delay, announced by AstraZeneca March 17, will give rival Galenica Group's *Veltassa* (patiromer) more time to dominate the hyperkalaemia market. ZS-9 was granted a recommendation for approval by the European Committee for Medicinal Products for Human Use (CHMP) in February, but approval in the US has been hung up by a manufacturing issue. In Europe, AstraZeneca is planning to market the drug as *Lokelma*, as long as it receives full approval by the European Commission. AstraZeneca said the new setback is also due to manufacturing and that the CRL followed an inspection of the ZS-9 manufacturing facility, which is in Texas. FDA issued the CRL to AstraZeneca several weeks before the action date for ZS-9, which was April 18. The CRL will not require any new clinical data and AstraZeneca is working with FDA to resolve the outstanding issues as soon as possible, according to the UK-based drug maker. Manufacturing issues have contributed to many CRLs in the last year. In 2016, 14 of 39 CRLs reviewed by the Pink Sheet were related to quality issues.

*jessica.merrill@informa.com, 20 March 2017*

## Biogen Secures First-Round Patent Win For Tecfidera

Biogen's victory over hedge fund manager Kyle Bass' inter partes review (IPR) challenge to a patent protecting its oral multiple sclerosis blockbuster *Tecfidera* lifts one overhang for the company, but it doesn't clear the intellectual property headwinds entirely. On March 21, the US Patent & Trademark Office's Patent Trial and Appeal Board (PTAB) rejected an IPR challenge against a key patent protecting

## Accusations Fly In Messy Ranbaxy Compensation Battle

The lead lawyer for Daiichi Sankyo Co. Ltd. has accused Indian businessmen Malvinder Singh and his brother Shivinder of lying about the value of their investment firm RHC Holding Pvt Ltd. in an ongoing legal battle over compensation related to the Japanese firm's ill-fated 2008 \$4.6bn acquisition of Ranbaxy Laboratories Ltd., then controlled by the Singhs. The brothers, who now own the leading Indian hospital chain Fortis Healthcare, have been waging a legal battle against a Singapore compensation order to pay hundreds of millions of dollars in compensation, after an investigative panel order last year relating to the alleged concealment of "critical" information about a US regulatory probe into faked testing results at Ranbaxy when they sold the Indian generics firm. The assets of RHC, the parent company of Fortis and other group companies, are meant to be security for the damages award, which totals at least \$391m at current exchange rates, and Daiichi is battling in a Delhi court to get the Singh brothers to cough up the funds. The lawyer was referring to what he alleged was a hefty INR15bn (\$229m) difference between RHC's value as contained in the tycoons' affidavits and the figure submitted by auditors, India's Business Standard said. Replying for the brothers, Harish Salve, another prominent Indian lawyer, denied the allegation and said any difference between the valuations reflected the fact they were carried out on different dates, affecting the assets' realizable value. "Fair enterprise values do not need the deduction of liabilities. In an unlisted company, while making a sale, one may even make a premium over and above the declared value," Salve was quoted as saying. The Singh brothers are waging a legal battle against the arbitration order in both Delhi and in Singapore. The siblings argue "substantive objections" exist under India's Arbitration Act to the Singapore tribunal's right to award "consequential" damages to Daiichi. As a result, they say, the penalty is unenforceable in India.

*Penelope MacRae, 23 March 2017*

*Tecfidera* (dimethyl fumarate) until 2028. A separate patent interference case is pending before PTAB related to rival Forward Pharma AS's claim that it was the first to develop the 450 mg dose of dimethyl fumarate. Forward is developing its own dimethyl fumarate-based drug for MS, FP187, but it is still in Phase III development. The IPR decision is important, especially because Biogen bought itself a cushion in the event the Forward challenge goes against *Tecfidera*. In January, Biogen signed a licensing agreement with Forward for the rights to the company's intellectual property in exchange for \$1.25bn. If PTAB rules in favor of Forward, Biogen will be on the hook

to pay royalties on sales of the 480 mg dose of *Tecfidera*, 10% from 2021 to 2028 and 20% thereafter. The IPR outcome offers investors some reassurance, though not entirely. Providing a long runway for *Tecfidera* is critical for Biogen because it is the company's number one selling drug. *Tecfidera* generated \$3.97bn in 2016. The company has been under pressure because it has a near-term pipeline gap. Investors have been nervous about *Tecfidera*'s long-term growth prospects and the lack of products to fill the commercial portfolio, beyond the current launch of *Spinraza* (nusinersen) for spinal muscular atrophy.

*jessica.merrill@informa.com, 21 March 2017*

# A Druggable Target For PTEN-Deficient Prostate Cancer

MARK RATNER

*By taking a different slant on synthetic lethality – the therapeutic process behind AstraZeneca’s Lynparza – scientists have identified a potential new drug target for use in prostate cancer, the chromatin helicase DNA-binding factor CHD1.*

Using an approach called synthetic essentiality, researchers at the MD Anderson Cancer Center have identified the chromatin helicase DNA-binding factor CHD1 as a potentially specific drug target in cancers characterized by the presence of a common tumor suppressor gene.

Synthetic essentiality is a nuanced take on the concept of synthetic lethality, in which two different pathways converge on a common biological process and the inactivation of both of those pathways compromises the cell’s ability to maintain homeostasis.

Synthetic lethality has already played a notable role in cancer drug development: the discovery that cancers with BRCA mutations rely on the PARP enzyme for DNA repair, led to the development of PARP inhibitors such as AstraZeneca PLC’s Lynparza (olaparib) and niraparib, from Tesaro Inc for ovarian and other, cancers.

The concept behind synthetic essentiality is similar but different. “One could ask the question in a slightly different way,” explained Ronald DePinho, president of MD Anderson: is there something within a pathway that becomes important by virtue of a mutation in that pathway such that by inactivating it, the mutation would no longer affect tumorigenic processes? The answer, it seems, is yes.

In a Feb. 23 publication in *Nature*, MD Anderson scientists in genomics and cancer biology showed that inactivating CHD1 in tumors deficient in the second-most common tumor suppressor gene, phosphatase and tensin homolog (PTEN), inhibits cell proliferation, cell survival and tumorigenic potential. 70% of prostate cancers are PTEN deficient on initial diagnosis, as are a substantial portion of breast and other cancers.

The researchers used several techniques to show convincingly the role that CHD1

plays in the context of PTEN deficiency. A genomics analysis provided the initial link between them. Functional studies then documented the dependency of this synthetic essential gene in the context of PTEN tumor suppressor gene deficiency, followed by mechanistic studies that helped them understand why this linkage was essential. “That last point was perhaps the most important,” DePinho said, because in the past, functional screens used to look for synthetic essential genes in the context of oncogenic KRAS ultimately were not validated. In those cases, he says, “there was no real attempt to forge a mechanistic link.”

## CHD1: A DRUGGABLE TARGET

From that integrated analysis, the researchers were able to show that when inactivating PTEN, the protein CHD1 becomes stable. Plus, while inactivation of the CHD1 gene compromised the cancer cells with the tumor suppressor gene deficiency, those that have the tumor suppressor gene intact were not compromised. “If cells can tolerate the loss of function of that gene in other settings and only the cancer cells with that tumor suppressor gene deficiency are affected, it provides a therapeutic window,” DePinho said. Moreover, CHD1 is a potentially druggable target with a small molecule devised to block the pocket of the chromatin binding site.

They also found that many direct targets of the NF-κB protein complex, which regulates DNA transcription, were themselves regulated as a result of CHD1 being stabilized. “This was very gratifying,” DePinho said, because others have shown that NF-κB is important for prostate cancer progression.

“This study forged a direct link between two known pathways involved in the initiation and progression of prostate cancer,” he says. “It showed that inactivation of PTEN, which is a very important event in the initiation of prostate cancer, ultimately leads to progression of those initiated neoplasms through CHD-mediated activation of NF-κB targets.” CHD1 is a critical regulator of thousands of genes, he says, many of which are very important for can-

cer including NF-κB and myc. “One would imagine this is a significant compromise of cells that are now dependent on the expression and activation of thousands of genes,” he says.

The relative lack of impact of CHD1 inactivation in the context of activation of a PTEN wildtype setting is also a key finding. “It not only underscores the importance of the context or the opportunity for targeting CHD1,” said DePinho, but might also indicate that the toxicity of knocking down CHD1 may be modest relative to other types of inhibitors that have significant side effects because they tie into other important pathways in normal cells.

A significant fraction of prostate cancer patients are PTEN deficient homozygously and in many other cases PI3 kinase is activated. Assuming that collectively, the PI3 kinase pathway is activated in the majority of prostate cancer cases, the most common of them being the PTEN deletion, clinicians could apply a CHD1-oriented treatment strategy to a substantial fraction of prostate cancers. Thousands of cases of breast cancer per year would similarly benefit from it, DePinho said.

Having large genomic data sets at hand is a prerequisite for doing this kind of research – something not possible in years past. The ability to sequence and catalog copy number changes and transcriptomes in tens of thousands of tumors using resources such as The Cancer Genome Atlas and International Cancer Genome Consortium “begins to put us in a position to discern patterns with stronger statistical significance,” DePinho said. It offers an entry point to finding genes that are never deleted in the context of specific tumor suppressor gene deficiencies, he says, then determining if such genes provide a downstream signaling surrogate of that tumor suppressor gene deficiency that is critical for its cancer causing functions. ▶

*Published online 21 March 2017*

*Editor’s note: DePinho is stepping down as president of MD Anderson at the end of May but is expected to continue to play a role in translational research at the institution.*

Scrip's weekly Pipeline Watch tabulates the most recently reported late-stage, Phase III clinical trial developments for the more than 10,000 drug candidates under active research worldwide. To see changes to the progress of product candidates further back in the development pipeline, and a table of the week's product approvals, please visit our Pipeline Watch webpage at scrip.pharmamedtechbi.com.

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**Selected clinical trial developments for the week 17–23 March 2017**

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
<b>Phase III Results Published</b>			
Amgen Inc.	<i>Repatha</i> (evolocumab)	Positive CV outcomes in dyslipidemia	FOURIER; in the NEJM, March 18, 2017 .
Bayer AG/Janssen Pharmaceuticals Inc.	<i>Xarelto</i> (rivaroxaban)	venous thromboembolism	EINSTEIN CHOICE; in the NEJM, online March 18, 2017.
CSL Behring	CSL830 (C1-esterase inhibitor), subcutaneous	prevention of hereditary angioedema attacks	COMPACT; March 23, 2017 issue of the NEJM .
Neurocrine Biosciences Inc.	<i>Ingrezza</i> (valbenazine)	tardive dyskinesia	Kinect 3; March 21, 2017 issue of the American Journal of Psychiatry.
CTI BioPharma Corp.	pacritinib	myelofibrosis	PERSIST-1; online on March 20, 2017 in The Lancet Haematology.
Pfizer Inc.	bococizumab	dyslipidemia	SPIRE studies; in the NEJM online, March 17, 2017.
<b>Updated Phase III Results</b>			
AB Science	masitinib	amyotrophic lateral sclerosis	Study AB10015; Positive top-line results, the first for a tyrosine kinase inhibitor.
Novartis AG	<i>Cosentyx</i> (secukinumab)	psoriasis	A2302E1; modified course of the disease .
Portola Pharmaceuticals Inc./Lee's Pharmaceutical Holdings Ltd.	betrixaban	venous thromboembolism	APEX; reduced occurrence when dosing extended.
Amgen Inc.	<i>Repatha</i> (evolocumab)	cognitive function	EBBINGHAUS; no signs of an adverse effect.
Sanofi/Regeneron Pharmaceuticals Inc.	<i>Praluent</i> (alirocumab)	dyslipidemia	ODYSSEY CHOICE1; monthly dosing improved lipid levels.
<b>Phase III Interim/Top-line Results</b>			
Novartis AG	<i>Reasanz</i> (serelaxin)	acute decomp. heart failure	RELAX-AHF-2; missed primary endpoints in CV outcomes .
Eli Lilly & Co.	abemaciclib	breast cancer	MONARCH2; met PFS primary endpoint .
Jazz Pharmaceuticals PLC	JZP-110	obstructive sleep apnea	TONES 3,4; positive efficacy results.
Nektar Therapeutics	NKTR-181; first full mu-opioid analgesic	chronic pain	SUMMIT-07; met primary and secondary endpoints.
Bayer AG/Janssen Pharmaceuticals Inc.	<i>Xarelto</i> (rivaroxaban)	recurrent venous thromboembolism	EINSTEIN CHOICE; better than aspirin, no increased major bleeds.
<b>Phase III Initiated</b>			
RedHill Biopharma Ltd.	RHB-104	Crohn's disease	MAP US2; an open label extension study.
Boehringer Ingelheim GMBH/ Eli Lilly & Co.	<i>Jardiance</i> (empagliflozin)	chronic heart failure	EMPEROR HF; outcome studies, with and without diabetes.
Boehringer Ingelheim GMBH	nintedanib	progressive fibrosing lung diseases	PF-ILD; a group of patients distinct from those with idiopathic pulmonary fibrosis.
<b>Phase III Announced</b>			
Mundipharma International Corp. Ltd./Esteve	MR308	moderate to severe pain	STARDOM2; after surgery.

Source: Biomedtracker

**Impax Laboratories, Inc.** has appointed **Paul M. Bisaro** president and CEO and a member of the board, effective March 27. Bisaro will succeed **J. Kevin Buchi**, who has served as interim president and CEO since December 2016. Bisaro has 25 years of generic and branded pharmaceutical experience, most notably serving as executive chair of Allergan, plc (formerly Actavis, plc), president and CEO of Actavis (formerly Watson Pharmaceuticals, Inc.) and chair.

**Mylan NV** has appointed **Daniel Gallagher** chief legal officer with effect from April 17. A former commissioner of the US Securities and Exchange Commission (SEC) between Nov. 2011 and Oct. 2015, Gallagher joins Mylan from Patomak Global Partners, a consulting firm providing strategic advice, compliance consulting, and litigation and regulatory enforcement services, where he was president. Before being appointed an SEC commissioner, Gallagher served on the staff of the SEC in several capacities, including as counsel to both SEC commissioner Paul Atkins and chair Christopher Cox, working on matters involving enforcement, as well as trading and markets.

**Robert Tessarolo** has been appointed president and CEO of the dermatology

specialty company, **Cipher Pharmaceuticals Inc.**, effective April 17, and will be nominated for election as a director at the company's next annual general meeting in May 2017. Tessarolo was most recently vice-president and general manager at Celgene Corp., where he led the US inflammation and immunology business. Prior to that, he led the launch of Actavis, plc's Canadian specialty pharmaceutical division, where he served as president and general manager.

**Bridge Medicines**, a New York-based drug discovery company, has appointed **Dr William J. Polvino**, chief executive officer. **Dr Kathleen Metters**, who has served as the interim CEO upon the establishment of Bridge Medicines in October 2016, will continue to have an operating role, and will chair the scientific advisory board. Polvino has more than 26 years of industry experience, and was most recently president and CEO of Veloxis Pharmaceuticals. Prior to Veloxis, Polvino held positions at Helsinn Therapeutics (formerly Sapphire Therapeutics), where he also served as the company's president and CEO.

**Dr Kirk Shepherd** is joining the US subsidiary of **Eisai Co. Ltd.** as senior vice president, global medical affairs, oncology business group. He will be responsible for creating

and overseeing Eisai's global oncology medical strategies for the commercial and market access businesses. Shepard joins Eisai from Shire plc, where he served as senior vice president & head, global medical affairs following the company's acquisition of Baxalta Inc.

**Arena Pharmaceuticals Inc.** has appointed **Preston Klassen** chief medical officer and executive vice president of research and development. He will lead Arena's product development as the company aims to deliver critical data on three Phase II assets in 2017. Klassen brings more than 20 years of industry experience to Arena. He most recently served as chief medical officer at Laboratoris Sanifit, before that he was executive vice president, head of global development at Orexigen Therapeutics. Klassen has also held various positions at Amgen.

**Hutchison China MediTech Ltd.** has appointed **Dr Weiguo Su** executive director and a member of its technical committee with effect from March 27. Su has been the executive vice president and chief scientific officer at the company since 2012. Before joining in 2005, Su spent 15 years with the US research and development department at Pfizer, Inc. where his last position was director of the medicinal chemistry department.

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