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Amazon/Berkshire/JPMorgan Partnership Could Disrupt Pharma

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The world's largest retailer, one of the most successful investment firms in the US, and one of the world's biggest banks have banded together to lower health care costs and improve the quality of care for their employees, driving speculation about the impact for one of the biggest associated expenses: pharmaceuticals.

When **Amazon.Com Inc.**, Berkshire Hathaway and JPMorgan Chase & Co. announced on Jan. 30 that they are working together on ways to "address health care for their US employees, with the aim of improving employee satisfaction and reduce costs," biopharmaceutical and other health care companies' stocks slumped. The collaboration, while focused on the partners' concerns as employers, again raised the questions of what Amazon's own business intentions are in the health care arena.

Amazon's potential interest in distributing prescription drugs has been seen as both a peculiarity, given the complex regulation involved in such an endeavor for a retailer previously not working in this area, and as a disruptive force for US health insurance companies and managed care organizations (MCOs), in addition to pharmacy benefit managers (PBMs) and biopharma companies.

However, Amazon's move to obtain pharmacy distribution licenses appears to be – at least initially – an effort to support the online retailer's plans to sell and distribute medical devices and supplies. Asked about Amazon's interest in pharma product distribution and the online retailer's new partnership with Berkshire and JPMorgan Chase during **Pfizer Inc.**'s Jan. 30 fourth quarter earnings call, CEO Ian Read said: "We welcome any entrants to the distribution system that can improve efficiencies and ensure that patients get their medication at the appropriate cost and the appropriate time."

Read added that the distribution system, excluding the process of negotiating drug prices and rebates with payers, "is already highly efficient."

Johnson & Johnson CEO Alex Gorsky noted during that company's recent earnings call that it is keeping an eye on innovators in the biopharma and medical device field, but said J&J already works with Amazon and other online retailers to distribute its consumer health products.

J&J's stock closed down 0.9% at $142.43 per share on Jan. 30, while Pfizer fell 3.1% to $31.80. The PBM **Express Scripts Holding Co.** ended the day down 3.2% at $79.31.

PARTNERS' PHARMA PLANS NOT OUTLINED

The Amazon, Berkshire and JPMorgan partnership announcement did not shed any light on Amazon's pharma and medical device plans nor did the companies address drug costs directly in their press release. The three partners said they will create "an independent company that is free from profit-making incentives and constraints" with an initial focus on "technology solutions that will provide US employees and their families with simplified, high-quality and transparent health care at a reasonable cost."

Between them, the three companies have about a million employees and several

CONTINUED ON PAGE 8

Q4 Results
Roche, Pfizer, AstraZeneca, Amgen and Merck & Co all report (p4-15)

Infographic
A look at the state of the pharma industry (p6)

Approvals In 2018
10 first approvals due this year (p20)

from the editor

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In describing the "ballooning costs of healthcare" as "a hungry tapeworm on the American economy", Warren Buffett didn't do pharma stocks any favours. But investors' gut reactions may well have been a little too strong.

Drug pricing may not have been what Buffett and his counterparts at Amazon and JPMorgan Chase & Co had front of mind when they decided to partner to find innovative ways of addressing healthcare for their US employees (see cover story). In simple terms, their plan to set up a non-profit company to provide their large shared employee base with reasonably priced healthcare sounds quite a bit like a mutual insurance company, albeit turbo-boosted by the participation of the emperor of digital logistics. At least a part of its eventual success ought to be that the partners will reduce insurance costs simply by pooling resources to cut out the profit-making middleman.

Drug costs represent only around 15% of healthcare costs – and there is a pretty strong argument that taking medicines actually helps to reduce broader healthcare costs (including the costs to employers of employee ill health). As Amazon and friends begin their experiments in the healthcare space, pharma companies have an opportunity to get in on the act early. Medicines will remain an indispensable part of healthcare and that of course includes novel, high-value, patent-protected products.

And should the online behemoth eventually go on to participate in the medicines market, it's worth remembering that its true genius lies in disrupting traditional supply chains, not in cutting consumption or spending on products.

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Shingrix Seen Replacing Zostavax In EU & US as Shingles Standard Of Care
http://bit.ly/2Bi3ND5
Shingrix is likely to replace Merck & Co's Zostavax as the preferred shingles vaccine in the EU and US, following the GSK product's approval in the US and recent positive opinion in the EU. Sales in major markets could approach $700m by 2025.

Novo To Secure Licensing Or M&A Deal By Mid-2018
http://bit.ly/2GZ6kCv
Who is on *Scrip*'s list of potential licensing partners and M&A targets for Novo Nordisk, now that the company has renewed its hunt for new products to add to its hematology portfolio?

Deal Watch: Sanofi Finds Ideal 'Partner' For Leukine
http://bit.ly/2nSScSJ
Partner Therapeutics takes on Sanofi's immunostimulant. Novartis transitions struggling Arzerra for compassionate use only outside the US, with compensation to Genmab, while Shire licenses I.V. immunoglobulin candidate from AB Biosciences.

Vertex Cystic Fibrosis Forecast Brightens, With Gloomy Prospects For Competition
http://bit.ly/2nWqCUP
Vertex continued its growth story in cystic fibrosis during 2017. It also chose a pair of candidates for Phase III triple combination development, threatening to virtually seal off market entry to others.

Finance Watch: Another Mega-Round As Moderna Bucks Biopharma's IPO Trend
http://bit.ly/2EaaPwf
Moderna raised $500m to fund its growing pipeline, choosing once again to stay private rather than pursue an IPO. Also, AvroBio closed a $60m Series B round to advance its gene therapies for lysosomal storage disorders, Seattle Genetics led recent public company financings, and Vical is restructuring.

IPO Update: Seven In January As Big Returns, Solid's Slip-Up Contribute To Bubble Concerns
http://bit.ly/2H1dDJZ
Seven biopharma IPOs launched in the US in January with an average return of 52.8%. The most recent was Sol-Gel's on Jan. 31, but the largest was a $128m offering by ARMO. Solid had the most controversial IPO, but it still gave investors a 70.7% return, contributing to the question: Is biotech in a bubble?

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Roche: No Major M&A Needed To Offset Biosimilar Threat

KEVIN GROGAN kevin.grogan@informa.com

In its battle to combat the impact of biosimilars, **Roche** CEO Severin Schwan has said the Swiss major's new products will compensate for patent losses on some of its cancer blockbusters and a big merger is not needed to fill the revenue gap.

Severin Schwan

Speaking on a conference call with journalists this morning (Feb. 1) as Roche presented its financials for 2017, Schwan said, "There is no change in our M&A strategy whatsoever as we will continue to look for external opportunities through bolt-on acquisitions."

The pharmaceutical sector has seen a number of major transactions since the turn of the year, with **Celgene Corp.** paying $9bn for **Juno Therapeutics Inc.** and **Sanofi** getting back into the M&A game with proposed acquisitions of **Bioverativ Inc.** and **Ablynx NV** for $11.6bn and $3.9bn, respectively. However Schwan is not looking to tread the major M&A path, citing the announcement at the end of 2017 to buy San Diego-based rare cancer specialist **Ignyta Inc.** for $1.7bn as a good example of the type of transaction Roche is interested in.

Rather than buying its way out of trouble, Roche is backing its new products to offset the battering from biosimilar competition to some of its big-selling cancer therapies. *MabThera/Rituxan* (rituximab) is already suffering market share erosion in Europe, down a whopping 26% in the fourth quarter, while rivals to *Herceptin* (trastuzumab) and *Avastin* (bevacizumab) are lining up.

On the topic of biosimilars, Schwan said "we will certainly see an acceleration of the decline" of MabThera in Europe in 2018 as copies only came onto the market in the latter part of 2017. Biosimilars of Herceptin will arrive this year but the effect of versions of Avastin will not be felt for a while, and sales of the latter in the fourth quarter were actually up 1% despite competition from immunotherapies.

Schwan went on to say that the strong performance of Roche's new products will be able to compensate for the biosimilar effect "and even potentially even slightly grow our business," helped by productivity measures. He highlighted the stellar performance of the multiple sclerosis drug *Ocrevus* (ocrelizumab), which was only launched in the US in the second quarter but brought in CHF869m ($932.4m).

The therapy was approved in Europe earlier in January and Schwan told *Scrip* that while prices on the continent have declined moderately over the past few years, Roche was confident that payers recognize "the innovation and medical differentiation our products offer patients."

Schwan noted that the PD-L1 inhibitor *Tecentriq* (atezolizumab) and the lung cancer drug *Alecensa* (alectinib) and *Ocrevus* contributed CHF1.4bn of new sales in 2017, representing 65% of Roche's pharmaceuticals division's growth. Tecentriq, which is approved for second-line lung cancer and bladder cancer, brought in CHF487m of that total, and the CEO told *Scrip* that the company had seen good uptake in those indications.

More importantly, he added, were two high-profile readouts in first-line non-small cell lung cancer and renal cancer. In December, Roche reported that the combination of Tecentriq with Avastin met the primary endpoint of progression-free survival in the Phase III IMmotion151 study in first-line renal cancer patients with PD-L1 expression of at least 1%, following on the heels of the Tecentriq/Avastin combo demonstrating improved PFS in the Phase III IMpower150 study – a 38% reduced risk of progression – in first-line advanced NSCLC.

These were the first two of eight Tecentriq trials that are expected to read out by the middle of this year, Schwan confirmed. "We are very confident based on the data that Tecentriq will play a leading role in various cancer types and we have to wait for the final clinical readouts and also compare the data to competitive products, but so far, so good."

Like all CEOs at the moment, Schwan was asked about the impact of US corporate tax reform and he noted that Roche's tax rate will fall from 26.6% in 2017 to the low 20% range this year. The company expects 2018 sales to be stable or grow by a low-single digit percentage and while profits were forecast to grow in line with sales, core earnings per share should now rise by a high-single digit, thanks to the better US tax rate.

After the media call, Schwan dashed off to catch a flight to London to join his management colleagues for an investor meeting (which *Scrip* is attending) to give more insight on Roche's financials and future plans.

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Roche's Ocrevus: A Rare First-Year Blockbuster

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Roche's multiple sclerosis drug *Ocrevus* (ocrelizumab) appears to have set a new bar for commercial drug launch success among recent launches (excluding drugs for hepatitis C). Ocrevus generated $935m (CHF869m) in sales in 2017 in just nine months after launching in the US in April, nearly reaching blockbuster status in under a year on the market.

Drugs that reach $1bn in sales that fast don't come around every year. Ocrevus has outpaced other notable launches in the last six years, including **Pfizer Inc.**'s *Ibrance* (palbociclib), **Novartis AG**'s *Cosentyx* (secukinumab), **Bristol-Myers Squibb Co.**'s *Opdivo* (nivolumab), **Biogen**'s *Tecfidera* (dimethyl fumarate), **Johnson & Johnson/Bayer AG**'s *Xarelto* (rivaroxaban) and **Regeneron Pharmaceuticals Inc.**'s *Eylea* (aflibercept).

One launch that does stand out is **GlaxoSmithKline PLC**'s HIV drug *Tivicay* (dolutegravir), which together with a combination pill *Triumeq* (abacavir/dolutegravir/lamivudine) generated $1.85bn (£1.3bn) in a full 12 months on the market in 2015, after launching late in 2014, not an easy direct comparison.

Even $200m in launch-year sales is generally considered a commercial success, a signpost that a drug is on a track toward eventual blockbuster status.

Ocrevus is a key drug for Roche as it looks to move forward into an era that will include biosimilar competition to many of its longstanding blockbusters, including *Herceptin* (trastuzumab), *Avastin* (bevacizumab) and *Rituxan* (rituximab).

Ocrevus was approved by the FDA in March as the first drug for an underserved patient population, primary progressive MS (PPMS) patients, as well as for relapsing-remitting MS (RRMS). The strong efficacy data supporting the approval and competitive pricing have likely powered the launch. Roche priced Ocrevus at a 20% discount to other MS therapies on average, including the standard interferons. *(Also see "Roche Set For Disruptive Entry To MS Market With 'Brave' Ocrevus Pricing Strategy" - Scrip, 29 Mar, 2017.)* Ocrevus was only recently approved in Europe. *(Also see "All Systems Go as Roche MS Drug Ocrevus Secures EU Okay At Last" - Scrip, 12 Jan, 2018.)*

The drug was an early standout among the 2017 class of drugs. *(Also see "A Year To Remember For US Drug Launches" - Scrip, 29 Dec, 2017.)* But Roche's year-end financials, reported Feb. 1, revealed the drug has surpassed other big launches in the last five years based on revenues. Hepatitis C drugs were excluded because of their unusual launch trajectory involving a fast initial uptake that slowly recedes as patients are treated, and some HIV drugs also had stronger early sales. **Gilead Sciences Inc.**'s *Sovaldi* (sofosbuvir) is well recognized as the most notable launch of all time after it generated $10.28bn in 2014 following its launch in December 2013. *(Also see "Head Of The Class: A Star Stands Out Among 2014 Drug Launches" - Pink Sheet, 5 Jan, 2015.)*

Among more traditional launches in the last six years, Ocrevus' revenues have outpaced industry's fastest success stories. Multiple sclerosis is clearly a strong therapeutic category to launch into. Biogen's oral multiple sclerosis pill Tecfidera generated the next highest revenues in the same time period; Tecfidera generated $876m in 2013 after launching in April of that year. *(Also see "Tecfidera Stands Out From The Pack Of 2013 Drug Launches" - Pink Sheet, 13 Jan, 2014.)*

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> Even when it comes to one of the best-selling drugs of all time, Pfizer's Lipitor (atorvastatin), Ocrevus surpassed the bar, though just barely

Bristol's immuno-oncology blockbuster Opdivo generated $942m in 2015, but that was after a full year on the market as it was approved by FDA in December 2014. Regeneron's Eylea likewise is remembered among the best new launches, but generated $838m in 2012, a full year after launching in late 2011. J&J/Bayer's blood thinner *Xarelto* (rivaroxaban) brought in $864m in a full year in 2013 after launching in the second half of 2012.

Pfizer's first-in-class CDK-4/6 inhibitor Ibrance yielded $723m in 2015 after launching in February. Novartis' Cosentyx, revered as a recent commercial success that generated $2.1bn in 2017, only generated $261m in 2015 following its launch that February.

Going back even further into the drug archives, even when it comes to one of the best-selling drugs of all time – Pfizer's *Lipitor* (atorvastatin) – Ocrevus surpassed the bar, though just barely. Lipitor generated $865m in sales in 1997 under the ownership of Warner Lambert after launching in February of that year.

Bristol's *Plavix* (clopidogrel) brought in $547m in its first full year on the market in 1999 and Merck's *Januvia* generated $667.5m in 2007, its first full year on the market.

With that historical context in mind, it's pretty clear Roche has a winner on its hands.

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THE STATE OF THE PHARMA INDUSTRY

[A snapshot of the pharmaceutical universe as we enter 2018]

4,143
The number of pharma and biotech companies with at least one product in active development[1]

659
The number of pharma and biotech companies with at least $1m in drug sales or R&D spending[2]

2.3M
People employed by these companies

15,267
The number of products in active development

2.7%
Increase on the same time-point in 2017[3]

34%
Are for cancer
(a 7.6% increase)

46 2017 | 22 2016

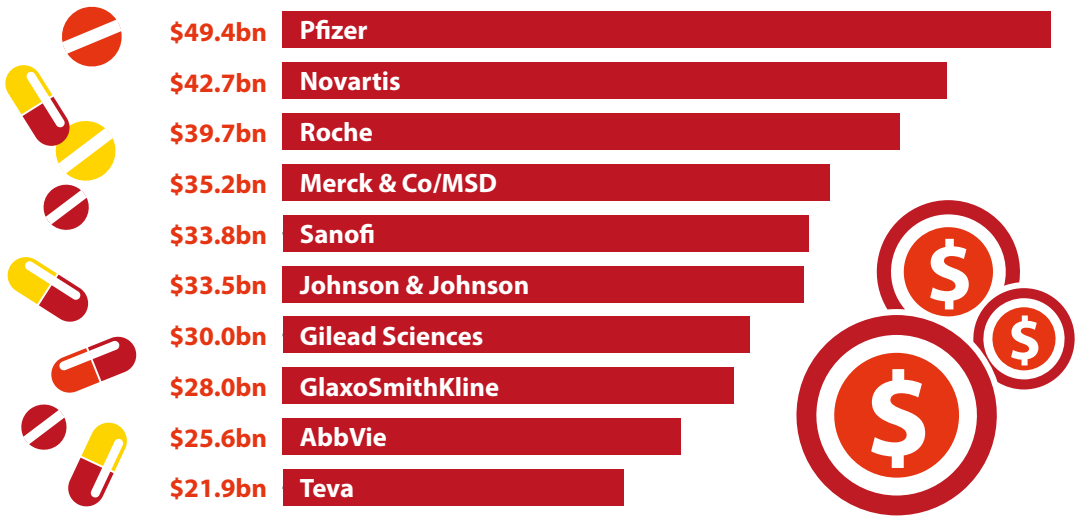
The number of novel drugs and biologics approved by the FDA. The number in 2017 breaks the previous record from 2015[4]

28 2017 | 29 2016

The number of products containing a new active substance approved for marketing in the EU in 2017, compared with 2016[5,6]

SOURCES:
[1]Pharmaprojects Jan. 4, 2018, [2]Scrip 100 data, [3]Pharmaprojects Jan. 4, 2018, [4]https://scrip.pharmaintelligence.informa.com/SC100122/A-Year-To-Remember-For- US-Drug-Launches, [5]https://scrip.pharmaintelligence.informa.com/SC100146/28-New-Drug-Approvals-In-EU-Cancer-Dominates-But-RA-Skin-amp-Blood-Disorders-Well-Served-Too, [6]European Commission's drug approvals database as of Jan. 4, 2018., [7]Scrip 100, [8]https://scrip.pharmaintelligence.informa.com/SC100144/IPOs-In-Review-Biopharma-Offerings-Bounced-Back-In-2017-As-Returns-Rose, [9]TrialTrove Jan. 22, 2018

TOP 10 COMPANIES BY FY 2016 DRUG SALES[7]



$3130.6bn
The market capitalization of the **top 50 pharma companies** *(Dec. 29, 2017)*

An increase over the year of
$274bn
from $2,857bn

The companies with the largest market cap increases in 2017

1	2	3
J&J	**AbbVie**	**Abbott Labs**
$65.8bn	**$54.4bn**	**$32.5bn**
$375.4bn (+21%)	$154.4bn (+54%)	100.0bn (+49%)

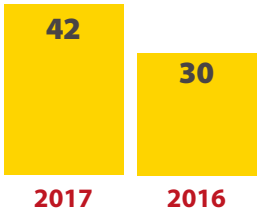
Biggest market cap losers

1	2	3
Teva	**GSK**	**Allergan**
-$17.6bn	**-$16.1bn**	**-$15.5bn**
$19.3bn (-48%)	$88.7bn (-15%)	$54.4bn (-22%)

Top 100 companies
total R&D spend in 2016[7]

$137bn

42
The number of IPOs launched in the US in 2017, vs. 30 in 2016



11,107
Industry-sponsored Phase I-III trials ongoing[9]

TOP 10 BEST-SELLING DRUGS 2016 ($M)

1) **HUMIRA** ABBVIE *inflammation* **$16,514**
2) **HARVONI** GILEAD *Hepatitis C* **$9,081**
3) **ENBREL** AMGEN/PFIZER *inflammation* **$8,874**
4) **REMICADE** J&J/MSD *inflammation* **$7,612**
5) **REVLIMID** CELGENE *oncology* **$6,974**
6) **AVASTIN** ROCHE *oncology* **$6,886**
7) **HERCEPTIN** ROCHE *oncology* **$6,885**
8) **LANTUS** SANOFI *diabetes* **$6,324**
9) **RITUXAN** ROCHE *oncology* **$5,911**
10) **PREVNAR** PFIZER *vaccines* **$5,718**

CONTINUED FROM COVER

billions of dollars to spend on their shared problem of high and rising health care costs – a crisis that Berkshire Chairman and CEO Warren Buffett described in the partnerships' announcement as "a hungry tapeworm on the American economy."

Maulik Bhagat, managing director in the health care practice of AArete, a global consultancy specializing in data-informed performance improvement, noted that health insurance costs have been one of the fastest growing costs for large corporations for several years and it has impacted companies' abilities to attract and retain employees, because individuals' out-of-pocket costs have increased within employer-sponsored health insurance plans.

"At 1.1m employees and growing, [Amazon, Berkshire and JPMorgan Chase] are already a decent-sized 'health plan' in themselves and could essentially operate as its own 'payer entity' or possibly an 'Accountable Care Organization' for their employees," Bhagat said in comments shared with *Scrip*.

"At a minimum it gives them more power in holding their existing payer vendors more accountable for health and cost outcomes for their employees," Bhagat continued. "It gives them a chance to deliver better health care and reduced costs and change the market dynamics in the commercial health care space. Expand this to the number of captive and loyal customers these firms collectively touch and you suddenly have the possibility of this becoming a huge disrupting development."

Morgan Stanley estimated that the three companies employ 950,000 people, providing health care coverage for about 2.4m people, including family members, adding up to about $13bn in annual health care spending, about 15% of which was attributed to prescription drug costs.

"The principle of improving consumer transparency and removing friction in the shopping processes is consistent with [Amazon's] other business ventures," Morgan Stanley's analysts wrote in a Jan. 30 report. "That said, we expect this to be a slow process (test and learn) and don't expect material disruption overnight as disrupting the insurance sector will face regulatory hurdles (e.g., HIPAA requirements) and multiple industry complexities (strong sales efforts, relationships with doctors, insurance companies, claims technologies, building networks, etc.)."

ENTREPRENEURIAL APPROACH

Amazon Founder and CEO Jeff Bezos indicated in the Jan. 30 announcement that while the partners are taking an entrepreneurial approach, they plan to engage health care experts to achieve their goals. Bezos said "we enter into this challenge open-eyed about the degree of difficulty" and noted that "success is going to require talented experts, a beginner's mind, and a long-term orientation."

JPMorgan Chase Chairman and CEO Jamie Dimon made it clear that the partners will bring their collective and extensive resources to bear to solve the health care cost problem for themselves and potentially other companies. However, the three employers did not specify how their efforts could extend to other companies – by selling services, advising outsiders, inviting additional participants or none of the above.

"The three of our companies have extraordinary resources, and our goal is to create solutions that benefit our US employees, their families and, potentially, all Americans," Dimon said, suggesting that Amazon, Berkshire and JPMorgan Chase will share the results of their partnership with others.

Collective bargaining, in which companies pool their resources to negotiate a better deal for products and services, is nothing new. In fact, in health care Amazon, Berkshire and JPMorgan Chase are not the first companies to band together in recent years to address high costs, including drug prices.

The Health Transformation Alliance (HTA) formed in 2016 with about 20 large employers – including American Express, Coca Cola and IBM – seeking ways to cut their collective prescription drug costs.

The HTA, which has grown to 48 members, recently announced that it has launched its first pilot project aimed at reducing the amount of money spent on medicines, including fees paid to PBMs and the cost of prescription drugs. The project's goal also is to make sure patients are prescribed appropriate medicines, even if they're more expensive drugs, based on a belief that employers' overall health care costs will go down if workers are taking the best medicines for their medical conditions.

Pfizer's Read, during the company's earnings call, said he viewed the Amazon, Berkshire and JPMorgan Chase partnership as positive for the biopharma industry because of the role medicines can play in reducing health care costs. "I would see it as totally positive for our industry. Any attempts to lower health care costs are going to have to involve, my belief, using medicines to ensure adherence, to ensure the management – the proper management – of diseases," Read said.

"We represent 10% to 14% of health care costs," he continued, "so I would hope that private actors that come into this space would look at … it in a positive way of controlling costs. I think it's encouraging that private actors enter in this and it's encouraging for the use of modern pharmaceuticals."

VEHICLE UNCLEAR

It's not clear whether the three employers are creating their own health insurance company, MCO or PBM to manage their health care costs or if the independent firm will merely use the partners' collective power and capital to negotiate for lower-cost insurance, health care and services provided by third parties. Whether Amazon, any of Berkshire's subsidiary companies or JPMorgan Chase's financial services will be involved in the effort also is unknown.

"We were not surprised by today's announcement, as health care represents a large and growing industry with relatively high profit margins – in other words, just the type of sector Amazon typically targets," Loop Capital Markets analyst Anthony Chukumba said in a Jan. 30 note to Amazon investors. "We find it noteworthy neither of Amazon's partners are currently in the health care industry. That said, given the combination of Amazon's technological expertise, Berkshire Hathaway's operational experience, and JPMorgan Chase's deep pockets, we are initially optimistic about the partnership's chances of long-term success."

The companies did not reveal who will lead their independent health care cost-focused firm or where it will be headquartered, but they did name individuals that each partner chose to focus on the project: Berkshire Hathaway investment officer Todd Combs, JPMorgan Chase Managing Director Marvelle Sullivan Berchtold, and Amazon Senior Vice President Beth Galetti.

Morgan Stanley's analysts noted that Berchtold "has a strong background in health care M&A. Berchtold was focused on M&A and capital markets at Allen & Overy before joining Novartis in 2009.

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Pfizer, Poised For A Tax Reform Windfall, Talks About Ways To Reinvest

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Pfizer Inc. is about to get what CEO Ian Read has long advocated – a windfall from US corporate tax reform that he said will even the playing field for US-based multinational companies.

During its fourth quarter earnings call Jan. 30, Pfizer said it expects its 2018 tax rate will fall to 17% from a 23% rate in 2017 and that the change will be sustainable going forward. The company is also poised to repatriate up to $24bn in cash on profits from overseas.

Read even took a moment to take some credit. "I do believe that Pfizer played a major role in putting a spotlight on the disadvantageous corporate tax situation for US multinationals," he said. The company certainly did get a lot of attention when it tried to buy **AstraZeneca PLC** in 2014 and **Allergan PLC** in 2016, in part to take advantage of those companies' ex-US tax domiciles. *(Also see "It's The End Of Pfizergan, So Pfizer Will Have To Grow It Alone" - Scrip, 7 Apr, 2016.)*

'We will remain disciplined in our approach, with value creation for shareholders remaining our compass'

Earlier this year, Read suggested Pfizer would put a pause on any large M&A to wait to see if US tax reform was passed. *(Also see "Pfizer Hits Pause On M&A To See How US Tax Reform Plays" - Scrip, 1 Aug, 2017.)*

Now that the US Congress did pass tax reform in December, investors want to know what Pfizer will do with the extra cash it stands to receive, with many wondering how the cushion could impact the company's appetite for M&A, and industry's more generally.

"We are currently reviewing our capital allocation opportunities under the new tax code," Read said during the call. "We will remain disciplined in our approach, with value creation for shareholders remaining our compass."

But Pfizer came to its fourth quarter financial presentation with more details on the impact of tax reform and potential reinvestment opportunities than most drug makers have so far – although **Johnson & Johnson** also announced its intent to prioritize spending on operations. *(Also see "J&J Shows Grace Under Pressure From Biosimilars And Other Threats" - Scrip, 23 Jan, 2018.)*

The company plans to return cash to shareholders in the form of dividend payments and share repurchase. In December, Pfizer's board of directors authorized a $10bn share repurchase program, and the company said it expects to distribute quarterly payments of $0.34 per share in common stock in addition to $5bn in share repurchases in 2018.

In addition, the company vowed to reinvest in the US and its employees including:

- $5bn in capital projects in the US over five years, including strengthening Pfizer's manufacturing presence
- $200m contribution already made to the Pfizer Foundation, which supports improvements in healthcare delivery
- $500m contribution to its employee pension plan
- $100m for a one-time bonus to be paid to all non-executive Pfizer employees in the first quarter

In addition, Pfizer said it expects to pay $15bn over eight years to the US Treasury from repatriation tax liability resulting from tax reform.

As for M&A, Pfizer said it has the capacity to do large deals and small deals, but Read kept his language reasonably open to interpretation.

"We'll continue to look at M&A from the point of view of value for our shareholders and will be directed by the science and the opportunities, and we also look at opportunities across the other spectrums, which is dividends and the buybacks and investment in the business," he said.

But he also acknowledged that the company had the capacity to do a mega-merger before tax reform and continues to.

"I do believe there will be a need for consolidation," he said. "I think these things come in waves. I think everybody is looking at potential combinations and consolidation."

And, he pointed out, Pfizer has a "core competency" when it comes to integrating large companies into Pfizer.

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Amgen Invests In Deals, Share Buybacks And Manufacturing As Sales Dip

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Amgen Inc. plans to put its $41.7bn in cash as of the end of 2017 to work in 2018 in ways that may boost future earnings and "shareholder value," seeking acquisitions of drugs or companies that can help reverse the big biotech's flat to declining revenue trend.

There are not a lot of commercial-stage products for sale, so Amgen more than likely will purchase pipeline assets that could take years to bring to market – and years to significantly boost revenue. But investors hoping for near-term returns are in luck, because the company revealed in its fourth quarter earnings report on Feb. 1 that it has allocated $14.4bn to buy back outstanding Amgen shares via $4.4bn in prior share buyback commitments and a newly authorized $10bn program, which could be completed during the first half of 2018.

Employees also stand to benefit from the company's cash stockpile and tax savings through the construction of new manufacturing facilities and increased take-home pay. Also, Amgen's committed $3.5bn for new capital expenditures over the next five years, including $750m this year. The expenditures include a new $300m state-of-the-art biomanufacturing facility and an extra $300m for the company's venture capital fund.

"We intend to use our resources to continue to invest in our people and the attractive long-term growth opportunities we see in our industry, including M&A where it fits our focus, while also returning capital to our shareholders," Amgen CEO Bob Bradway said at the start of the company's Feb. 1 earnings conference call.

Bradway and other executives pointed to Amgen's "volume-driven growth" despite the fact that sales overall dropped 3% year-over-year to $5.8bn in the fourth quarter of 2017 and declined 1% for the full year to $22.8bn.

Certain product sales did climb based on volume – the PCSK9 inhibitor *Repatha* (evolocumab) for high cholesterol soared 126% in 2017 to $319m for the year, the cancer drug *Blincyto* (blinatumomab) jumped 52% to $175m, *Prolia* (denosumab) for osteoporosis rose 20% to nearly $2bn and the multiple myeloma therapy *Kyprolis* (carfilzomib) gained 21% to reach $835m globally.

However, reduced demand, lower prices or a combination of the two drove down sales of key Amgen brands with *Neupogen* (filgrastim) for neutropenia falling another 28% to $549m globally as biosimilars competition continued in 2017. Similarly, sales of the anemia blockbuster *Epogen* (epoetin alfa) fell 15% to $1.1bn. The TNF inhibitor *Enbrel* (etanercept) for rheumatoid arthritis and other inflammatory diseases suffered from lower prices as the company tried to keep up with its competition in the US and abroad, with sales falling 9% for the year to $5.4bn.

CASH AT THE READY FOR DEALS

Amgen stands ready to execute deals for products that can help offset revenue declines and for companies with technology platforms that can be used to generate multiple novel therapies. Bradway and Amgen's Chief Financial Officer David Meline said during the company's presentation and Q&A session during the J.P. Morgan Healthcare Conference in January that deal-making is the main priority for the company's $39bn in overseas cash, which it can access based on recent US tax reform.

Bradway reiterated Amgen's position during the company's earnings call that having access to overseas cash puts the company on a level playing field with its peers based outside the US. Amgen expects its US tax rate to be 14% to 15% in 2018 on a non-GAAP basis compared with 18% in 2017, which the company said will allow it to invest in capital expenditures, increased wages and philanthropic endeavors while continuing to execute value-creating deals.

"Since 2011, we have invested more than $42 billion in research and development, innovation-based acquisitions and long-term capital expenditures," Bradway noted.

The CEO later implied, when asked whether the company plans to use its cash to capitalize on consolidation of companies in the biopharmaceutical industry, that Amgen would consider both larger transactions and smaller bolt-on acquisitions.

"We are well-positioned to address ongoing changes in the health care market; we expect there will be ongoing changes and we are well-positioned to capitalize on the consolidation for our shareholders. We have been consistent in saying that we have the financial capacity and we are interested in looking for deals that we think we can add value in our areas of focus. So, you know, we will continue to do that," Bradway said. "We have felt for some time that there are pockets of excess capacity in the industry and we will look to see whether we can help to create some value by being part of the consolidation."

Meline later added more color on Amgen's appetite for larger deals, saying that "in terms of the opportunities out there, you know we have been, I think, pretty clear that we are focused in particular on the six areas where we have decided to establish a commercial presence. So, we tend to orient ourselves towards those opportunities and we're quite clear in the market that we want to see everything of any size that might be of interest to us across those areas."

However, Bradway noted in an earlier comment that "it's hard to find deals that are both accretive and add to the long-term return on capital for shareholders. We will continue to be disciplined."

IS BIGGER BETTER FOR GROWTH?

A large transaction could be just what Amgen needs based on its new growth philosophy. Going forward, Bradway noted, the company sees sales of products for large markets as drivers of volume-driven growth, such as the LDL cholesterol-lowering product Repatha, which had the cardiovascular benefit from the massive FOURIER outcomes trial added to its US label on Dec. 1. *(Also see "Outcomes Claim May Help Amgen Make Case For PCSK9 Inhibitor Repatha" - Scrip, 1 Dec, 2017.)*

"With pressure on prices globally, we think revenue growth will be more tightly linked to volume growth than was the case historically. In this regard, medicines that serve the needs of large numbers of patients will be particularly attractive growth drivers. Repatha is a clear example of this," he said early in Amgen's earnings call.

The CEO also pointed to Prolia as an important growth-driver in the large postmenopausal osteoporosis market, where he noted that only 25% of eligible women are on treatment. The CGRP receptor inhibitor *Aimovig* (erenumab) for migraine headaches, which is pending US FDA approval, and the asthma candidate tezepelumab also were included in the basket of large-market products that Amgen will depend on for future sales growth.

Jefferies analyst Michael Yee estimated in a Feb. 1 research note that between Amgen's repatriated ex-US cash, year-end cash balance and its ability to secure debt, the company "has at least $50bn-$60bn minimum of theoretical capacity. We think neurology is an area they should look at given large market opportunities, recent de-risked assets, and [as a] bolt-on after migraine is now a part of their commercial biz."

Any new big-market products won't be boosting revenue soon enough to impact the near-term drag on Amgen's revenue from its declining legacy assets. The company projected $21.8bn to $22.8bn in 2018 revenue, which would be flat to 4.4% lower than 2017's total. The range also falls below analyst consensus of $22.9bn for this year.

"Important is 2018 guidance that appears 'below' consensus … incorporates lots of scenarios for potential generics/biosimilars – so if they do not come as fast or do not come, it would possibly imply upside to where consensus is," Yee wrote. "We appreciate the market may have uncertainty in this period – and uncertainty can be a challenging dynamic until it plays out."

Amgen's stock fell 1.7% in after-hours trading to $182.35.

MORE LOWER-COST COMPETITORS COMING SOON

Meline attributed most of the wide range in Amgen's revenue guidance – a $1bn spread versus historical guidance ranges with a difference of just $300m to $400m between the low and high ends – to uncertainty over the patent exclusivity of *Sensipar* (cinacalcet). It is approved for secondary hyperparathyroidism in patients with chronic kidney disease who are on dialysis.

The drug's composition of matter patent expires in March, but discussions with the FDA over Sensipar's pediatric exclusivity and litigation over the drug's formulation patent are ongoing, he said. *Parsabiv* (etelcalcetide) is the company's follow-on calcimimetic product, which could offset some of the revenue lost to Sensipar generics.

Simultaneously, the specter of *Neulasta* (pegfilgrastim) biosimilars also is looming over Amgen with a lower-cost version of the long-acting neutropenia drug pending approval in Europe, though the entrance of a biosimilar in the US is less certain.

"My understanding is that Amgen is baking in biosimilar competition on Neulasta in [the second half of 2018]. Recall, **Mylan NV** has guided to an action date in 'mid-year,'" Evercore ISI analyst Umer Raffat wrote in a Feb. 1 note.

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Using Data-Driven Insights To Systematically Improve Clinical Trial Feasibility

Sponsors have long sought to develop patient and site-centric trials to help improve enrollment and retention. These considerations typically occur during protocol design while leveraging a broad range of subjective sources like investigator and patient input, but can also occur, more ideally, during the protocol feasibility process. Nevertheless, objective sources are often still lacking when measuring patient and site burden.

Data-driven insights are vital to robust and comprehensive feasibility processes and to efficient and effective development programs. The process is best served by objective assessments of foundational elements of the protocol concept such as objectives, endpoints and procedures. Clinical development organizations have come to recognize the benefits of this objective approach and to incorporate feedback from potential investigators and insights from real-world data sources into their protocol designs. The result is the development of protocols that meet the clinical and statistical outcomes of the trials while minimizing site and patient burden.

How to optimize the feasibility process

The downstream benefits of applying data-driven insights to the design and optimization of study protocols are significant. Protocols created without such insights rely on subjective experiences, repetition of previous or unproven trial design strategies and guesswork. This can lead to slow enrollment and poor retention rates. To improve the chances of success, study teams incorporate epidemiological data, objective analyses of earlier studies and feedback from key investigators and opinion leaders into their feasibility processes.

Epidemiological data gives clinical development teams a historical snapshot of the disease incidence and prevalence within a patient population and helps shape the early feasibility strategies. However, the evaluation of the restrictiveness of inclusion/exclusion criteria during the protocol concept design phase provides the greatest insight into the ability to successfully recruit for the trial.

If the criteria place too many constraints on the clinical investigators who are recruiting for the study, the overall rate of enrollment will suffer. Data-driven study design practices that look at patient availability relative to the inclusion/exclusion criteria shed a light on which variables may cause the greatest challenge to recruitment. The sometimes elusive end goal of identifying the greatest number of patients available in an active disease state at the time of enrollment is further complicated by a highly restrictive protocol design with many onerous procedures that may deter site and patient participation.

Traditional protocol feasibility practices evaluate the inclusion/exclusion criteria in addition to the planned procedures in the Schedule of Events to assess the likelihood of identifying patients for the trial and keeping those patients engaged for the duration of the study. The feedback from key investigators and opinion leaders has been central to this process. Without a data-driven approach to these discussions, determinations of protocol viability have been consistently driven by this subjective process. However, novel technologies and data sources are beginning to shape a much more focused and intelligent path to patient and site-centric trial design.

Quantifying patient and site burden

Clinical development teams seek objective insights about the complexity of the study design in order to assess the impact on the site personnel executing the study and patient volunteers. Without applying a quantitative measure of site and patient burden, changes to trial design based on potential impact to patient recruitment and retention remain wholly subjective.

The industry's struggle to operationalize its approach to patient and site-centric trial design is evident in data on protocol complexity. A focus on the needs of patients and sites should result in studies that have the minimum number of visits and procedures required to meet the outcomes of the trial.

However, as the complexity of the science behind clinical trials has evolved in recent years, so too has the inclination of clinical scientists to increase the number of objectives, endpoints and associated procedures. Yet the number of visits, procedures and the frequency of those procedures per protocol have increased sharply over the years.

This leads to an opportunity for data-driven insights into the patient and site experience to improve clinical protocols and drive downstream operational efficiencies. To realize this future, the industry must seek ways to quantify the patient and site experience.

The number of times a patient needs to visit the site, the number of procedures they undergo at each visit and the time commitment to participate in the study are the main drivers of patient burden. Additional details such as the degree of invasiveness, pain and anxiety associated with the individual procedures also contribute significantly to the overall perception and experience of burden that a patient will endure over the duration of a trial.

These variables have a similar impact on the reduction in site burden as well. Protocols with fewer visits and procedures per subject, in addition to the selection of procedures that are typical for studies of similar indication and phase, result in less work for site personnel.

This leads to an opportunity for data-driven insights into the patient and site experience to improve clinical protocols and drive downstream operational efficiencies

The benefits of operationalizing patient and site-centric design

The benefits of making trials less burdensome for patients and sites will be far reaching. A higher portion of patients will consider participation in a clinical trial and will be committed to remaining in the trial to its completion. Sites will have more time for recruitment, retention and other patient relationship management tasks that are critical to the efficient generation of high-quality clinical data and positive patient experiences in clinical research.

The business partnership between sponsors and sites are further strengthened by the opportunity for investigators to work on well-designed trials that place their needs and those of patients at the forefront of the clinical program development effort.

Sponsors are the ultimate beneficiary. Confidence in the stability and integrity of the clinical program within a sponsor further bolsters the critical relationship between high-quality sites and the clinical teams. Ultimately, this results in trials that successfully recruit patients and collect data faster and more efficiently during study conduct. This is the reward that awaits companies that bring objectivity to the currently-subjective process of patient and site-centric trial design.

About Medidata Solutions

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Medidata Solutions is the leading global provider of cloud-based solutions for clinical research in life sciences, transforming clinical development through its advanced applications and intelligent data analytics. The Medidata Clinical Cloud™ brings new levels of productivity and quality to the clinical testing of promising medical treatments, from study design and planning through execution, management and reporting. We are committed to advancing the competitive and scientific goals of global customers, which include over 90% of the top 25 global pharmaceutical companies; innovative biotech, diagnostic and device firms; leading academic medical centers; and contract research organizations.

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Merck Plans $12bn In Capital Investments

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Merck & Co. Inc. is planning $12bn in capital investments over the next five years to add capacity for key growth-drivers in oncology, vaccines and animal health, the company said during a Feb. 2 earnings call.

Merck reported $35.4bn in full-year 2017 pharmaceutical sales, up 1% from the prior year. The company's PD-1 inhibitor *Keytruda* (pembrolizumab) was an important contributor, with $1.3bn in fourth quarter sales, up 169% from the year-ago period, and $3.8bn for 2017, up 172%. **Bristol-Myers Squibb Co.** has been guiding $4.9bn in annualized sales for its competing *Opdivo* (nivolumab).

The strength of Keytruda, *Bridion* (sugammadex) and the company's animal health division more than offset headwinds from the loss of patent exclusivity for products like *Zetia* (ezetimibe), *Vytorin* (ezetimibe/simvastatin) and *Remicade* (infliximab), as well as competition for *Zostavax* (Zoster vaccine), the company said.

In addition, US tax reform bodes well for growth in the years ahead. CEO Kenneth Frazier said the company is pleased that the US Congress and the administration enacted tax reform, which helps to "level the playing field for US-based companies and increases our financial flexibility by providing us access to overseas cash."

The impact of the new legislation to Merck in the fourth quarter was a $2.6bn provisional charge, which reflects a one-time transition tax of about $5bn on foreign earnings deemed to be repatriated, that was partially offset by changes in deferred tax liabilities, Chief Financial Officer Robert Davis said.

"While tax reform does not fundamentally change our capital-allocation priorities, it does improve our flexibility and enhances our ability to deploy capital in support of our strategy to invent new medicines that address key unmet medical needs, benefiting patients and driving sustainable long-term shareholder value," Davis said.

Consequently, in addition to funding its growing investment in R&D as well as seeking value-creating business development opportunities, Merck is planning $12bn in capital investments, about $8bn of which will be spent in the United States.

"We also remain committed to our dividend, which we increased for the seventh year in a row last November. Finally, to the extent we don't deploy capital towards business development deals over time, we look to return it to the shareholders," Davis said.

The company anticipates that the full-year non-GAAP tax rate in 2018 will be in the range of 19% to 20%, which is a few percentage points lower than what it would have been absent reform, said Adam Schechter, president of global human health.

Despite the tax reform benefit, the 2018 rate will be slightly higher compared with 2017 due to the onetime benefit in 2017 – tax items related to foreign tax credits – that will not repeat in 2018, execs explained. But beyond 2018, the company anticipates some "additional favorability" in the tax rate.

"If I was putting something out there, I'd say probably another percentage down from where we were going to be in 2018 as we move forward in '19 and beyond," Davis said.

Deutsche Bank analyst Jami Rubin noted during the earnings call question and answer portion that despite phenomenal news for Keytruda, Merck's shares have been flat for the last two years.

The company passed a major milestone in January when Keytruda demonstrated an overall survival benefit in combination with chemotherapy for first-line non-small cell lung cancer (NSCLC) in the pivotal KEYNOTE-189 study. But pivotal combination data for the same indication is due this year from Bristol and other competitors – **Roche**'s *Tecentriq* (atezolizumab) and **AstraZeneca PLC**'s *Imfinzi* (durvalumab) – so Keytruda's position in first-line NSCLC is subject to change.

Rubin questioned why, unlike its big pharma peers who are talking of consolidation, Merck has downplayed its interest in recent years for a transformational deal.

Frazier responded that the company is "actively engaged in looking for the best opportunities to enhance its pipeline." This includes looking at deals with all types of structures, including acquisitions and partnerships, collaborations and licensing.

"We also don't restrict ourselves as we do our scan across things based on size and structure and stage of development. We are looking for the best opportunity to create the strongest longer-term portfolio for Merck," Frazier said.

However, large transformational deals haven't "necessarily provided the ability to those companies when they finish their synergies to drive their pipelines going forward," he said.

"So I'm very much focused on what will allow this company to be a strong innovator five, 10 years from now. And if that kind of deal would help us do that, then I would look at it differently," the CEO added.

ONCOLOGY "PILLAR OF GROWTH"

Looking ahead, oncology will continue to be a "real pillar of growth," for Merck, execs said.

Schechter noted that 2017 was an "exceptional year" for the company's oncology franchise.

Currently in the US, more than 55% of Keytruda sales are in lung cancer, about 15% in melanoma, about 5% each for head and neck and bladder cancer.

In the US, Keytruda continues to lead new patient starts across nearly all indications and the company is building on its leadership position in metastatic lung cancer, with increased adoption of the combination of Keytruda with chemotherapy – **Eli Lilly & Co.**'s *Alimta* (pemetrexed) plus carboplatin in non-squamous patients, Schechter said. This was the combination tested in the KEYNOTE-189 study that just reported and was used in a Phase II study that supported accelerated approval for first-line NSCLC.

"Keytruda is the only I-O agent to show an overall survival benefit in the first-line setting as a monotherapy in high expressers and as combination therapy with Alimta and platinum chemotherapy in non-squamous patients in an all-comers population. Anecdotal feedback from physicians has been very positive, and they are looking forward to seeing the full results from the KEYNOTE-189 study," Schechter said.

Success in KEYNOTE-189 "should catalyze even broader use of this combination," the exec added.

In January, Lynparza was approved for a new indication in the second-line treatment of HER2-negative metastatic breast cancer in patients with a germline BRCA mutation.

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Managing Expectations: "We're Still On Target" Says AstraZeneca CEO

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With growing product sales and a bulging, promising pipeline, once-troubled **AstraZeneca PLC** looks to be on the road to recovery and 2018 will be a key year for that transition, according to CEO Pascal Soriot.

Presenting the group's fourth-quarter and full-year market update on Feb. 2, Soriot told analysts and reporters that 2017 "was indeed a turning point for us. We made encouraging progress across the entire company, certainly very much from a pipeline viewpoint, but it's also starting to show as far as commercial delivery. We had accelerated goals in the last quarter, and it bodes well for 2018."

He was speaking amid the glow of much-improved R&D productivity which has generated rising revenues, helping to offset painful generic drug competition.

Since 2011, AstraZeneca has seen a four-fold increase in research productivity, after a narrowing of disease focus and cuts in laboratory workers and staff. Its success rates for progression from candidate drug nomination to Phase III completion has increased from 4% in 2005-2010 to 19% in 2012-16, and that improvement has continued into 2017.

ANALYSTS APPLAUD

Analysts say that R&D renaissance – combined with expanding product launches - augurs well for a future which will concentrate on the three core therapeutic areas: respiratory, cardiovascular and metabolic disease, and oncology. For example, second-generation SGLT2 inhibitor *Farxiga* (dapagliflozin) and blood thinner *Brilinta* (ticagrelor) achieved blockbuster status and *Tagrisso* (osimertinib) reached $955m to become AstraZeneca's largest selling oncology medicine.

"Although 2017 remained a difficult year, AstraZeneca's sales performance improved throughout as its pipeline-driven transformation begins to manifest as launch products gained sales momentum across growth areas of oncology, respiratory and cardiovascular & metabolic disease, as well as in emerging markets," Datamonitor Healthcare analyst Edward Thomason told *Scrip*.

"Now in 2018, AstraZeneca looks ready to once again see growth reversing several years of consecutive product revenue decline caused by blockbuster expiries."

Bernstein analyst Tim Anderson agreed, adding: "AstraZeneca is at an inflection point in financials – revenue growth is returning in 2018 … the resumption of EPS [earnings per share] growth is not far away."

AstraZeneca flagged that 2018 will be a busy year in terms of pipeline flow. Bernstein's Anderson said, "the next 18 months will help define whether AstraZeneca has successfully been able to turn around what historically has been a weaker R&D track record, something not a lot of companies have been able to achieve."

Datamonitor Healthcare's Thomason added: "2018 will be a pivotal year for AstraZeneca as its launch drugs *Imfinzi* (durvalumab), *Tagrisso* (osimertinib), *Lynparza* (olaparib), and the recently approved *Fasenra* (benralizumab) grow and help offset the generic erosion of *Crestor* (rosuvastatin), which lost its blockbuster status in 2018 and continues to feel pressures in Europe and Japan. 2018 will also be a key year for the company's late-stage pipeline, with multiple pivotal clinical trial readouts and regulatory decisions that will lay the foundations for AstraZeneca's long-term recovery and outlook."

Sharing that confident outlook, CEO Soriot predicted AstraZeneca will hit its 2023 annual sales target, first projected in 2014 when it was fighting off an unwanted takeover from **Pfizer Inc.**

Since then a stronger dollar means the target has shifted slightly but Soriot said nothing had changed fundamentally.

"The $45bn target reflected the exchange rate of the day; the dollar has since strengthened so the $45bn [target] is now around $40.5 to $41bn [based on today's currency exchange rates]. If the dollar weakens it can go back closer to the $45bn but we are completely on track with the target that we set ourselves back in 2014," Soriot told reporters Feb. 2 when presenting the company's fourth-quarter and full-year update. "What we are doing is developing what I'd call our perfect portfolio for our strategy. We either divest a product or we partner it in the case of a new product and we continue investing in our core businesses and we build a perfect portfolio that's completely in line with our strategy," he told reporters.

FRAGILITY REMAINS

Still, the fragility of AstraZeneca's turnaround was underscored by reminders of just how uncertain drug discovery can be: the company quietly dropped three investigational drugs during the last quarter of 2017 due to poor clinical results: It discontinued developing tralokinumab, an investigational anti-IL-13 human immunoglobulin-G4 monoclonal antibody, in severe uncontrolled asthma; dropped asthma targeted AZD9898, and ended development of MEDI-573, a human antibody that neutralizes insulin-like growth factors which are overexpressed in multiple types of cancer.

"Everybody's very proud of the progress we've made, but there was no intent to declare victory," Soriot told analysts when asked whether he'd be advising rival pharma companies how to mend their R&D operations.

Sean Bohen, AstraZeneca's chief medical officer, echoed that cautious tone, adding that "going from mid-single-digit percent success of a candidate through to getting a drug to what looks like 20% in our more recent experience, this is great progress but it's not exactly declaring victory, because then 80% of the time you still fail."

"But we do feel like we're doing a lot better, and that that's playing out now in how our R&D investment is realizing into launches and market opportunities," Bohen said.

Soriot said it came down to execution.

"All of us can read the same cooking recipe. It doesn't make us a world-class chef," he said.

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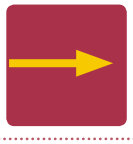

AstraZeneca Links With Alibaba And Tencent In China 'Digital Health' Push: http://bit.ly/2E7jls9

Bristol Debuts Opdivo/Yervoy Data In New First-Line Lung Cancer Bid

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Bristol-Myers Squibb Co. overshadowed its fourth quarter and full year 2017 results by previewing the long-awaited results of the CheckMate 227 study of its *Opdivo/Yervoy* combination in first-line lung cancer. But questions about the chances for approval on these early results may mean BMS waits until late this year or early 2019 for the overall survival data, leaving **Merck & Co. Inc.** an even larger window to stake its claim in the largest market for immuno-oncology.

The ongoing Phase III CheckMate 227 study showed that Bristol's PD-1 inhibitor Opdivo (nivolumab) and CTLA-4 inhibitor Yervoy (ipilimumab) demonstrated a "highly statistically significant" improvement in progression-free survival (PFS), compared to chemotherapy, in first-line non-small cell lung cancer (NSCLC) patients who have high tumor mutation burden (TMB), regardless of PD-L1 expression status. Bristol got permission from the US FDA to alter the endpoint for this arm of the trial to focus on high TMB patients, using 10 mutations per megabase as the cutoff.

Bristol tried to argue during the Feb. 5 investor call that the TMB data represents a way forward for approval of the Opdivo/Yervoy combo in first-line NSCLC, but analysts generally think Bristol will need overall survival (OS) data to file the combo for approval.

The Opdivo/Yervoy combination is Bristol's last, best shot at the first-line NSCLC market, as Opdivo monotherapy faced a stunning defeat in the setting in 2016 in the CheckMate 026 trial. *(Also see "'Total Disaster' In First-Line Lung Cancer For BMS's Opdivo" - Scrip, 10 Oct, 2016.)*

And where BMS has met with failure, competitor Merck has found success with its anti-PD-1 agent *Keytruda* (pembrolizumab). Not only did it gain the first approval for monotherapy with an IO drug in first-line lung cancer in 2016, a few months later it gained the first combination approval in the lucrative market for Keytruda plus chemotherapy. *(Also see "Keytruda/Chemo Combo Approval Means Merck Holds Crown, For Now" - Scrip, 10 May, 2017.)* (An ongoing part of CheckMate 227 is looking at Opdivo plus chemotherapy.)

Bristol Chief Scientific Officer Tom Lynch told the earnings call that the results provided a further validation of the role for anti-CTLA4 therapy in combination with Opdivo, as the third tumor type where a benefit has been shown using the Opdivo/Yervoy combo. The data also help establish TMB as a biomarker.

Over the past 30 years, Lynch said, "lung cancers [have] become a group of related diseases defined by distinct biomarkers that drive biology and treatment – EGFR, ALK, ROS 1, RET and PD-L1, just to name a few. Today, we add TMB to this list to define a subtype of patients who clearly derive benefit from combination immunotherapy treatment regardless of their PD-L1 status."

The Opdivo/Yervoy combination already is approved for melanoma and is under FDA review for first-line renal cell carcinoma.

Lynch stressed the contribution coming from Yervoy; Bristol is the only firm to have both a PD-1 and CTLA-4 asset on the market, although **AstraZeneca PLC** has its CTLA-4 agent tremelimumab in development, including combination trials with its own PD-L1 inhibitor *Imfinzi* (durvalumab). "Our analysis of the data thus far makes us very confident that Yervoy is a big part of what we're seeing today," Bristol's CSO said. "It's not just Opdivo, but Yervoy is part of this as well."

The lower dose being used, every six weeks, is well tolerated, Lynch noted. Yervoy has more safety issues than the PD-1/L1 checkpoint inhibitors.

In a same-day note headlined "Nice Save, But Tough Road Ahead," BMO Capital Markets analyst Alex Arfaei said revising the endpoint was a risky move for Bristol, but better than the alternative if it would have failed the trial otherwise.

BRISTOL'S LEAD OVER MERCK DISSIPATING

In the interim, Merck has been able to make up much of Bristol's early lead in the PD-1/L1 space, executing quite well in the first line NSCLC market. *(Also see "Merck's Keytruda Claims Market Leadership In First-line Lung Cancer" - Scrip, 30 Jul, 2017.)* More time unopposed should allow it to further entrench, and Opdivo's continued lead has shown the importance of being first, delivering well and moving into new markets.

But recent quarters are showing changing dynamics. Sales figures show that while Opdivo's sales roughly doubled Keytruda's from the third quarter of 2015 through the first quarter of 2017, Merck's second-to-

market anti-PD-1 has made up significant ground, drawing almost level in net sales during the fourth quarter of 2017: $1.36bn for Opdivo to just under $1.3bn for Keytruda. (*See chart.*)

WHERE DOES THIS LEAVE BRISTOL?

Despite the promise of the TMB data, BMO's Arfaei said Bristol remains a couple years behind Merck in first-line lung. "We highly doubt that Bristol can file based on TMB PFS results; it will likely have to wait for OS data in late 2018/early 2019, suggesting that Bristol will not get to the first-line NSCLC market until late 2019/early 2020, giving Merck plenty of time to get established," he added.

Morningstar analyst Damien Conover, however, does expect the combination to gain approval based on unmet need.

Conover envisions a scenario in which Merck and Bristol split much of the first-line NSCLC market, with Merck dominant among PD-L1-expressing patients and Bristol winning over high-TMB patients with low PD-L1 expression. Conover said in a Feb. 5 note that the latter cohort might comprise 25% of the first-line NSCLC space. Despite the lack of OS data, "we expect the combination will gain approval based on the unmet need in this lethal cancer," he added.

"While the immuno-oncology first-line NSCLC market remains highly competitive with Merck securing the first-mover advantage and **Roche** following quickly behind [with its PD-L1 inhibitor *Tecentriq*], Bristol's unique positioning with a combination treatment (using CTLA-4 drug Yervoy) and the prospective identification of TMB should enable the firm to gain share despite a later entrance to the first-line NSCLC market," Conover said. He also predicted that OS data in the PD-L1-positive patients should report out in late 2018 or early 2019.

Seamus Fernandez of Leerink Partners called the data "a clear win" for Bristol, citing management's stated optimism that the combo would also show an OS benefit in the PD-L1-positive cohort. A labeling indication for patients with high TMB could be lucrative for Bristol, Fernandez wrote Feb. 5, given projections that 45% of first-line NSCLC patients may fall into that category, regardless of PD-L1 status. He added that Bristol is continuing to follow the high-TMB patients for OS as a secondary endpoint.

Morningstar expects Bristol will wind up with a quarter of the $12bn NSCLC market. "While NSCLC holds the most potential in immuno-oncology, Bristol's strong competitive positioning in renal, liver and small-cell lung cancer should lead to close to $3bn in sales," Conover said.

ELIQUIS, OPDIVO LEAD SOLID COMMERCIAL PERFORMANCE

Overall, 2017 was a strong year for Bristol, CEO Giovanni Caforio said, as its full-year sales grew 7% to $20.8bn, with fourth quarter revenue up 4% to $5.4bn. US business posted a strong quarter during the final three months of 2017, with sales rising 7% to $2.9bn. However, international sales stagnated, rising 1%, but down 3% when impacts from foreign exchange were factored in.

Leading the way for Bristol was anticoagulant *Eliquis* (apixaban), whose full-year sales rose 46% to $4.9bn. Opdivo was another winner, increasing 31% to $4.9bn, while Yervoy yielded solid 18% growth to $1.2bn.

For 2018, Bristol projects a tax rate of between 20% and 21%, saying that the impact of US tax reform has been neutral for it in the early going. However, the firm expects its tax rate to dip into the high teens in the next few years, as the law takes effect. Analyst Vamil Divan of Credit Suisse pointed out in a Feb. 5 note that the rate's midpoint of 20.5% "is higher than peers, but in-line with what we believe investors were expecting after the company commented on Jan. 5 that the impact of tax reform would be 'roughly neutral'" to its expected 2018 tax rate.

Bristol reported $9.3bn in cash at the end of 2017 and Caforio said business development remains a priority, but did not offer specifics.

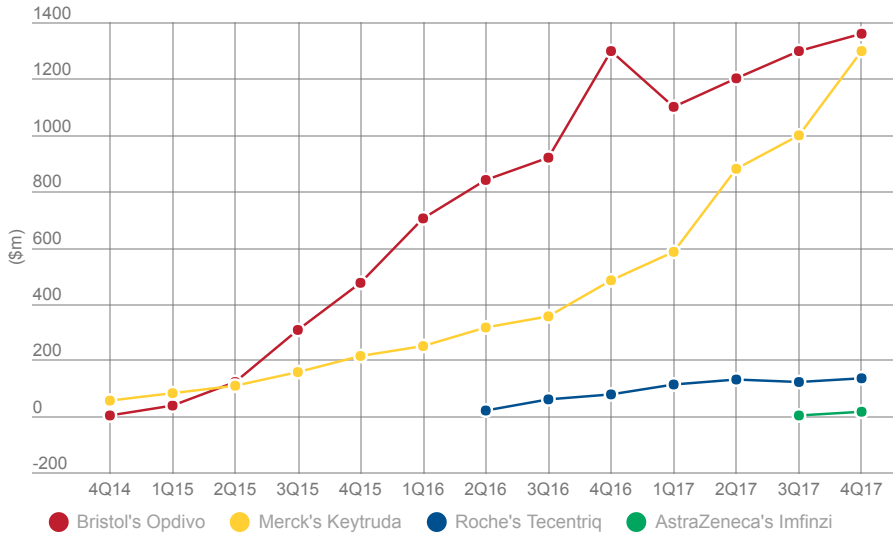
"A year ago, I spoke about the work we were doing to evolve our operating model. And today, I'm pleased to say we are delivering across the company with a disciplined approach to resource allocation," the exec told the earnings call. "We are creating a better company, which moves fast and is more competitive. We are strengthening our capabilities, particularly in translational medicine. And we are investing in our pipeline and commercial capabilities to support future growth. This will continue to be a critical focus going forward."

The switch to looking at TMB in CheckMate 227 is an example of the company moving quickly. BMS has presented data supporting TMB's value in other trials last year, but despite pressure from investors and analysts, had not publicized it was applying it to the ongoing CheckMate 227 trial. *(Also see "A Biomarker For Bristol: Mutation Burden Shows Promise In Small Cell Lung Cancer" - Pink Sheet, 16 Oct, 2017.)* It turns out Bristol was working on that complicated change with the FDA.

"Based on our understanding of this disease, we made bold and innovative changes to our program as the science evolved. Today's results validate our approach," Caforio said.

Published online 5 February 2018

Sales Of PD-1/L1 Inhibitors



Lilly/BI's Basaglar: A Rosier Outlook For US Biosimilars?

JESSICA MERRILL jessica.merrill@informa.com

Eli Lilly & Co. and **Boehringer Ingelheim GMBH** have had notable commercial success with the launch of *Basaglar* (insulin glargine), a copy of **Sanofi**'s blockbuster *Lantus*. After launching in the US in late 2016, the insulin generated $311.1m in the US and $432.1m globally in 2017, a strong showing for a new drug launch and particularly in an emerging area like follow-on biologics.

"We have seen excellent uptake," Lilly Diabetes and Lilly USA President Enrique Conterno said during the company's fourth quarter earnings call Jan. 31. "We're now basically capturing about 25% of the new patients in the basal insulin class, so we are excited about the growth prospects."

Lilly/BI's early success with Basaglar is quite different from the story that has unfolded with **Pfizer Inc.**'s *Inflectra* (infliximab-dyyb), a biosimilar version of **Johnson & Johnson**'s *Remicade* (infliximab). Inflectra, partnered with **Celltrion Inc.** generated just $118m in its first year on the market, with uptake curbed by what Pfizer has called exclusionary contracting on the part of J&J.

There are big differences between the two examples of course. Most notably, Basaglar is not officially a biosimilar, because insulins were not originally approved as biologics. Thus, Basaglar was approved by the FDA through a separate NDA via the 505(b)(2) pathway rather than through the 351(k) pathway for biosimilars. It launched in December 2016 after Lilly worked out a patent settlement with Sanofi.

Despite Lilly's early commercial success with Basaglar, it's not clear how the revenue gains are translating to the bottom line, given that the company has offered steep rebates to secure preferred formulary access over Lantus in some cases. *(Also see "UnitedHealthcare Prefers Basaglar Biosimilar At Lantus' Expense" - Scrip, 22 Sep, 2016.)*

"We do have high rebates," Conterno acknowledged during the earnings call. Lilly launched Basaglar at a discount of 15% to 20% versus Lantus initially.

Additionally, the growth might not be sustainable long-term if more Lantus copies reach the market, as expected. **Merck & Co. Inc.** and its development partner **Samsung Bioepis Co. Ltd.** have one that was tentatively approved by the FDA in July; the launch is delayed pending a patent dispute resolution with Sanofi. *(Also see "Merck's Lantus Copy Lusduna Poised For US Market Pending Litigation" - Scrip, 20 Jul, 2017.)* **Mylan NV** also has a version of insulin glargine under review at FDA; it was just approved in Europe.

Meanwhile, Lilly is poised to face its own biosimilar competitor in Sanofi, which is launching *Admelog* (insulin lispro), a follow-on to Lilly's *Humalog*, which generated $1.72bn in the US and $2.87bn worldwide in 2017.

Basaglar is one of the new drugs that is expected to drive growth for Lilly as its diabetes portfolio comes under more pricing pressure. Among the other high-profile growth drivers are the GLP-1 *Trulicity* (dulaglutide) for diabetes, *Taltz* (ixekizumab) for atopic dermatitis and psoriatic arthritis, the breast cancer drug *Verzenio* (abemaciclib) and the SGLT-2 inhibitor *Jardiance* (empagliflozin). All of these drugs are in categories crowded with multiple rivals, however.

Two of the newest launches are the IL-17 inhibitor Taltz and the CDK-4/6 inhibitor Verzenio. Taltz is competing against the well-entrenched *Cosentyx* from **Novartis AG**, while Verzenio is going up against **Pfizer Inc.**'s fast mega-blockbuster *Ibrance* (palbociclib) as well as a newer entrant from Novartis, *Kisqali* (ribociclib). Taltz generated $559.2m in 2017, its first full year on the market. Verzenio generated $21m after launching in the fourth quarter.

TAX REFORM AND REBATE POLICY

Like many other US-based drug manufacturers, Lilly stands to benefit from US corporate tax reform. The company said it expects its corporate tax rate to be lower in 2018 at 18% from prior guidance of 21.5%.

As a result of the tax legislation, Lilly said it now estimates it will have access to more than $9bn in cash and investments.

"We do not intend to hold this $9bn of cash and investments for the long-term," CFO Joshua Smiley said "Over the course of 2018 and 2019, we'll deploy this cash thoughtfully across our capital allocation priorities." That will include capital investments, pipeline development, business development and returning cash to shareholders, he added.

"We do have ambition to step up our game in BD," CEO David Ricks noted. Phase I and Phase II assets are the sweet spot for target. "It's because that's where Lilly is relatively underrepresented, and there's a lot more to go after a price points we think are attractive."

On the policy front, Ricks also sounded enthusiastic about initiatives in the US to bring the rebate to patients at the pharmacy counter. It's a policy issue the Centers for Medicare & Medicaid Services (CMS) is currently reviewing although there is a lot of disagreement across the different factions of the industry about how that could impact health care spending. ([A#PS122343]

Pharmaceutical manufacturers tend to have a more favorable view of changing the current rebate practice, while pharmacy benefit managers generally say it would increase insurance premiums.

Ricks came out strong on the fourth quarter call in full support of the change.

"Not passing through the rebates subjects the very ill to the cost burden versus spreading that over a much larger base," he said. "We think that's what insurance is for, and therefore we advocate for it."

"To me, it is one of the simplest levers to pull to actually change the cost at the pharmacy counter for drugs in America, and I think the US should do it," he said.

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10 First Approvals To Look Out For In 2018

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With barely time to draw breath after its record-breaking approval tally in 2017, the US FDA has moved headlong into another busy year with around 40 user fee dates falling in 2018. Here *Scrip* takes a look at those products heading towards first approval that have potential to disrupt their particular markets.

The field set for the biggest shake up is migraine with the initial three products nearing approval from the first major new drug class since the triptans – the calcitonin gene-related peptide (CGRP) antagonists. Biopharma analysts forecast the overall global migraine prevention market for CGRP drugs could reach $6-7bn.

But as the triptans are now off patent, there are questions over payers' willingness to pay for the new wave of products despite their considerable promise in targeting a specific migraine mechanism and their prophylactic efficacy. The large migraine patient population and the high unmet need for new therapies concern payers worried about how the high volume might impact costs.

AMGEN/NOVARTIS'S AIMOVIG

Novartis AG and **Amgen Inc.** were first to file for approval of a CGRP therapy in the US and EU and as such are likely to set the bar on pricing, following a first-in-class launch in 2018, with *Aimovig* (erenumab). The PDUFA target date is May 17. Novartis is reported to be considering a value-based reimbursement scheme that would target erenumab to patients that respond best to therapy.

Erenumab is set apart, Novartis says, as it is the only antimigraine antibody that is fully human, and targets the CGRP receptor as opposed to the ligand. Analysts at Jefferies expect erenumab to be launched in the second half of 2018, and to achieve sales of $701m in 2021, with sales peaking at $1.5bn.

TEVA'S FREMANEZUMAB

Rival **Teva Pharmaceutical Industries Ltd.** deployed a priority review voucher to speed the review of the BLA for its product fremanezumab, making it the closest to catching the Novartis/Amgen product. The company filed a biologic license application (BLA) with the FDA in October and the PDUFA date is slated for June 15.

Teva spent up to $150m to acquire a priority review voucher from an undisclosed seller in Q3 2017 and redeemed it for fremanezumab for preventive treatment of migraine; the BLA submission was announced in October.

Fremanezumab's differentiating feature is its potential for quarterly dosing, as opposed to monthly dosing for its competitors. Data from the Phase III HALO study showed similar efficacy to monthly dosing when fremanezumab was administered every three months in chronic migraine patients.

ELI LILLY'S GALCANEZUMAB

Now left in fremanezumab's wake, a verdict from the FDA for **Eli Lilly & Co.**'s galcanezumab is expected in October following FDA acceptance of a BLA on Dec. 11, 2017. In the Lilly product's favor is the fact that it may be complemented by another of its offerings, the oral acute migraine product lasmiditan, to offer to treating physicians a one-stop-shopping opportunity across multiple headache indications. Lasmitidan is expected to be filed in the second half of 2018.

Last May when positive data from three pivotal galcanezumab studies (EVOLVE-1, EVOLVE-2 and REGAIN) were released, analysts at Leerink predicted around a $1bn in peak sales for the product, although at that time it was still expected to be second to market.

GILEAD'S BICTEGRAVIR

A priority review voucher (purchased from **Sarepta** on the back of approval of its Duchenne muscular dystrophy product *Exondys 51*) is also being used to accelerate the approval process for **Gilead Sciences Inc.**'s fixed-dose combination of bictegravir, a novel investigational integrase strand transfer inhibitor, and emtricitabine/tenofovir alafenamide, a dual-NRTI backbone, for the treatment of HIV-1 infection in adults. The user fee goal date for the product, abbreviated as B/F/TAF, is Feb. 12, 2018.

Pending a favorable FDA decision, Datamonitor Healthcare is forecasting peak sales of $5.8bn for B/F/TAF across the US and five major EU markets which would stabilize Gilead's overall HIV franchise, which is facing several patent expirations in the next five years.

In May 2017, the US FDA granted Orphan Drug designation to B/F/TAF, once-daily single tablet regimen, for the treatment of HIV-1 infection in pediatric patients. Shortly after, in August, Gilead Sciences announced that the FDA had granted the NDA a priority review. Meanwhile, an EU Marketing Authorization Application for B/F/TAF was validated in July 2017, and is now under evaluation by the EMA.

Currently, B/F/TAF has an advantage over other protease inhibitor regimens on the market, as bictegravir does not require boosting (addition of another drug such as ritonavir or cobicistat to raise circulating levels). If approved, B/F/TAF is likely to be more attractive than *Triumeq* (dolutegravir/abacavir/lamivudine) due to safety concerns with abacavir.

THERATECHNOLOGIES' AND TAIMED BIOLOGICS' TROGARZO

Another novel HIV drug expecting an approval decision is **Theratechnologies Inc.**'s and **TaiMed Biologics Inc.**'s *Trogarzo* (ibalizumab), a humanized anti-CD4 antibody selected to allow CD4 function while simultaneously inhibiting entry of HIV into CD4+ T cells. With its novel mechanism of action, ibalizumab has the potential to become the first FDA-approved monoclonal antibody for the treatment of HIV/AIDS.

The product is targeted at patients who no longer respond to conventional oral HIV therapies, a market which is estimated to be about 20,000 to 25,000 patients in the US. The BLA submission is based on results from the single-arm Phase III TMB-301 trial of ibalizumab in combination with an Optimized Background Regimen (OBR) of antiretroviral medications selected based on treatment history and the results of viral resistance and tropism testing, where it showed impressive efficacy.

Trogarzo's original user fee date was Jan. 3, but that was extended to April 3 when the FDA requested additional chemistry, manufacturing and controls (CMC) information in late November. However, Theratechnolo-

gies believes approval could happen before April based on its ongoing dialog with the agency. The application has been granted Priority Review. Additionally, ibalizumab has received Orphan Drug and Breakthrough Therapy Designation for HIV/AIDS.

Analysts at Echelon Wealth Partners assume that ibalizumab will be launched in the first half following a first-quarter approval and that it will generate 2018 gross revenues in the US market of Can$19.2m, increasing to Can$64.6m in 2019 and then to Can$130.4m in 2020. Sales in 2023 could reach Can$500m.

J&J'S APALUTAMIDE

Just as **Johnson & Johnson**'s blockbusting prostate cancer therapy *Zytiga* (abiraterone acetate) is expected to be hit by generic competition later this year in the US, the company is looking to an approval for apalutamide to extend the franchise. Apalutamide is an androgen receptor antagonist being developed for the treatment of men with non-metastatic castration-resistant prostate cancer (nmCRPC). The NDA was granted Priority Review designation and an approval decision from the FDA is expected in April. J&J is hoping EU regulators will follow the US in fast-tracking the drug.

If successful, apalutamide will become the first targeted therapy specifically indicated for use in the nmCRPC population. The filing was based on data from the Phase III SPARTAN trial in which treatment with apalutamide led to improvements in metastasis-free survival in chemotherapy-naïve nmCRPC patients with rapidly rising prostate-specific antigen levels despite receiving continuous androgen deprivation therapy (ADT). Janssen will present the data during an oral presentation at the ASCO Genitourinary Cancers Symposium later this month.

It will have competition though. **Astellas Pharma Inc.**'s *Xtandi* (enzalutamide), also an androgen receptor antagonist, was approved in 2012 to treat late-stage (metastatic) castration-resistant prostate cancer that has spread or recurred and Astellas is expecting to submit a sNDA for nmCRPC in the first half of 2018. Another late-stage androgen receptor inhibitor being developed for nmCRPC is Bayer's darolutamide which is expected to enter the market in 2019.

Nevertheless, apalutamide is positioned to be the first agent approved to treat nmCRPC and Datamonitor Healthcare is forecasting label expansions based on ongoing Phase III trials that will propel apalutamide sales to $385m in 2026.

MERCK AND SUN'S TILDRAKIZUMAB

In May 2017, **Sun Pharmaceutical Industries Ltd.** announced that the FDA had accepted the BLA submitted by **Merck & Co. Inc.** for tildrakizumab, a monoclonal antibody inhibitor of IL-23 targeting the P19 subunit being evaluated for the treatment of moderate-to-severe plaque psoriasis. Allowing for the standard 12-month review period, the estimated PDUFA date is expected to fall between March and April. Additionally, an MAA for tildrakizumab was validated in March 2017, and is now under evaluation by the EMA.

Tildrakizumab has the potential to control the pathogenic cells responsible for systemic inflammation in psoriasis with limited impact on the immune system due to its ability to target IL-23 selectively. It follows Johnson & Johnson's IL-23 inhibitor, *Tremfya* (guselkumab), which was approved for psoriasis in July 2017, while AbbVie's risankizumab, a third IL-23 inhibitor, is expecting US regulatory submissions for psoriasis in the first half of 2018.

Datamonitor Healthcare forecasts that these three IL-23 inhibitors, which all target the P19 subunit, will create more treatment options for psoriasis, but will also lead to the psoriasis market becoming increasingly saturated which could limit their commercial prospects.

Overall, the psoriasis market is expected to experience downward pressure from the arrival of biosimilars of AbbVie's *Humira* (adalimumab) and the other key marketed anti-tumor necrosis factor (TNF) products **Pfizer Inc.**/Amgen's *Enbrel* (etanercept) and Johnson & Johnson's *Remicade* (infliximab), but analysts at Datamonitor Healthcare still expect market value in the US, Japan, and five major EU markets to increase from about $8.8bn in 2016 to $9.4bn in 2025.

The BLA filing for tildrakizumab is based on two pivotal Phase III trials (reSURFACE 1 and 2).)

PORTOLA'S ANDEXXA

Portola Pharmaceuticals Inc. is expecting finally to receive FDA approval for the Factor Xa anticoagulant reversal agent *AndexXa* (andexanet alfa) on Feb. 2 after it announced last August that the FDA had accepted its resubmitted BLA for its use as a reversal agent in patients who have uncontrolled or life-threatening bleeding while taking the two leading Factor Xa inhibitors – **Bristol-Myers Squibb Co./Pfizer Inc.**'s *Eliquis* (apixaban) and **Johnson & Johnson/Bayer AG**'s *Xarelto* (rivaroxaban).

The company resubmitted the application after a complete response letter from the FDA that cited manufacturing issues among other things.

Of the five novel oral anticoagulants now approved by the FDA, four are Factor Xa inhibitors. In addition to Eliquis and Xarelto, FDA has cleared **Daiichi Sankyo Co. Ltd.**'s *Savaysa* (edoxaban) and Portola's own *Bevyxxa* (betrixaban), which was approved in June for a niche indication for patients hospitalized for acute medical illness and at risk of thromboembolic events. **Boehringer Ingelheim GMBH**'s direct thrombin inhibitor *Pradaxa* (dabigatran) was the first on the market in 2010.

The lack of a reversal agent for these drugs is a concern for doctors who may need to reverse the anticoagulation effects of these medications in cases of emergency bleeding or surgery. This worry is thought to have hindered the uptake of the Factor Xa inhibitors.

The resubmission includes supplemental information primarily related to analytics and manufacturing, as requested by the FDA in the complete response letter. It also includes additional data from the ANNEXA-4 study of patients with Factor Xa inhibitor-related bleeding.

RIGEL'S TAVALISSE

Another product with a difficult past is **Rigel Pharmaceuticals Inc.**'s *Tavalisse* (fostamatinib). The company had to downsize in order to marshal its resources to bring the oral spleen tyrosine kinase (SYK) inhibitor to market after mediocre clinical results in chronic or persistent immune thrombocytopenic purpura (ITP).

It was granted an orphan designation in August 2015, and the FDA accepted a filing in June 2017, with a PDUFA target action date of April 17, 2018. Previously, the FDA communicated to Rigel that it planned to hold an Advisory Committee meeting to review the Tavalisse application but reversed this decision in September 2017.

The NDA is supported by data from three Phase III FIT trials of Tavalisse in ITP. Two

CONTINUED ON PAGE 23

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

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

Selected clinical trial developments for the week 26 January–1 February 2018

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
Phase III Results Published			
Novartis AG	*Kymriah* (tisagenlecleucel)	acute lymphoblastic leukemia, B-cell	ELIANA (pivotal Phase I/II); *NEJM*, Feb. 1, 2018.
Novo Nordisk AS	*Ozempic* (semaglutide)	diabetes, type 2	SUSTAIN-7; *The Lancet Diabetes & Endocrinology* online; Jan. 31, 2018.
Sumitomo Dainippon Pharma Co. Ltd.	napabucasin	colorectal cancer	*The Lancet Gastroenterology & Hepatology* online, Jan. 31, 2018.
Phase III Interim/Top-line Results			
AstraZeneca PLC	glycopyrronium/ budesonide/formoterol inhaler	chronic obstructive pulmonary disease	KRONOS; improved lung function, vs dual combinations.
Johnson & Johnson	*Stelara* (ustekinumab)	axial spondyloarthritis	Studies stopped due to endpoints missed in related study.
Meiji Seika Pharma Co. Ltd./Eisai Co. Ltd./ Newron Pharmaceuticals SPA	safinamide	Parkinson's disease	Primary endpoint met in Japanese study.
Updated Phase III Results			
Sumitomo Dainippon Pharma Co. Ltd.	APL-130277 (apomorphine) sublingual film	Parkinson's disease	CTH-300; met endpoints, well tolerated.
Phase III Initiated			
Bayer AG	molidustat	anemia due to chronic renal failure	MIYABI HD-C; in dialysis independent patients.
Roche	*Tecentriq* (atezolizumab)	breast cancer, triple negative	IMpasssion132; in relapsing recurrent disease.
BeiGene (Beijing) Co. Ltd./ Celgene Corp.	tislelizumab	esophageal squamous cell cancer	An anti-PD-1 antibody.
Cara Therapeutics Inc.	*Korsuva* (CR845/ difelikefalin)	pruritus associated with chronic kidney disease	KALM-1; in hemodialysis patients.
Medeor Therapeutics Inc.	MDR-101, a cellular immunotherapy	kidney transplant rejection	To induce immune tolerance.
Updated Phase II Results			
MediciNova Inc.	MN-166 (ibudilast)	multiple sclerosis, progressive	SPRINT-MS; reduced disability progression.
TG Therapeutics Inc.	ublituximab	multiple sclerosis	Depleted B-cells, efficacy signs.
Oncology Venture APS	*LiPlaCis* (cisplatin) liposomes	metastatic breast cancer	Clinical benefits observed.
Vaxart Inc.	H1 influenza tablet vaccine	flu prophylaxis	Reduced rate of infection.
Abeona Therapeutics Inc.	EB-101, gene- corrected autologous cell therapy	epidermolysis bullosa	Improved wound healing.
PTC Therapeutics Inc./Roche	RG7916	spinal muscular atrophy	SUNFISH; efficacy signs.
ChemoCentryx Inc.	CCX872	pancreatic cancer	Signs of improved survival.

Source: Biomedtracker

CONTINUED FROM PAGE 21

are small randomized placebo-controlled studies (Studies 047 and 048) and one is an open-label extension study (Study 049). While results from one of the Phase III trials did not meet statistical significance, this was due to one additional responder in the placebo group, and overall results from the studies appeared similar (18% of Tavalisse treated patients achieved a sustained response [SR] in each study, compared with 0% and 4% of the placebo groups). Hence, there was some question whether the FDA would accept a combined analysis that was highly statistically significant, but given the consistent results and the FDA's decision not to hold an advisory committee meeting, it is likely the drug will be approved, say analysts at Biomedtracker.

The benefit of Tavalisse was modest, though the treatment population had experienced at least one previous ITP therapy, including one-third of patients undergoing prior splenectomy, the only potentially curative treatment, the analysts note.

Tavalisse addresses the root cause of ITP by interfering with the signaling that occurs when antibodies to the platelets bind to immune cells. Hence, it could be a useful alternative or adjunctive treatment in some patients to other therapies that stimulate platelet production or modulate the immune system differently.

ABBVIE'S ELAGOLIX

AbbVie Inc. estimates that its women's health drug, the oral gonadotropin-releasing hormone (GnRH) antagonist elagolix–partnered with **Neurocrine Biosciences Inc.** – could bring in more than $2bn in annual sales by 2025 in the treatment of endometriosis and uterine fibroids.

Elagolix has been granted priority review for the management of endometriosis with associated pain with a PDUFA date of May 4. Assuming positive results, AbbVie anticipates submitting a supplemental US NDA submission for elagolix in the treatment of uterine fibroids in 2019. There have been no new treatments for endometriosis-associated pain in well over a decade, but competition is hotting up.

Elagolix is seen as an alternative to injected peptide GnRH receptor inhibitors such as AbbVie's *Lupron* and Allergan's *Trelstar*. While there are no FDA-approved agents for long-term medical treatment of uterine fibroids, Lupron was approved in 1990 for temporary (up to three months) preoperative use to reduce uterine fibroid-related blood loss and to correct the ensuing iron-deficiency anemia.

Elagolix has two competitors in **Myovant Sciences Ltd.**'s GnRH antagonist relugolix (in Phase III for both endometriosis and uterine fibroids) and **Allergan PLC**'s oral selective progesterone receptor modulator ulipristal acetate (*Ella*), which is already approved in Europe for the treatment of uterine fibroids and has an NDA pending at FDA; a decision is expected in the first half of 2018.

AbbVie is currently conducting two replicate Phase III studies evaluating the efficacy and safety of elagolix in combination with estradiol/norethindrone acetate for the management of heavy menstrual bleeding associated with uterine fibroids in premenopausal women and data are due to report in the first quarter. The addition of estradiol add-back is to prevent side effects such as hot flashes and loss of bone mineral density. The two studies, M12-815 and M12-817, have enrolled 400 and 385 patients, respectively.

Published online 2 February 2018

Stada Arzneimittel AG has appointed ***Peter Goldschmidt***, who heads the North American operations of Novartis generics unit Sandoz to take over as chief executive officer from ***Claudio Albrecht***. The industry veteran, who has held various leadership positions in Europe, Asia and the US over the past 28 years, will join the German group on Sept. 1 when Albrecht, who took over as CEO at the end of September, will take up a pre-planned non-executive position. Goldschmidt, a German national, will be the fifth CEO in less than 18 months for Stada, which was acquired by the private equity firms Bain Capital and Cinven Partners last year.

David Kendall is joining **MannKind Corp.** to become its chief medical officer. Most recently, he served as research physician and vice president of global medical affairs for Lilly Diabetes and prior to joining Eli Lilly, he was chief scientific and medical officer at the American Diabetes Association.

Astellas Pharma Inc. has chosen ***Kenji Yasukawa*** to succeed ***Yoshihiko Hatanaka*** as president and CEO. Currently chief strategy and chief commercial officer, the Japanese drugmaker said Yasukawa has more than 30 years of experience in the pharmaceutical industry. Hatanaka will become chairman of the board.

At **Novo Nordisk AS**, ***Jesper Brandgaard*** will step down as chief financial officer on Feb. 15, to be replaced by ***Karsten Munk*** Knudsen, who is currently senior vice president of corporate finance. Brandgaard will continue as executive vice president responsible for biopharm and legal affairs. The Danish drugmaker also noted that Goran Ando, chairman of the board of directors, has decided not to seek re-election at the annual general meeting in March, and current board member Helge Lund has been proposed to replace him.

Wolfgang Baiker has been named as **Boehringer Ingelheim Pharmaceuticals Inc**.'s US president and CEO, succeeding ***Paul Fonteyne***. Currently senior vice president, human pharma supply and global quality and head of the biopharma business unit, Baiker has been with the company for 29 years. Fonteyne, who is to retire at the end of 2018, will remain as chairman of the Boehringer USA board.

Dova Pharmaceuticals Inc. has named ***Mark Hahn*** as its CFO, replacing Doug Blankenship who has agreed to step down. Hahn was CFO at Cempra from 2010 until it was acquired by Melinta Therapeutics in November last year, where he spearheaded the company's initial public offering and follow-on financings, raising over $500m over seven years.

Poland's **Selvita SA** has appointed ***Steffen Heeger*** to the role of chief medical officer. Previously, he was head of clinical development and operations at Morphosys AG and also had a nine-year tenure at Merck Serono as head of medical affairs.

UK gene therapy specialist **Orchard Therapeutics** has added ***Harry Malech*** to its scientific advisory board. He is currently deputy chief of the Laboratory of Clinical Immunology and Microbiology and chief of the Genetic Immunotherapy Section at the National Institute of Allergy and Infectious Diseases.

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