Shire PLC has confirmed it has received another revised acquisition proposal from determined suitor Takeda Pharmaceutical Co. Ltd., which ups the Japanese company’s offer from the equivalent of £47 per ordinary share to around £49 per share.

The deal, if agreed, would value Shire – which currently exceeds Takeda’s roughly $33bn market capitalization by some $17bn – at around £46bn ($64.3bn). However, certain conditions and due diligence remain to be completed, meaning that formal finalization could take several more weeks, assuming no other bidders come forward.

Takeda shares slid by around 5% in early trading in Tokyo on April 25, apparently on ongoing investor concerns over how the deal will be financed and its effect on Takeda’s debt, credit status and share dilution. They had slumped by around 7% by mid-afternoon, potentially further complicating the share component of the acquisition and meaning that more Takeda stock may need to be offered.

Reports in Japan have suggested that a consortium of banks in Japan is planning to offer Takeda several trillions of yen in bridge loans, but concerns that the company may be biting off more than it can chew financially have led to its shares falling about 18% overall since it first disclosed discussions with Shire, which has seen its own valuation surge.

“The Board of Shire has indicated to Takeda that it would be willing to recommend the Revised Proposal to Shire shareholders, subject to satisfactory resolution of the other terms of the possible offer,” Takeda said in a statement.

The company had disclosed late on April 24 in Japan that it had made another revised offer, following its latest and fourth, of £47 per share. (Also see “Sweet Enough? Takeda Raises, Adds Cash To Shire Offer” – Scrip, 22 Apr, 2018.)

**DISCUSSIONS**

Takeda confirmed that its new revised proposal comprises 0.839 new Takeda shares (to be issued in Japan and as ADRs in the US) and $30.33 in cash per Shire share. Based on Takeda’s share price at the time and current exchange rates, this implies an offer of around £49 per Shire share (comprising £27.26 in new Takeda shares and £21.75 in cash).

The cash component remains around 44% of the total, despite some analysts saying Takeda may have to further raise this percentage to make an offer more attractive.

Existing Shire shareholders would also be entitled to any dividends paid by Shire prior to the completion of any final transaction, and would own around 50% of the merged operation.

The two companies said they would continue to engage in discussions, and Takeda stressed that any firm offer remains subject to agreement of certain other terms, completion of due diligence, and final approval by its own board.

The deadline for an offer under the UK takeover code (under which Shire falls) has now been extended from April 25 to 5pm UK time on May 8, and may be further extended with regulatory and Shire’s consent.

Published online 24 April 2018
If an industry has multiple companies launching similar products at around the same time, what does that say about the efficiency and cost-effectiveness of the industry itself? If those products are highly expensive and yet important for society, is it reasonable for the companies to continue to expect people to accept high prices?

Jessica Merrill’s analysis of the rate at which second and subsequent therapeutics in a particular class are reaching the market (p6-8) is food for thought for the pharmaceutical industry as a whole. Even while individual firms may have improved their R&D productivity, leading to more drugs reaching the market overall, companies could still work together better (whether through M&A or partnerships) to make pan-industry R&D productivity more effective in meeting global health needs at affordable prices.

The cost of developing a new drug is often cited in justifying high medicine prices. But why should payers cover the additional cost of two separate companies developing similar but competing high-priced brands? As pushback on drug pricing is likely only to increase as patients expect more and more access to increasingly sophisticated therapeutics, partial consolidation is an avenue that big pharma should explore. Pooling resources rather than trying to speed multiple ploughs through the same furrow could free firms up to explore more novel mechanisms. And where that isn’t possible, then industry needs to be more active still in divesting assets to competitors. Big companies may be pruning their pipelines (see p10) but competition in some disease and target areas remains unhealthily high.
**inside:**

**COVER** / Takeda Closes In On Shire With Revised £49/Share Offer

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**exclusive online content**

**Stock Scan Q1 2018: A Slump And A Proper Correction** https://bit.ly/2HRt6fl

The story of the first quarter of 2018 is the impact of the general stock downturn at the end of January and the selective recovery that followed. But even though AbbVie and others had their own private yo-yos, the real correction took a while.

**Next-Generation CAR-Ts Tackle First-Generation Safety, Solid Tumor Challenges** https://bit.ly/2HVOtxb

New strategies to overcome safety, solid tumor and other challenges associated with CAR-T therapies – and some early clinical data for patients treated with Poseida's, Celyad's and Autolus' novel products – were featured at the American Association for Cancer Research (AACR) meeting.


A new US drug spending report from IQVIA parses out how rebates impact drug spending and explores affordability for patients. The data show drug makers offset about 28% of drug spending and provide some support to industry’s arguments on drug pricing.


Scrip investigates the big issues Israel's biopharma sector need to overcome in order to maintain momentum and achieve sustainable success.

**India Leads Global 65% Surge In Antibiotics Use** https://bit.ly/2Jpd4Kk

Human antibiotic consumption globally jumped dramatically between 2000 and 2015, with India posting the biggest rise, reports a new US study, which calls for a radical policy rethink to prevent antimicrobial drug resistance soaring.

**Deal Watch: Fresenius Drops Bid For Akorn, Citing Data-Integrity Concerns** https://bit.ly/2qWV43m

Janssen and Bristol team to develop next-generation oral anticoagulant, while UCB buys Proximagen’s nasal spray candidate and Duke spinout focused on genomics.

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27 April 2018 | Scrip | 3
Novartis Allays Concerns Over Cosentyx Sales Miss

KEVIN GROGAN kevin.grogan@informa.com

Eyebrows have been raised over the first-quarter performance of Novartis AG’s psoriasis blockbuster Cosentyx (secukinumab) but the company has stressed that the drug is making major advances as first-line therapy in dermatology but more strikingly in its rheumatology indications.

Although sales of $580m, up 35% on the like, year-earlier period, looks like a decent return, Cosentyx revenues were 9% lower than consensus estimates and well down on the $615m made in the fourth quarter of 2017. Novartis said Q1 sales of the drug, which brought in over $2bn last year, were impacted by “destocking at the specialty pharmacy level and rebating for enhanced access to earlier lines of therapy” in the US.

On a conference call, Novartis CEO Vas Narasimhan said that he was happy with the growth trajectory of Cosentyx in psoriasis but stressed the performance of the drug in psoriatic arthritis (PsA) and ankylosing spondylitis (AS). Citing new-to-brand prescription (NBRx) data, he said that in dermatology, Cosentyx had 17% market share in January 2018 and 42% for PsA and AS.

Paul Hudson, head of Novartis’ pharmaceuticals division, noted that the inventory issue and rebates explain the difference between Q4 last year and this quarter but the take-home was how those rebates had resulted in a rise in volumes and enhanced access for the interleukin-17A inhibitor to earlier lines of therapy. He noted that having previously been competing in the second-line setting, Cosentyx is now “in the big pool” that is the anti-TNF naïve market, taking share from the likes of Humira (adalimumab), Enbrel (etanercept) and Remicade (infliximab).

Hudson said that Novartis’ entry into the aforementioned big pool has resulted in “low, double-digit access” to TNF-naïve and indeed treatment-naïve patients, adding that when it comes to what he termed “thoughtful rebating,” the volume rise means “we know we’ve made the right call.” The company also recently started two head-to-head trials looking to show superiority of Cosentyx over Humira for AS and PsA. (Also see “Novartis’ Cosentyx Goes Head-To-Head With Humira”– Scrip, 9 Jan, 2018.)

Hudson went on to remind listeners on the call that in terms of potential market size, the opportunity for Cosentyx in AS and PsA is as great as that for psoriasis. While acknowledging the concerns of some observers when the Q1 results were initially released, he said that “I am very comfortable where Cosentyx sits.”

The pharma chief that the NBRx data is the main indicator of how well Cosentyx is doing in the US and he is happy with its performance in all indications and geographies, noting that the therapy is the market leader in Germany in biologics-naïve patients. The underlying performance is strong “and we are exactly where we expected to be” with Cosentyx, he said.

The notion that Cosentyx should be perceived purely as a psoriasis product has been firmly put to bed and Hudson noted that Novartis had spent the last six months building field force capacity for each indication. He said that the move ensured accountability and there was no need to bolster the number of reps.

While talking up AS and PsA, Hudson also maintained that Cosentyx was “uniquely differentiated” in psoriasis. He was responding to a question about Johnson & Johnson’s head-to-head ECLIPSE trial comparing its anti-interleukin-23 drug Tremfya (guselkumab) with Cosentyx which is due to read out in the second half of 2018.

He said Novartis was “somewhat flattered” that J&J is taking on Cosentyx but noted that the primary endpoint of ECLIPSE in moderate to severe plaque psoriasis patients over 48 weeks of treatment is non-inferiority (superiority is a secondary endpoint). Hudson did not seem overly concerned and the company has repeatedly claimed that IL-17a is the best mechanism to target.

Analyst Eric Le Berrigaud at Bryan Garnier issued a same-day investor note before the conference call stating that “we do expect people to talk a lot about a quite disappointing number for Cosentyx… which is for the first time negative in sequence.” However, he added that, “We do not see anything truly worrying in that number since prescription trends are still very solid and confirm clear advantage to first mover in the class.”

Laura Sutcliffe at Berenberg wrote to investors saying that “while destocking should be a one-time event, reductions in net pricing via rebating will not be, and it is possible that we are starting to see the effects of a more competitive landscape in psoriasis.” She added that Novartis “should remain well positioned, however – it has a robust clinical program to expand Cosentyx indications and will hope to grow volumes much faster than anything it has to give up on net price as a result.”

Overall, for the first quarter, core net income rose 4% to $2.98bn, whiles sales also climbed 4% in constant currencies to $12.69bn.

TSAI POACHED FROM AMGEN TO BE NEW CMO

Meantime, Narasimhan has scouted his replacement as chief medical officer, the role he held before becoming CEO earlier this year, and poached John Tsai from Amgen Inc.

Tsai, who will also have the title of head of global drug development and be a member of the Novartis’ executive committee, had only been CMO at Amgen since May last year. Prior to joining Amgen, he spent eleven years with Bristol-Myers Squibb Co. as global head of clinical development for marketed products and clinical operations.

Tsai started his career at GE as an electrical engineer before returning to school to study medicine. Narasimhan said that “his expertise across multiple therapeutic areas, including cardiovascular, oncology and neuroscience combined with his background in electrical engineering will be a source of great strength for Novartis.”

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At J&J, Oncology Closes In On Immunology As The Leading Pharma Franchise

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Johnson & Johnson's oncology franchise is gaining in prominence, narrowing the gap in the first quarter with the company's top-selling immunology franchise. Global oncology sales grew 45% to $2.31bn in the quarter, powered by strong growth of Darzalex (daratumumab), Imbruvica (ibrutinib) and Zytiga (abiraterone). Meanwhile, growth in immunology is slowing, with worldwide sales growing 3.8% to $3.04bn.

Oncology is now solidly the second top pharma franchise at J&J, outpacing cardiovascular/metabolic, neuroscience and infectious disease. J&J reported first-quarter financial results April 17, highlighting the strong growth in oncology.

Sales of two newer brands, the multiple myeloma drug Darzalex and the leukemia and lymphoma drug Imbruvica, are on a power growth track. Darzalex sales grew 69.4% to $432m worldwide in the first quarter, while sales of Imbruvica grew 43.5% to $587m. Imbruvica growth is largely coming from first-line chronic lymphocytic leukemia and growth more generally in the CLL market. Chief Financial Officer Dominic Caruso said the US CLL market has grown by an estimated 15%.

Darzalex sales were driven by growth in second-line multiple myeloma, and the leukemia and lymphoma drug Imbruvica, are on a power growth track. Darzalex sales grew 69.4% to $432m worldwide in the first quarter, while sales of Imbruvica grew 43.5% to $587m. Imbruvica growth is largely coming from first-line chronic lymphocytic leukemia and growth more generally in the CLL market. Chief Financial Officer Dominic Caruso said the US CLL market has grown by an estimated 15%.

Caruso took a few moments to highlight some of J&J's financial accomplishments during his tenure, notably exceeding its competitors for total shareholder returns over the last three-, five- and 10- and 20-year periods. “We returned two times more value to our shareholders than compared to our closest competitor over the last five years,” he noted.

The more mature prostate cancer drug Zytiga also turned in a strong performance, with worldwide sales growth of 61.6% to $845m, driven by a new indication for patients with metastatic high-risk castration sensitive prostate cancer. The indication was approved by the FDA in February based on the Phase III LATITUDE study. (Also see “J&J’s Apalutamide, Astellas/Pfizer’s Xtandi On Par For Non-Meta-static Prostate Cancer” - Scrip, 9 Feb, 2018.) J&J’s next-generation androgen receptor inhibitor, Erleada (apalutamide), was also approved in February.

**REMICADE SALES CONTINUE TO FACE PRICING PRESSURE**

Growth in immunology is slowing as J&J’s top-selling drug, the tumor necrosis factor (TNF) inhibitor Remicade (infliximab), is facing new competition from biosimilars. The launches of Pfizer Inc.’s Inflectra (infliximab-dyyb) and Merck & Co. Inc.’s Renflexis (infliximab-abda) have put pressure on Remicade, mainly through price; J&J has sought to defend its blockbuster franchise by offering steeper rebates.

The strategy largely has been successful. Remicade continues to hold about 95% of the US infliximab market by volume, according to J&J. Nonetheless, Remicade sales took a hit, down 22.5% in the US to $916m. But J&J said the drop in sales was partly due to a one-time pricing adjustment in the year-ago period related to a payer’s delayed rebate claims. The company said that without that adjustment, US sales would have declined by about 16%, driven by price erosion.

Stelara (ustekinumab) continued its strong growth trajectory, with worldwide sales up 28.9% to $1.06bn. J&J is also hoping a new drug for psoriasis, the first-in-class IL-23 blocker Tremfya (guselkumab), will drive immunology growth in the near-term. The drug generated $72m in the first quarter, following its debut last year. (Also see “J&J’s First-In-Class Tremfya Poised To Join A Crowded Psoriasis Market” - Scrip, 14 Jul, 2017.) Despite solid efficacy data supporting the drug’s approval, Tremfya is competing in a crowded market, including another class of highly effective new drugs that block IL-17.

J&J’s Immunology Therapeutic Area Head Susan Dillon left the company in March, succeeded on an interim basis by Newman Yeilding, the head of immunology development. The quarterly call was also the last for Caruso, who announced his retirement from the company in March after nearly 12 years as CFO and will be succeeded by Joseph Wolk on July 1.

Caruso took a few moments to highlight some of J&J’s financial accomplishments during his tenure, notably exceeding its competitors for total shareholder returns over the last three-, five-, 10- and 20-year periods. “We returned two times more value to our shareholders than compared to our closest competitor over the last five years,” he noted.

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Fast And Furious: How The First-To-Market Advantage Is Shrinking

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The competitive dynamics in the pharmaceutical market appear to be intensifying, with second- and third-to-market drugs reaching the market faster behind first-in-class drugs than ever before. Faster competition reduces the window of market exclusivity for first-in-class drugs, putting more pressure on new drug launches and impacting drug pricing and rebating strategies.

Notable first-to-market races have played out across several high-profile newer drug classes like interleukin-17 blockers for psoriasis, PD-1/L1 inhibitors for cancer, IL-5 inhibitors for asthma, SGLT-2 inhibitors for diabetes and PCSK9 inhibitors for high cholesterol.

What a decade ago might have been years between a first-in-class drug and second-in-class follower has shrunk to just months in some cases (see chart below).

Sanofi/Regeneron Pharmaceuticals Inc.’s PCSK9 inhibitor Praluent (alirocumab) was approved by the US FDA just one month ahead of Amgen Inc.’s Repatha (evolocumab) in July 2015. GlaxoSmithKline PLC’s IL-5 inhibitor Nucala (mepolizumab) was approved just four months ahead of the next competitor, Teva Pharmaceutical Industries Ltd.’s Cinqair (reslizumab) and followed 18 months later by a third IL-5 blocker, AstraZeneca PLC’s Fasenra (benralizumab), approved by the FDA in November 2017.

The upcoming CGRP antagonist class of migraine drugs includes drugs from Novartis AG/Amgen, Teva and Eli Lilly & Co. all racing to reach the market later this year.

Analysis of the intensifying competitive dynamics remains largely anecdotal, and it’s hard to know exactly how much impact competition is having on pricing dynamics, particularly for expensive biologic drugs. Races to be the first to market have always existed. The anti-TNF blockbusters Remicade (infliximab) and Enbrel (etanercept), for example, were both approved months apart in 1998, although for different indications initially. It was a full year after Enbrel reached the market that Remicade added an indication for rheumatoid arthritis, in November 1999.

THE LEAD NARROWS

But experts agree the window for first-to-market exclusivity appears to be shrinking, impacting the drug launch environment and pharmaceutical sector sentiment.

“Hyper-competition makes it increasingly difficult for investors to forecast revenue for key franchises, which are likely to face new competitive entry and further market fragmentation on an annual basis,” Leerink analyst Geoffrey Porges said in a January research report looking at what he called category crowding. “This also decreases our confidence in the general ability of drug developers to sustain market share or maintain positive price growth beyond a fixed short-term period, unless significant barriers to entry exist.”

The Tufts Center for the Study of Drug Development may have the most definitive data on first-to-market exclusivity timelines, having analyzed the market dynamics in three studies over two decades, the most recent of which was conducted in 2016.

TCSDD concluded that the timeline between first- and second-to-market drug launches has indeed narrowed considerably. The most recent study, published in Clinical Pharmacology & Therapeutics in December 2016, found that the mean length of time from first-in-class FDA approval to second-in-class approval fell 49% in the period from 1998-2004 versus the period from 2005-2011, from 4.9 years to 2.5 years.

Looking at recent drug approvals, it seems the pace of development has intensified even further, at least for certain classes of potential blockbuster drugs.

Leerink’s Porges homed in on three specific therapy areas – non-small cell lung cancer, hemophilia A and rheumatoid arthritis – and found that the number of treatment options in each area has doubled since the year 2000. He concluded that while a newly approved drug was once able to retain its position on the market for five or more years, the time to next drug approval in a given indication has eroded to less than one year in all three therapeutic areas.

Lots of factors are contributing to the uptick, including improvements in science and R&D efficiency that allow drug manufacturers to develop compounds and antibodies more quickly and move them more rapidly into clinical development. The FDA has also worked to approve new drugs in a timely manner. The current FDA Commissioner Scott Gottlieb has talked about how more competition in a drug category could fuel price competition and help reduce drug costs.

“There is an increased focus of companies pursing the same disease area,” said Raphael Natanek, a partner at the healthcare consulting company Bain & Co. “When a company launches [a new drug], the follow-up product that is launching behind is often six months, and the one after that is another six to 12 months. Instead of having one big launch and a wait of three to four years, you have a very small window.”

The crunch to get to market is impacting how drug makers think about their mid- to late-stage clinical trials, balancing the need to get to market quickly with the desire to differentiate the product from the competition. “There is a huge trade off that is worse than ever between the need to launch rapidly and the need to address the intensifying evidence needs,” said Ed Schoonveld, managing principal, value & access at the healthcare consulting firm ZS Associates. “You can satisfy those evidence needs – but now you are going to be fifth to market.”

ME TOO OR ME BETTER?

First-in-class still appears to hold an important competitive advantage, industry experts agree. “In classes where you have followers generating novel data or choosing to do a head-to-head trial to displace a first in market, you’ve seen substantial ability to catch up,” said ZS Principal-Product Development Ben Hohn. But, he added, “even a slightly better drug, if not dramatically better, may take quite awhile to catch up to the market leader.”

It took Regeneron Pharmaceuticals Inc.’s VEGF inhibitor Eylea (aflibercept) for age-related macular degeneration, with a dosing advantage, three years to catch up to a similar level of US revenues as
Roche’s Lucentis (ranibizumab) after it launched in late 2011. Lucentis, meanwhile, enjoyed a lengthy period of exclusivity on the market, having been approved in June 2006.

Medivation Inc’s androgen receptor inhibitor Xtandi (enzalutamide) is another drug that was second to market behind Johnson & Johnson’s Zytiga (abiraterone) by about 16 months, but managed to outpace US sales of Zytiga in its second full year on the market; Zytiga must be taken with a steroid, a requirement Xtandi doesn’t share.

Looking at more recent launches, Novartis’ IL-17 inhibitor Cosentyx (secukinumab) has so far been able to hold onto its first-to-market advantage, generating $2.1bn in sales in 2017, while Lilly’s second-to-market Taltz (ixekizumab) generated $559.2m in 2017, its first full year on the market after launching in mid-2016. Sales of Cosentyx in the first quarter, reported April 19, were strong, up 35% to $580m, but the revenues were below consensus estimates and down from the fourth quarter performance, raising some eyebrows among investors nervous about the competitive dynamics. The company attributed the performance to destocking at the specialty level and rebating to enhance access at earlier lines of therapy.

TIME TO LAUNCH: A LOOK AT THE LENGTH OF TIME FROM FIRST TO SECOND TO MARKET

Initial US FDA approval dates for first round of drugs in various classes.

**SSRIs for depression - 4 years**
- Prozac, December 1987
- Zoloft, December 1991
- Paxil, December 1992

**Tumor necrosis factor inhibitors for autoimmune diseases - 3 months**
- Remicade, August 1998
- Enbrel, November 1998

**GLP-1s for type 2 diabetes - 4.5 years**
- Bydureon, April 2008
- Victoza, January 2010
- Trulicity, September 2014

**VEGF inhibitors for eye diseases - 5 years**
- Lucentis, June 2006
- Eylea, November 2011

**DPP-4 inhibitors for type 2 diabetes - 3 years**
- Januvia, October 2006
- Onglyza, July 2009
- Tradjenta, May 2011

**Factor Xa inhibitors as blood thinners - 9 months**
- Pradaxa, October 2010
- Xarelto, July 2011
- Eliquis, December 2012

**Androgen receptor inhibitors for prostate cancer - 16 months**
- Zytiga, April 2011
- Xtandi, August 2012

**Direct-acting antivirals for hepatitis C -12 months**
- Sovaldi, December 2013
- Harvoni, October 2014
- Viekira Pak, December 2014

**SGLT-2 inhibitors for type 2 diabetes -10 months**
- Invokana, December 2013
- Farxiga, January 2014
- Jardiance, August 2014

**PD-1/L1 inhibitors for various cancers - 6 months**
- Keytruda, September 2014
- Opdivo, March 2015
- Tecentriq, May 2015

**PARP inhibitors for ovarian cancer - 2 years**
- Lynparza, December 2014
- Rubraca, December 2016
- Zejula, March 2017

**IL-17 inhibitors for psoriasis -14 months**
- Cosentyx, January 2015
- Taltz, March 2016
- Soby, February 2017

**CDK4/6 inhibitors for breast cancer - 2 years**
- Ibrance, February 2015
- Kispar, March 2017
- Verzenio, September 2017

**PCSK9 inhibitors for high cholesterol - 1 month**
- Prexari, July 2015
- Repatha, August 2015

**IL-5 inhibitors for asthma - 5 months**
- Nucala, November 2015
- Cinqair, March 2016

**CAR-T therapies for blood cancers - 2 months**
- Yescarta, August 2017
- Yesceala, October 2017

MORE COMPETITION = LOWER PRICE?

The big question is how increased competition impacts price. Parsing out the impact of competition on drug pricing comes down to rebating and contract negotiations with payers so it’s hard to know exactly how competition is impacting drug pricing, particularly when it comes to newer, expensive biologics. Experts who work on pricing strategies have a mixed view of how big of an impact competition is having on price but agree competition in most therapeutic areas does put downward pressure on prices through more aggressive rebates.

“The answer is yes, it is resulting in lower net prices without question,” said Roger Longman, the CEO of Real Endpoints, a market access-focused consultancy. “What you are seeing is significantly lower net prices to payers in competitive markets.”

ZS Associates’ Schoonveld said that when it comes to some of the newer biologics on the market, the more competitive price reductions are still happening in Europe more than in the US. “When the differentiation between products is smaller that obviously leaves more opportunities for payers and provider organizations to make choices and drive rebates,” he said.

CONTINUED ON PAGE 8
Win-Win For Alnylam And Dicerna With RNAi Trade Secrets Settlement

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The settlement of a lawsuit centered around trade secrets linked to gene-silencing intellectual property looks like a win for both of the protagonists in the legal tussle – the ribonucleic acid interference (RNAi) specialists Alnylam Pharmaceuticals Inc. and Dicerna Pharmaceuticals Inc.

A jury trial scheduled to begin April 23 in the US has been avoided with an agreement that will see Dicerna pay Alnylam $2m upfront and hand over around 983,000 of its shares. On April 20, when the suit was settled, Dicerna stock ended the day at $12.01, up 18% on the previous day.

The settlement between the two biotech companies resolves a lawsuit that Alnylam filed against Dicerna in 2015, accusing the latter of misappropriating trade secrets related to RNAi technology Alnylam acquired when it bought Sirna Therapeutics from Merck & Co. Inc. in 2014, beating off competition from Dicerna. The suit included claims that Dicerna hired Merck staff who helped the company develop a “strikingly similar” technology called GalXC.

Dicerna denied the allegations and filed a counterclaim alleging that Alnylam’s lawsuit was frivolous and anti-competitive as it was scuppering potential partnerships. However, agreement has now been reached, with neither side admitting wrongdoing, and as the share price jump showed, investors see the lawsuit settlement as a very positive step for Dicerna.

Dicerna will still have to pay Alnylam another $13m over the next four years, depending on revenues the former gets from any GalXC-based partnerships, excluding any amounts received from its existing non-alcoholic steatohepatitis (NASH) collaboration with Boehringer Ingelheim GMBH.

There are some other restrictions but on the whole, analysts are saying that Dicerna has negotiated a decent deal. Umer Raffat and Jon Miller at Evercore ISI noted that the firm does not have to pay any milestones or royalties to Alnylam and none of its programs or disease targets is impacted by the settlement. The sums it is paying are “substantially below the expected cost of a trial” and “the upfront payment will not materially change their runway,” they said in an April 23 note.

This was confirmed by Dicerna CEO Douglas Fambrough who said that with the settlement, “we are now able to focus the entirety of our resources on the advancement of our key clinical and discovery programs.” Top priority is an ongoing Phase I trial of DCR-PHmC, the company’s lead compound for the treatment of all forms of primary hyperoxaluria (PH), as well as the expected advancement of multiple other GalXC-based programs.

Not having the distraction of an ongoing legal spat with Dicerna benefits Alnylam, which is hoping for its first product approval soon. Patisiran, the first RNAi drug to triumph in Phase III trials, has been filed for hereditary ATTR amyloidosis and the company is hoping for a green light in the US this summer and in Europe by the end of the year.

Even before approval of patisiran, Alnylam is also focusing on its next-generation amyloidosis candidate, ALN-TTRsc02. The European Medicines Agency’s Committee for Orphan Medicinal Products is recommending orphan drug status. Alnylam expects to advance ALN-TTRsc02 into Phase III trials later this year.

Meantime, while the Dicerna legal tussle is over, Alnylam’s litigation lawyers are being kept busy with an ongoing patent dispute with the UK’s Silence Therapeutics PLC. In the latest chapter of the row, last month the US firm filed a declaratory judgment action in a Boston court to seek a finding of non-infringement of certain Silence patents, while the London-based company brought patent infringement proceedings in Portugal against patisiran.

In an interview at the end of last year, Barry Greene, Alnylam’s president, told Scrip that “from the very beginning we had an upfront, explicit strategy to consolidate all the IP required to develop and commercialize RNAi therapeutics...it is our belief today that anyone developing RNAi therapeutics requires our IP to commercialize them.”

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In an interview at the J.P. Morgan Healthcare Conference in January, Novartis Pharmaceuticals CEO Paul Hudson talked about the competitive rebating dynamics for Cosentyx in psoriasis. He said Lilly launched Taltz with “aggressive” rebating, but Cosentyx was able to maintain its leadership in new patient prescriptions at the end of 2017.

“Regarding the rebate situation, we’ve been thoughtful in ’18,” he said. “We’ve not been casual or desperate for a headline of new patient growth. We’ve been considerate around what is appropriate, and we believe our access is the same and in some cases better than it was in ’17.” He continued to point to strong growth in new patient prescriptions in the first quarter conference call and said the increased rebates helped Cosentyx secure access in the anti-TNF naïve market.

In the IL-5 asthma space, AstraZeneca PLC launched its third-to-market Fasenra (benralizumab) at a wholesale acquisition cost of $28,000 to $33,000 per year, which, according to the company, is a bit below the competition.

AstraZeneca Executive Director-Inhaled Respiratory Marketing Domenick Fanelli said the category hasn’t experienced a lot of rebating pressure yet. “I’m comfortable that the pricing we have chosen is an appropriate price and a reasonable price,” he told Scrip.

Steve Cutts, vice president of pharmacy services and clinical strategy for the pharmacy benefit manager Magellan Health Services Inc., said the level of rebating for biologics for asthma has not been at the level seen with the older inhaled respiratory products for asthma. That’s partly because the biologics are reimbursed under the medical benefit rather than the pharmacy benefit.

“Medical rebating in particular is really just starting to pick up,” he said.

Cancer, in particular, is a therapy area that has not experienced significant price competition despite the fact there are now several classes of drugs with multiple competitors, including PD-1/L1 inhibitors in melanoma and lung cancer, PARP inhibitors in ovarian cancer and CDK4/6 inhibitors in breast cancer.

“You just have much more severe consequences to make the wrong choice, so in oncology, payers have just been more hands-off in forcing these choices,” Schoonveld said.

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For the first time the number of products currently being developed by the pharmaceutical and biotech industries has risen past the 15,000 mark, but the milestone was reached in the face of the lowest rise in the growth rate for five years.

New data from Informa Pharma’s Pharma R&D Annual Review 2018 from its R&D database Pharmaprojects show that there were 15,267 products in the pipeline when it took its annual snapshot in January. This represents the seventh consecutive year of expansion, but there has been a slowdown in the rate of increase this year, with the 2018 pipeline growing by just 2.7%, well down from last year’s growth rate of 8.4% (see Figure 1).

The report’s author Ian Lloyd, senior director for Pharmaprojects, said the figures may have been flattened to a certain extent by continued efforts by the editorial team to ensure that the database is as accurate as possible. “It’s tough to estimate the extent of this effect, but it’s fair to say that in the absence of any organic pipeline growth, this would have led to a net shrinkage in the number of R&D projects. Ergo, the pipeline is still growing, it’s just a little harder to ascertain at what rate.”

Figure 1 shows the total number of candidates in the R&D pipeline as of January 2018, and how this has changed since the start of the century. By pipeline here, we mean that we are counting all drugs in development by pharmaceutical companies, from those at the preclinical stage, through the various stages of clinical testing and regulatory approval, up to and including launch. Launched drugs are still counted, but only if they are in still in development for additional indications or markets.

This theory is lent credence by the fact that the number of products at the preclinical stage shot up by 7.3% compared with last year’s figure, far outpacing the pipeline’s average growth rate to move beyond 8,000 for the first time. This is the figure that one would expect to be most prone to the effects of internal editorial actions, Lloyd said.

The total rise was fueled by a decent 3,807 new drugs debuting in development, although this figure itself fell slightly short of 2016’s record of 4,005. Many of these preclinical projects have come out of tiny start-ups. At the other end of the pipeline around 300 products were removed from the Launched tally as they are only included if they are in still in development for additional indications or markets (see Figure 2).

The figures for the clinical development stages are where the data are considered the most robust due to integration with Pharmaprojects sister database Trialtrove. Here the number of drugs currently at the Phase I stage has increased slightly above the overall rate (up 3.0%), but the figure for Phase II appears flat, while there is actually a decline of 1.9% at Phase III. Figure 2 looks at the global status of each drug in the pipeline so that each is counted only once.

To put this into more context, Figure 3 looks further back down the years to get a better handle on emerging trends over time, and shows a slowing of the growth rates at the Phase II and Phase III stage.
This may not be entirely a bad thing,” said Lloyd. “Clinical trials are a huge expense, so the industry simply having more and more drugs in the clinical stages of development, unless it is similarly matched by increases in drug launches, will become untenable. As can be seen, the numbers of drugs at each clinical stage are about double those seen a decade ago. Sadly, the level of drug launches is not.”

**WHICH COMPANIES DOMINATE?**

Novartis AG has cemented its position at the top with a second year in first place for numbers of products in the pipeline, though its pipeline size has shrunk by 28 drugs, narrowing its lead over its nearest rival Johnson & Johnson (J&J), which climbed up three places to claim the 2018 runner-up position and is one of only two Top 10 companies to increase the sizes of their portfolios (the other being Takeda Pharmaceutical Co. Ltd.). However, given this was achieved via its acquisition of Actelion Pharmaceuticals Ltd., and with 20 pipeline products, J&J’s overall increase in pipeline size of two candidates looks somewhat less impressive, Lloyd noted. “In fact, in an unprecedented scenario, only six of the Top 25 actually grew their pipelines at all” (Table 1).

Despite having fewer pipeline products, AstraZeneca PLC was able to rise three places in the chart to claim third position, with Pfizer Inc. and Roche completing the top five. The latter ties with GlaxoSmithKline PLC (GSK) and Merck & Co. Inc., in terms of number of R&D products, but these companies are placed at six and seven, respectively, by considering the number of products which each company originated, rather than in-licensed, Lloyd noted. GSK posts the biggest fall within the Top 10, new CEO Emma Walmsley having implemented a radical refocusing of the company’s pipeline during the year. There’s just one new entry in the top 25, as Gilead Sciences Inc. re-joins after a year out.

**TOTAL COMPANIES**

The pharma universe continued its expansion in 2017 with 670 new companies being added to the Pharmaprojects database, down from the high of 750 seen during the previous year, but still above the 618 seen in both of the preceding years (see Figure 4). This still makes it the second highest ever number of newcomers in a single year. This has helped push the total number of companies involved in pharma R&D to a new peak, as Figure 4 illustrates. “But, just as with drug numbers, expansion has slowed,” Lloyd commented.

Since the total number of companies with pharma R&D pipelines is up by just 131, or 3.3%, to reach a total for 2018 of 4,134, this means 539 firms exited active R&D.

The number of companies with just a single drug in the pipelines has again risen, going up to 1,627 from the 2017 equivalent figure of 1,578, whereas those with two has fallen slightly from 679 to 657. Percentage-wise, this means these small enterprises account still account for more than half of the industry at 55.2%, but for the first time, this proportion is down on last year, when it stood at 56.4%.

The US’s dominance of the pharma industry increased slightly last year. A breakdown of where pharma companies are concentrated, shows that a further 1% of firms are now based compared with 2017’s figure. China has also increased its share by 1%, but this represents a rapid expansion rate for this nascent market for R&D, Lloyd noted. Pharmaprojects is reporting 262 Chinese companies developing new drugs, up from 219 a year ago. Europe slipped back slightly overall, but the UK’s share is held firm at 6%.

**THERAPY, CATEGORY AND DISEASE**

When the pipeline is broken down by therapy area there is no sign that cancer’s star is set to wane any time soon (see Figure
There was a 7.6% increase in the number of oncology drug candidates this year, a growth rate which is close to three times that of the overall pipeline.

Over a third of all drugs in development have at least one oncology indication attached to them, whereas it was just over a quarter at the decade’s start. On the minus side, the biggest decline was seen in anti-infectives, which with 2,238 candidates reports a 9.3% reduction in its pipeline at a time when new drugs are much needed for new drugs. “This almost entirely reverses the big increase of 11.1% seen in this group of drugs in 2017,” Lloyd noted. Cardiovascular products were down 7.2%, while immunological and blood & clotting also posted declines. On the other hand, second-placed neurologicals also grew, at around the average rate of 2.4%, as companies still try to crack difficult CNS diseases like Alzheimer’s.

Lloyd noted: “Ovarian cancer (up 12.4%), brain cancer (12.1%), and acute myelogenous leukemia (14.4%) have all made significant advances, but the top two of breast and non-small cell lung cancer both demonstrated double-digit percentage increases themselves (up 11.2% and 14.0%, respectively).”

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Holistic Approach Needed To Transform R&D Process, ICON Says

**Holistic approach**

ICON has undertaken research, assisted by ISR Research, and conducted an industry survey with Informa’s Pharma Intelligence, to examine the challenges facing pharma and find solutions. This includes a holistic approach to transforming the clinical trial process. The top three challenges identified by respondents in ICON-Pharma Intelligence’s survey were patient enrolment, site start up and regulatory approval delays/changes.

Interestingly, respondents also identified study start up, patient recruitment and retention and product development as three key areas with the most potential for generating savings and efficiencies. It is clear from the survey that those who participated have a growing understanding that to really gain traction and change, a holistic approach must be adopted to secure trial transformation. New trial design is essential, along with the adoption of a new corporate and scientific approach that supports the clinical trial process throughout the enterprise from the ground up.

We have now entered a healthcare era that requires more targeted therapies, more orphan indications and personalised medicines – with opportunities for enhancement and integrated support via disruptive technologies, powerful statistical analysis, and artificial intelligence (AI). However, the ICON-Pharma Intelligence survey showed that despite the recognition of the need for a holistic approach, only one in five respondents indicated they have a holistic/integrated initiative to drive clinical trial transformation.

Including data from its survey, ICON has published a white paper on how to improve R&D efficiency. Patient centricity needs to be at the heart of new strategies as the pharmaceutical industry works to move away from its traditionally disease-focused approach to R&D. ICON demonstrates that the recognition of the need for a holistic approach, only one in five respondents indicated they have a holistic/integrated initiative to drive clinical trial transformation.

Pharma is at a most critical point in its evolution. It is being held back by a lack of flexibility, speed and mastery of analytical power. The R&D process that has been its foundation now underpins an inefficient clinical trial process that is costly, often unprofitable and which makes it harder to successfully meet the changing and challenging demands of disease in the 21st century. The model of three fixed study phases is no longer viable to produce the therapeutic solutions that are required to meet increasingly complex healthcare demands dominated by an aging population with multiple health needs.

The reality of the industry’s position is that to gain approval in the US for a new pharmaceutical product costs more than $2.5 billion, representing an increase of 145% in just 15 years, according to the Tufts Center for Drug Development. Furthermore, the stakes are high risk as only 7% of first-in humans drugs receive regulatory approval.

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and ethnic minority populations.

In the 21st century, the power of the internet has dramatically empowered patients to become knowledgeable about health and disease and to share knowledge with each other. One in 20 Google searches are for health-related information. There are also technological developments and devices that are enablers in gathering real-world data.

E-health
27% of survey respondents said that using smart phones, developing novel outcome measures and remotely collecting data will improve operations. ICON emphasises that big data, new outcome measures and endpoints generated from mobile devices, sensors and wearables supplied to patients need to be rigorously validated. The challenge is to establish and structure data, from a range of diverse technologies, that can be understood and interpreted to gain meaningful patient and scientific insights. Outcomes need to be modeled and validated. “Although people can access a lot of data, making it talk to one another is an unsexy but really important piece of work that needs to be done,” commented Rob MacKenzie, Executive Vice-President and Chief Development Officer at Pfizer, speaking at the 2017 FT Global Pharmaceutical and Biotech Conference.

Statistical analysis and AI can be harnessed for managing data integration and interpretation. These tools can lead to improvement in trial performance at every level, including modelling investment return. AI, big data and risk-based monitoring were among the top technologies recognised in the survey.

There is now evidence building that using these new technologies and approaches in clinical trials can save millions in development costs. Case studies by ICON have shown that applying adaptive design can accelerate time to market and eliminate $5 million in expenditure.

Another new approach thanks to technological advances is siteless trials. The virtual trial alleviates the sometimes unmanageable burden on patients of frequent clinic visits for monitoring when participating in clinical studies. CentreWatch, which provides clinical trial information to trial professionals and patients, has found that 18% of clinical trial patients drop out of trials after they have enrolled and that difficulty reaching clinic locations is a negative factor. The adoption of e-visits and telemedicine can reduce trial costs considerably. Sanofi’s tie-up with Science 37 in 2017 to allow patients to be monitored from home, is one example. Patients were equipped with a smart phone to be monitored via a cloud-based research platform. Science 37 suggested that such technology could reduce typical trial time by at least 30% and that virtual clinical trials could reduce trial time by as much as two years.

Collaboration
Taking a holistic approach to trial transformation is not just about adopting new technology, gathering and interpreting big data and applying new resulting strategies. It also requires internal, external and interdisciplinary collaboration.

There needs to be collaboration between sites, investigators and also internal corporate functions such as clinical development teams and commercial teams. And externally, a critical element is strategic partnerships. Tufts advocates that the role of contract research organisations is becoming increasingly significant as these businesses become more involved in clinical research and are recognised as strategic partners. Many CROS have already adopted the technologies discussed. For example, ICON has incorporated various technologies such as electronic data capture, real-time analytics and data apps into its programmes, including partnerships with Intel, McKinsey & Co believes that with the growth in specialisation of clinical research, partnerships between sponsors and CROS are likely to grow in value.

This holistic approach, if diligently embraced and applied, will transform the clinical trial process and the way the pharmaceutical industry operates so that it will ultimately produce more effective therapeutic products, increasingly address patient unmet need and achieve higher returns on investment.


About ICON
ICON plc is a global provider of outsourced development solutions and services to the pharmaceutical, biotechnology and medical device industries. The company specialises in the strategic development, management and analysis of programmes that support clinical development. With headquarters in Dublin, Ireland, ICON currently operates from 97 locations in 38 countries and has approximately 13,250 employees. Further information is available at ICONplc.com.
In The Hot Seat: Bristol Defends IO Position Amid Sliding Stock And Forecasts

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Faced with a backlash over the showing of its Opdivo/Yervoy combo in first-line lung cancer – the big prize in immunoncology – at the American Association for Cancer Research (AACR) meeting, Bristol-Myers Squibb Co. is defending its long-term strategy, which is grounded in a chemo-sparing, biomarker-driven, multi-mechanism approach across tumor types.

The company was put in the defensive position on April 16 after the AACR meeting and the New England Journal of Medicine (NEJM) featured full data from landmark Phase III studies in first-line metastatic non-small cell lung cancer (NSCLC) with Merck & Co. Inc.’s PD-1 inhibitor Keytruda (pembrolizumab) emerging as a new standard of care. Merck’s KEYNOTE-189 study compared Keytruda with doublet chemotherapy – Eli Lilly & Co.’s Alimta (pemetrexed) and cisplatin or carboplatin – versus chemo alone in non-squamous NSCLC while Bristol’s CheckMate-227 study tested its PD-1 inhibitor Opdivo (nivolumab) with its CTLA-4 inhibitor Yervoy (ipilimumab) against pemetrexed and carboplatin or cisplatin in squamous and non-squamous NSCLC.

Updated data from Roche’s Phase III IMpower 150 study of its PD-L1 inhibitor Tecentriq (atezolizumab) with its VEGF inhibitor Avastin (bevacizumab) and the chemotherapies carboplatin and paclitaxel were presented the same day at the AACR meeting and were positive, but had a lower profile than the Keytruda trial. (Also see “Roche’s IMpower150 Gets AACR Applause But Merck’s KEYNOTE-189 Big Winner”, Scrip, 17 Apr, 2018.)

Merck emerged as a clear winner at the meeting, as the company demonstrated a striking overall survival benefit on top of progression-free survival (PFS), with a regimen inclusive of pemetrexed, which is more commonly used in the US, and data that were perceived as better than its competitors. During the meeting’s plenary session, Yale University expert Roy Herbst declared the combination the new standard of care for first-line NSCLC.

Bristol had changed its trial design to focus on PFS in a subset of patients with a high tumor mutation burden (TMB) and reduced the risk of recurrence or death by 42% in this group, but showed only a trend for improvement in overall survival (a 21% reduction in risk), a much more important endpoint. (Also see “Bristol’s Opdivo/ Yervoy Bid Will Show Whether Tumor Mutation Burden Is Ready For Prime Time”, Scrip, 5 Feb, 2018.)

Furthermore, discussing results during the plenary session at the meeting, biomarker expert David Rimm, director of pathology tissue services at Yale University, said that TMB is interesting, but called attention to the many challenges of using this new measure, including lack of standardization, high cost and the need for much more tissue for evaluation. “We have to really make sure that our pathologists know what we are up against when we do TMB. I am not sure it will be standardizable. But certainly it is not standardized yet,” Rimm said.

He also expressed doubt that PFS will translate to an overall survival benefit, because tumors with high mutation burden may be more likely to learn to adapt to immunotherapy in the longer term.

“Is TMB ready for prime time? I don’t believe so. I think it is not ready yet for use in patient care,” Rimm said.

As for Roche’s IMpower 150 study, the PFS result was significantly improved, with a 39% reduction in risk across subgroups of patients with varying levels of PD-L1 expression, and there was an overall survival benefit but the company hasn’t disclosed the magnitude of that OS benefit yet and the chemo backbone is not commonly used in the US.

DEFFENDING THE DATA

Bristol provided a vigorous defense for the data during an April 16 investor meeting. The company has great faith and confidence in the Opdivo and Yervoy as a chemo-sparing IO/IO combination that offered improved PFS across the spectrum of PD-L1 expression with deep and long responses and an exciting overall survival curve in NSCLC patients with high TMB, Chief Scientific Officer Thomas Lynch told the call.

Execs said that the PD-1 inhibitors are similar in terms of efficacy and that different outcomes are likely due to differences in trial designs, including patient populations.

Fouad Namouni, oncology development head at Bristol, sees the early survival data as encouraging. In an analysis of the subset of patients with high tumor mutation burden (290 out of 1,739), the one-year survival rate was 67% for the Yervoy/Opdivo combination versus 58% for the chemo combo. Median overall survival was 23 months for the IO combo versus 16.4 months for chemo, so Opdivo and Yervoy were able to add seven months, he noted.

The data are really consistent and paradigm-changing, Namouni maintained.

Bristol expressed pride in describing an important new biomarker in lung cancer – TMB – that can help identify a population that derives excellent benefit in this setting, which should be of great interest to patients and payers and drive more testing.

“I think one of the most important points of ‘227 today is it provides a very clear path forward in non-small cell lung cancer for the combination of Opdivo and Yervoy,” Lynch said.

Lynch also noted that the combination has already demonstrated improved overall survival in melanoma and renal cell carcinoma.

FDA approved the Opdivo (3 mg/kg)/Yervoy (1 mg/kg) combination in first-line renal cell carcinoma patients at intermediate and poor risk (about 75% of the population) on April 16. The combination demonstrated an overall survival benefit regardless of PD-L1
expression in the CheckMate 214 study, which tested the regimen against Pfizer Inc.’s tyrosine kinase inhibitor Sutent (sunitinib). (Also see “Bristol’s Strong SITC: IDO, 1L Kidney Cancer And New Mechanism Data Bode Well” - Scrip, 13 Nov, 2017.)

In addition to the combination data in lung cancer, Lynch flagged results from a pilot study of Opdivo as a monotherapy in neoadjuvant lung cancer, which was also presented during the plenary session at the AACR meeting on April 16. Neoadjuvant (preoperative) therapy may be given to debulk tumors and/or to improve the rate of major pathological response, which is associated with better survival.

The study tested two preoperative doses (3 mg/kg every two weeks) of Opdivo in 21 patients with surgically resectable Stage I, II or IIIa NSCLC. Results were simultaneously published by Drew Pardoll, of the Sidney Kimmel Comprehensive Cancer Center in Baltimore, Md., and colleagues, in the NEJM.

Out of 21 tumors removed, 20 were completely resected. A major pathological response was reported in nine out of 20 tumors (40%). Investigators reported that the pre-treatment tumor mutation burden was predictive of response to PD-1 blockade.

“In a study of neoadjuvant chemotherapy for nonsquamous NSCLC, 22% of tumors had a major pathological response to therapy and such responses were associated with long term survival. In this context, the rate of major pathological response that was reported in our pilot study is encouraging,” Pardoll and colleagues concluded.

Safety also was deemed acceptable in the trial.

A limitation of the study, of course, was its small size. The Phase III CheckMate 816 study of Opdivo/Yervoy versus Opdivo/chemotherapy or chemotherapy alone in neoadjuvant treatment of NSCLC is ongoing.

**ABSORBING BLOWS**

Bristol’s pep talk did not appear to sway the market.

The company’s share price has taken a beating in recent days – it dropped by 7% to a close of $54.08 on April 16 and by 3% to a close of $52.38 on April 17.

Bristol declined to comment on its filing strategy for CheckMate 227, but analysts believe that it will be difficult to get approval with TMB data alone, without OS data, or for it to be accepted in practice even if it is cleared.

Credit Suisse analyst Vaml Divan said in an April 17 note that “doctors we speak to” were consistent in believing the TMB data is interesting and worth further study and that TMB is an important biomarker that will gain adoption over time, though there are still challenges.

“They were more mixed on whether the CM-227 data as it currently stands in patients with high tumor mutation burden warrants regulatory approval and, even if approved, if physicians will use the regimen before there is a clear overall survival benefit seen,” Divan explained.

Analysts also expressed concern that a CheckMate 227 arm with Opdivo monotherapy in high TMB (using cut-point of >13 mutations per megabase) and PD-L1-positive patients did not show improved PFS relative to chemotherapy. Consequently, some are now questioning whether Keytruda is simply a better agent than Opdivo, though as Evercore ISI Group analyst Umer Raffat and others have pointed out this has not been the case in other indications.

Concerns about the first-line NSCLC performance led some analysts to shave their forecasts for Opdivo and Bristol sales, which reached $4.9bn and $20.8bn respectively in 2017. (Also see “Bristol Debuts Opdivo/Yervoy Data In New First-Line Lung Cancer Bid” - Scrip, 5 Feb, 2018.)

Morgan Stanley analyst David Risinger, for example, downgraded Bristol’s stock from overweight to equal weight on April 17.

“We had assumed that Bristol’s Opdivo + Yervoy combination regimen would play a meaningful role in first-line lung cancer, which is the largest cancer market. Following disappointing data relative to Merck’s 189 trial, we cut 2019e Opdivo sales by 17% from $6.4 to $5.3bn, total revenues by 5% from $23.9bn to $22.8bn, and [earnings per share (EPS)] by 8% from $3.91 to $3.62. We lowered 2023e total company revenues by 13% from $31.8bn to $27.6bn (including reductions in IO pipeline candidates) and EPS by 21% from $6.69 to $5.29,” Risinger said.

Morningstar forecasts that the first-line NSCLC market for PD-1/L1 inhibitors will be worth $9.5bn in 2022 and that Merck will dominate due to its first mover advantage, though Bristol and AstraZeneca PLC will benefit from having a CTLA-4 inhibitor that can be used in combinations. Morningstar estimates that Merck will take a 45% share of first-line NSCLC followed by Roche in second place with 35%. Bristol is expected to take 19%, potentially targeting patients who did best in Bristol’s study (high TMB and PD-L1-negative) as well as older patients less willing to endure side effects of chemotherapy.

Morningstar also believes that Roche may have an advantage in the second-line setting, which in total will be worth $3.5bn in 2022, due to three-week dosing and strong data.

For total PD-1/L1 sales, Morningstar predicts $30bn at peak, dominated by Merck 34%, Bristol with a 30% share and Roche with 22%.

Data for both Bristol and Merck at the AACR meeting in an area of unmet need like NSCLC is likely to reinforce high demand by the medical community for the companies’ immuno-oncology drugs, “strengthening both firms’ wide moats,” Morningstar analyst Damien Conover said.

Credit Suisse’s Divan noted that the Keytruda combination improved survival in every subgroup analyzed, including by 41% in patients “with no PD-L1 expression where Keytruda monotherapy has not previously made an impact.” Credit Suisse decreased the target price for Bristol stock from $62 to $58.

Bristol’s success in the market may come down to the company being able to “effectively market the message that the IO/IO combo would allow patients to avoid chemotherapy and/or save chemo for potential use in a second line setting,” Divan said.

William Blair analyst Matt Phipps, however, sees upside in the stock and Bristol-Myers as “one of the few growth franchises in large-cap pharma.”

The analyst highlighted some of the positives for the stock in an April 17 note. The combination of Opdivo and Yervoy may see uptake in nonsquamous patients with high TMB and low PD-L1 expression and also squamous patients, where there are no currently approved PD-1 combination regimens, though trials of competitors are due in the near term.

These two subtypes represent 20% of first-line patients and therefore a $1.5bn opportunity in the US alone, Phipps said.

“We have revised our estimates to account for increased competition in the first-line NSCLC setting, but still see significant growth opportunities for Opdivo, both in NSCLC and other tumor types,” Phipps said.

Morningstar sees Bristol’s Yervoy and Opdivo as well-positioned in several cancers outside of NSCLC, which it expects will represent about 70% of long-term sales. Published online 20 April 2018
Merck KGaA Down-Plays Further Deals After Consumer Health Sell-Off

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Merck KGaA could use some of the €3.4bn ($4.2bn) it will receive from the all-cash sale of its global consumer health business to strengthen its remaining business sectors, in healthcare, life sciences and performance materials, but the primary use of net proceeds from the sale of the consumer health business to Procter & Gamble Co., announced on Apr. 19, will be to speed up the deleveraging process, the German multinational said.

‘INCREASED FLEXIBILITY’

Merck had net financial debt of €10.1bn at the end of fiscal 2017, mainly due to the acquisition of Sigma-Aldrich Fine Chemicals. “We are resolutely working to quickly lower our acquisition-related debt-to-equity ratio,” said CEO Stefan Oschmann when the company’s year-end results were reported in March 2018. The sale is expected to close by the end of the fourth quarter 2018, subject to regulatory approvals and other conditions.

Although Merck said the sale would allow it to “increase flexibility to strengthen all three business sectors,” the possibility of further deals in the near future was thought unlikely by Bernstein analysts. “We expect all €3bn in post-tax benefit to be used to de-lever rapidly to get below 2-times net debt/EBITDA by the end of 2018,” they commented. Analysts at Morgan Stanley also believed the divestment would be positive for the company.

The pharma-related consumer health sector has undergone notable change over the past few years: last month, GlaxoSmithKline PLC spent $13bn on buying Novartis AG’s 36.5% stake in the companies’ consumer healthcare joint venture, enabling GSK to gain clarity about how much it could invest on pharma R&D and business development.

At the beginning of 2017, Sanofi acquired the consumer products brands of Boehringer Ingelheim GMBH, in exchange for its Merial animal health care business.

And Procter & Gamble was previously thought to be in the running to acquire the consumer health business from another pharmaceutical company, Pfizer Inc.

SPECIALTY FOCUS

The consumer health divestment will allow Merck to concentrate on its strategy of becoming a global specialty company, buoyed by recent launches of the multiple sclerosis therapy, Mavenclad (cladribine), and the checkpoint inhibitor co-developed with Pfizer, Bavencio (avelumab). Merck said the consumer health business had been sold at an attractive price, reflecting the high asset value and performance.

As part of the deal, around 3,300 employees will move over to Procter & Gamble, subject to employee consultations. Key products in Merck’s consumer health business include the combination vitamin B product, Neurobion, and the nasal decongestant, Naswin (oxymetazoline), which are global brands, and the vitamin D product, Vigantol, which is primarily marketed in Europe.

Procter & Gamble said the purchase would “improve its OTC geographic scale, brand portfolio and category footprint in the vast majority of the world’s top 15 OTC markets.” The acquisition will replace the PGT Healthcare joint venture P&G had with Teva Pharmaceutical Industries Ltd., that is ending on July 1, 2018, pending regulatory approval; the two companies said their priorities were no longer aligned.

Despite sales growing above the average for the consumer health sector, at 6% rather than around 4%, over the past few years, the consumer health business of Merck accounted for only a small part, 6%, of its overall activities – in 2017, net sales of the consumer health business amounted to €911m, a 7.6% increase, while total sales at Merck reached €15.3bn.

Published online 19 April 2018

Sanofi’s Generics Business To Be Sold To Advent

Advent International aims to invest in Zentiva BV and build a new independent European generics leader, as the private equity firm and Zentiva’s parent, Sanofi, announced they had entered exclusive negotiations for Advent to acquire Zentiva for €1.9bn ($2.3bn). The offer is “firm, binding and fully financed,” the companies said on Apr. 17, and the acquisition is expected to close by the end of 2018.

For Sanofi, the divestment will reduce the number of business sectors in which it operates, allowing it to concentrate on making new acquisitions in pharma and consumer health, and giving it extra funds with which to do so. In 2017, the Paris-headquartered big pharma exchanged its animal health business for Boehringer Ingelheim GMBH’s consumer health portfolio, and started to prepare for the divestment of its European generics operations.

At that time, several private equity firms and a pharma company were said to be interested in generics business, and now Advent, a global investment firm that has also invested in other European generics companies over the years, has come out ahead.

“At €1.92bn, the transaction represents around 2.5-times Sanofi’s European generics sales in 2017 of €760m,” commented analysts at Generics Bulletin. “The price is roughly in line with the €2bn that had been widely mooted.” they added.

“Generics is clearly a space that interests Advent. The private-equity (PE) fund recently spent around $124m on snapping up Endo International PLC’s Somar generics unit in Mexico,” the Generics Bulletin analysts add. Advent says it will support the Zentiva management and invest in its operations, production facilities and R&D pipeline.

The European generics sector has undergone several rounds of M&A and consolidation, driven by pricing pressures but also supported with moves to increase generic prescribing.


john.davis@informa.com, 17 April 2018
Experts Challenge GSK Triple Inhaled COPD Therapy Claims

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A claim by researchers associated with the IMPACT trial, sponsored by GlaxoSmithKline PLC, that triple therapy for chronic obstructive pulmonary disease (COPD) with inhaled glucocorticoid, a long-acting muscarinic antagonist (LAMA) and a long-acting beta agonist (LABA) is better than dual therapy of either inhaled glucocorticoid-LABA or LAMA-LABA has been questioned in a New England Journal of Medicine editorial.

‘We don’t believe it presents an accurate picture of the favorable benefit/risk profile of Trelegy Ellipta’

Reporting, in the current NEJM issue, the findings of the IMPACT trial, the clinical researchers concluded that triple therapy with fluticasone furoate, umclidinium and vilanterol resulted in a lower rate of moderate or severe COPD exacerbations than fluticasone furoate-vilanterol or umclidinium-vilanterol and that the triple therapy also resulted in a lower rate of hospitalization due to COPD than umclidinium-vilanterol.

The IMPACT study was a randomized trial involving 10,355 patients with COPD comparing 52 weeks of a once-daily combination of fluticasone furoate at a dose of 100 micrograms, umclidinium at a dose of 62.5 micrograms and vilanterol at dose of 25 micrograms (triple therapy) with fluticasone furoate-vilanterol (100 micrograms and 25 micrograms, respectively) and umclidinium-vilanterol (62.5 micrograms and 25 micrograms, respectively). Each regimen was administered in a single Ellipta inhaler and the primary outcome was the annual rate of moderate or severe COPD exacerbations during treatment.

According to the NEJM paper, the rate of moderate or severe exacerbations in the triple therapy group was 0.91 per year compared with 1.07 per year in the fluticasone furoate-vilanterol group and 1.21 per year in the umclidinium-vilanterol group. The annual result of severe exacerbations resulting in hospitalization in the triple therapy group was 0.13 as compared with 0.19 in the umclidinium-vilanterol group. There was a higher incidence of pneumonia in the inhaled glucocorticoid groups than in the umclidinium-vilanterol group, and the risk of clinician-diagnosed pneumonia was significantly higher with triple therapy than with umclidinium-vilanterol.

While acknowledging that the IMPACT trial has several strengths, Samy Suissa and Jeffrey Drazen, in an accompanying editorial, describe results as challenging to interpret and questioned whether they provided robust enough evidence for stepping up to single-inhaler triple therapy in clinical practice.

In particular, Suissa and Drazen noted that the withdrawal of inhaled glucocorticoids from patients receiving LAMA-LABA dual therapy might have contributed to the higher number of exacerbations seen in the first month of the trial. “During the subsequent 11 months of follow-up, the incidence of exacerbations with LAMA-LABA was practically identical to that with triple therapy. This phenomenon probably explains the lower incidence of exacerbations with LABA-inhaled glucocorticoid than with LAMA-LABA, a finding diametrically opposite to those of the FLAME trial. Consequently, this aspect of the trial design probably resulted in falsely exaggerating the benefit of triple therapy in comparison to the LAMA-LABA comparator group,” they wrote.

Until further evidence is available, Suissa and Drazen argue that clinicians should rely on the updated GOLD 2017 guidelines recommending that escalation to triple therapy occur only after maximized bronchodilator treatment with LAMA-LABA regimens and be limited to patients with more symptomatic GOLD group D COPD with frequent exacerbations. “Although single-inhaler triple therapy offers simplicity in treating COPD, any potential benefit could be lost and potential undue harm induced if triple therapy is expanded to patients with GOLD groups A, B and C COPD,” they concluded.

But GSK said it disagrees with the opinion in the editorial. “We do not agree with the long-held view of Dr. Suissa, which he repeats in his critique of IMPACT published in the editorial,” the company said in a statement. “We don’t believe it presents an accurate picture of the favorable benefit/risk profile of Trelegy Ellipta that the study and broader evidence base supports.”

“IMPACT was designed in consultation with the FDA, to mirror elements of typical clinical practice,” the company added. “The results clearly demonstrate the range of clinically relevant patient benefits of Trelegy Ellipta vs Anoro and Breo. These include reducing moderate/severe exacerbations and improving lung function and quality of life, as well reducing hospitalizations and on-treatment all-cause mortality compared to Anoro. We will present further data at ATS and to other relevant scientific, guideline and regulatory bodies who will ultimately determine how IMPACT will inform the management of COPD.”

Published online 20 April 2018
ImmuPharma Puts On Very Brave Face After Lupus Drug Flop

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The UK’s ImmuPharma PLC is insisting that its investigational lupus drug Lupuzor (forigerimod) still represents a “significant opportunity” despite extremely disappointing top-line results from a much-anticipated Phase III trial.

Data from the initial analysis based on 202 patients, including those who withdrew from the study, showed that Lupuzor plus standard of care (SOC), such as steroids, anti-malarials and methotrexate, was more effective than placebo plus SOC (52.5% versus 44.6%). However the high response rate in the placebo group meant the primary endpoint of statistical significance was not reached.

ImmuPharma added that Lupuzor also demonstrated a superior response rate over placebo (68.8% versus 59.2%) in the 153 patients who completed the study and stressed that for those patients who had anti-Ds DNA autoantibodies (a recognized biomarker for lupus), the difference was 61.5% versus 47.3% for placebo. The company also stressed that the study “confirmed the outstanding safety profile of Lupuzor,” with no serious adverse events reported.

In addition, ImmuPharma pointed out that it is running an “investigator and patient-led” open-label extension study permitting all patients who participated in the trial to receive Lupuzor for the next six months. Chairman Tim McCarthy said in a statement that “whilst we are disappointed with Lupuzor’s novel mechanism of action, the lack of dangerous seizures with currently available therapies.

Despite the brave face ImmuPharma put on the data, the investment community was less than convinced about Lupuzor’s potential and the firm’s shares crashed 77% to close at 34.3 pence on April 17. Edward Thomason, company analyst at PharmaVitae, told Scrip that “there is no way management can hide the fact that this news was a crushing but hardly unsurprising defeat,” adding that the drug’s development history had raised unrealistic hopes for success and “failure to gain significance will likely spell the end for Lupuzor in lupus for good.”

‘WHOLLY UNREALISTIC’

He went on to say that although Lupuzor’s prospects remains uncertain with an open-label extension study ongoing, PharmaVitae “doesn’t see a realistic future for the drug, and views ImmuPharma’s management commentary on ‘ongoing discussions with a number of larger pharmaceutical companies’ as a distraction and wholly unrealistic given the drug’s results and future.” However, given ImmuPharma’s share price nose-dive, “any potential suitor will be able to acquire the company cheaply,” Thomason added.

Gary Waanders, an analyst at Bryan Garnier, issued an investment note saying that “it is an achievement in itself for a small biotech company to complete a Phase III clinical trial in such a challenging indication as lupus.” He offered a glimmer of hope for ImmuPharma, saying the data from the patients with anti-DsDNA autoantibodies “warrant further clinical investigation and could represent a future route towards demonstrating clinical efficacy of Lupuzor in such a subset of patients. This signal of activity may be the carrot which attracts the involvement of a pharma partner.”

Karolina Kujawa, disease analyst at DataMonitor Healthcare (DMHC), told Scrip that drug discovery for lupus has proved to be particularly challenging, with many therapies failing to meet primary endpoints in Phase III studies. She acknowledged that “despite the general excitement around Lupuzor’s novel mechanism of action, the lack of strong efficacy results casts a shadow on the drug’s future success.”

Kujawa also cited the concerns of key opinion leaders recently interviewed by DMHC who were skeptical of the drug’s ability to demonstrate efficacy. Published online 17 April 2018

Epidiolex ‘No Longer A Pipe Dream’

Commercial prospects for UK-based GW Pharmaceuticals PLC will be transformed by expected approval and launch in the US of its cannabidiol-derived epilepsy drug Epidiolex, which analysts say could become a blockbuster and potentially open up a new market for cannabidiol-based medicines.

The clinical-stage biotech’s cannabidiol-derived epilepsy drug on April 19 got a unanimous AdCom endorsement, affirming the FDA’s belief that there are no obstacles to approval for the medicine.

Adjuvant Therapy

The Peripheral and Central Nervous System Drugs Advisory Committee thus voted 13-0 supporting the approval of the NDA for the investigational cannabidiol oral solution for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) and Dravet syndrome in patients two years of age and older. Importantly, the committee highlighted that Epidiolex did not show high risk of a fatal drug-induced liver injury, and showed limited adverse potential.

LGS and Dravet syndrome, which develop in childhood, are devastating forms of epilepsy with high morbidity and mortality rates and a significant burden on families and caregivers. More than 90% of patients with LGS or Dravet syndrome have multiple seizures per day, which puts them at constant risk for falls and injury. Physicians who treat LGS and Dravet syndrome patients struggle to reduce the sheer volume of dangerous seizures with currently available therapies.

Epidiolex is a liquid formulation of purified, plant-derived cannabidiol, a non-psychoactive cannabinoid, which is being studied for the treatment of a number of rare, severe pediatric-onset epilepsy disorders.

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18 | Scrip | 27 April 2018
Epixiolex is currently undergoing a priority review at FDA with a user fee goal date of June 27. An action date by the European Medicines Agency (EMA) is expected in the first quarter of 2019. It holds an orphan drug designation and a rare pediatric disease designation. If approved, Epixiolex would be the first ever FDA-approved medicine for Dravet syndrome patients.

‘No Obstacles to Approval’
FDA advisory committees are independent expert panels. Their votes are not binding but are considered by the FDA when deciding whether to approve a new medicine.

Still, analysts at Cantor Fitzgerald said in a reaction note that “given the positive AdCom decision in addition to the positive results seen in three pivotal trials in two distinct indications – which led to applause from the audience after hearing patient perspectives – we have increased our confidence in Epixiolex’s approval in the US to 100% probability of success, from 90% previously. We predict that the drug will be approved imminently, much before the PDUFA date.”

Launch Price
Cantor Fitzgerald foresees Epixiolex having a launch price of $36,000 in the US and $24,000 in the EU, with sales of $136m in 2019. Researchers at Clarivate Analytics expect Epixiolex to become a quick success, generating nearly $1.2bn by 2022. In its fiscal year ended Sept. 30, 2017, GW Pharma booked revenues of $11.0m and a net loss of $175.9m.

GW Pharma reportedly aims to market the drug for LGS and DS in children two years or older, at a target dose of 10 milligrams per kilogram per day, with the ability to receive dose adjustments up to 20 milligrams per kilogram per day. Management previously disclosed plans to hire approximately 70 sales representatives to address a group of 4,000-5,000 target treating physicians in the US and a smaller team of 30 sales reps in the five key European countries: Germany, France, UK, Italy and Spain.

Hanmi Halts Olmutinib After Alliances Crumble

Hanmi Pharmaceutical Co. Ltd. has decided to stop all further development of its third generation EGFR inhibitor Olita (olmutinib) following ZAI Lab Ltd.’s return of rights in the China region to the drug.

The South Korean company will instead focus on the development of its 20 other innovative drug assets including the novel oral pan-HER inhibitor poziotinib.

“We tried to develop Olita with a strong will, but decided to suspend the development on expectation the new drug’s value will substantially fall short of its future R&D cost,” explained the company in a statement.

MOVE UNSURPRISING
While Hanmi’s suspension of olmutinib is surely disappointing for the company and its investors, the move is somewhat unsurprising given the drug’s troubled development timeline, Datamonitor Healthcare analyst Dustin Phan told Scrip.

Despite showing promising early phase clinical activity, concerns regarding patients deaths, insider trading, and failed partnerships with Boehringer Ingelheim GMBH and then ZAI Lab appear to have negatively impacted confidence in olmutinib, the analyst noted.

South Korea’s Ministry of Food and Drug Safety (MFDS) decided in October 2016 to limit olmutinib to consenting non-small cell lung cancer (NSCLC) patients and monitor its use after distributing safety letters on several cases of serious adverse skin reactions that occurred during the clinical development of the drug.

“Even if the drug ultimately progressed through Phase III trials and gained full regulatory approval, olmutinib’s commercial success would likely have been limited due to competition from Targisso (osimertinib), which benefits from a significant first-to-market advantage,” Phan explained.

The global NSCLC market continues to grow increasingly competitive, and Hanmi’s move signals the company’s efforts to focus on more commercially viable and promising therapies.

The company still has an opportunity to capitalize on the lucrative NSCLC market through its partnership with Spectrum Pharmaceuticals Inc. and Luye Pharma Group Ltd. for the Phase II asset poziotinib, the analyst added.

Hanmi is slated to present progress of its lung cancer pipelines – comprising poziotinib and HM97211 – as well as other oncology pipelines at the ACCR meeting in Chicago.

LOSS OF ZAI LAB PARTNERSHIP
Hanmi made the halt decision in large part as ZAI Lab’s cancellation of its licensing deal has made it uncertain for the company to proceed with a planned Phase III trial in China, which is olmutinib’s biggest potential market.

According to Datamonitor Healthcare, the treatment of NSCLC in China provides a great commercial opportunity for pharmaceutical companies because of the sheer size of the market. There are 700,000 new cases of lung cancer in the country each year, and NSCLC constitutes about 85% of the total lung cancer patient population.

Pharma companies have been attracted by the high incidence of this disease, and the NSCLC pipeline has grown substantially both domestically and internationally.

The fact that competing drug Targisso is already launched in 40 countries and has begun to be reimbursed in South Korea has also made it tough for Hanmi to recruit patients for its Phase III trials, the company said.

Hanmi so far hasn’t been able to begin a Phase III study for olmutinib as it has had difficulty recruiting patients after Targisso was given reimbursement in South Korea, said Eugene Investment & Securities in a research note. The brokerage noted that Hanmi could have communicated better with investors, which the company has been telling it was planning to conduct multinational Phase III clinical trials, focusing on Asian regions.

Olita received approval from the MFDS in 2016 after completing a Phase II trial on condition it proceeds with a Phase III study after the launch.

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Gilead’s Biktarvy Set To Soar, But ViiV May Win In The End

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HIV market stalwart Gilead Sciences Inc. is once again positioned for huge success with its recently launched single-tablet regimen Biktarvy (BIC/F/TAF), but competitor ViiV Healthcare still could emerge as the market leader over the next decade, Datamonitor Healthcare analysts conclude.

The US FDA approved Gilead’s Biktarvy, which combines the integrase inhibitor bictegravir, the nucleoside reverse transcriptase inhibitor Emtriva (emtricitabine) and the second-generation nucleoside reverse transcriptase inhibitor tenofovir alafenamide (TAF), for initial or replacement therapy for HIV on Feb. 7. A 30-tablet bottle of Biktarvy costs $2,945.65, or $35,839 for 12 months of therapy.

The approval gives Gilead another big edge over its closest competitor, Viiv, a joint venture founded in 2009 and majority owned by GlaxoSmithKline PLC with Pfizer Inc. and Shionogi Inc.

Biktarvy will compete against ViiV’s Triumeq, which includes the popular unboosted integrase inhibitor Tivicay (dolutegravir), the reverse transcriptase inhibitor abacavir and the nucleoside analogue reverse transcriptase inhibitor Epivir (lamivudine). Gilead’s new product also is positioned against the non-proprietary combination of Tivicay as a single agent on top of Gilead doublets like Truvada (emtricitabine/tenofovir disoproxil fumarate, or TDF) and Descovy (emtricitabine/TAF).

Datamonitor’s latest HIV forecast, covering trends from 2017 to 2026, predicts the Biktarvy combination will be a “huge success,” with peak sales in 2022 of $5.8bn in the US and five major European markets (France, Germany, Italy, Spain and the UK).

Biktarvy will be preferred over ViiV’s Triumeq, partly because the latter’s abacavir component is associated with life-threatening allergic reactions and requires HLA-B*5701 testing to identify those at risk of hypersensitivity responses, Datamonitor analyst Ines Mihel concludes in the report.

Some patients get scared off by the potential risk for an allergic reaction, despite the availability of HLA-B*5701 testing, while the large size of the Triumeq pill is another drawback, one US key opinion leader told Datamonitor.

On Feb. 7, the same day Biktarvy cleared the FDA, ViiV filed patent-infringement litigation against Gilead in the US and Canada. ViiV claims that bictegravir infringes its patents for dolutegravir “and many other compounds that include dolutegravir’s unique chemical scaffold.”

GSK followed this up with a Feb. 8 announcement of the start of a new Phase III non-inferiority study called TANGO, comparing patients who switched from TAF-based regimens to a combination of Tivicay and Epivir, versus continuation on TAF regimens.

PATENT LOSSES LOOMING

The TDF backbone in Gilead’s older combinations like Truvada and Atripla (efavirenz/emtricitabine/TDF) began to lose patent protection in Europe in 2017. In the US, the patent will expire in 2021.

Gilead has been working to switch patients to new combinations that include the TAF backbone, which was designed to be more potent so it can be given in smaller doses and is considered safer, with fewer renal and bone mineral-related adverse events.

Payers have been skeptical about the real-world value of TAF over TDF, yet the available TAF-based therapies have achieved strong uptake, the Datamonitor report notes. “Although clinical improvements have only been measured with laboratory parameters, long-term data are reinforcing the advantages of TAF compared to TDF backbones,” it states.

“Key opinion leaders, notably in the US, are convinced about the bone and renal advantages. Additionally, with the aging HIV-infected population, reducing the incidence of bone and kidney toxicity is likely to grow in clinical importance, and could increase TAF’s cost-effectiveness in the long term,” the report adds.

The transition has been slower, however, in some countries like the UK, where TDF generics have been encouraged and doctors are less impressed with TAF, according to the report. Truvada generics have been available in Europe since September 2017 and are expected to enter the US market in December 2021.

CANNIBALIZATION AT GILEAD

Success for Biktarvy will come at the expense of the company’s own other TAF-based combinations, notably Genvoya (elvitegravir/cobicistat/emtricitabine/TAF), Datamonitor expects. Bictegravir is superior to elvitegravir, which requires a pharmacokinetic boosting agent and provides a lower barrier of resistance, hence rendering Genvoya “clinically redundant,” the report explains. Biktarvy’s price also is on par with Genvoya.

Genvoya has been the highest-selling single-tablet HIV regimen, due to its strong safety and efficacy profile as well as Gilead’s pricing strategy, Datamonitor noted.

“While TAF’s safety improvements are relatively marginal, Gilead has priced TAF-based successor products comparatively to their older TDF-based predecessors, providing physicians with a strong incentive to swap patients before there is significant payer pressure to prescribe cheaper generics,” the report states.

Gilead reported $3.7bn in sales for Genvoya in 2017, up from $1.5bn in 2016, and has touted the success of the launch. “At the end of 2017, Genvoya remained the most prescribed HIV therapy for treatment-naive and switch patients in the US and across the top five European markets. Genvoya represents the most successful HIV launch in the US and is the first HIV product to reach $3bn in annual sales,” Gilead Chief Financial Officer Robin Washington said during the company’s fourth quarter earnings call on Feb. 6.

Datamonitor predicts the genericization of Gilead’s emtricitabine/TAF combination Descovy in July 2021 in Europe and June 2025 in the US will have a big impact on Gilead as well as the overall market, triggering a contraction in total global HIV sales starting in 2024. Some payers will switch patients from newer branded single-tablet combination regimens like Genvoya and Johnson & Johnson’s single tablet Symtuza (darunavir/cobicistat/emtricitabine/TAF), which is currently under FDA review, to the cheaper option of a generic Descovy combined with a third antiretroviral standalone agent, the analysts predict.

Tivicay is forecast to capture patient share from Gilead’s TAF-based single-tablet
regimens due to anticipated pressure from payers, the report says, who will want to promote cost savings through combining Tivicay with a cheaper generic fixed-dose combination backbone. Physicians view Tivicay as the best agent to be added on, due its high barrier to resistance, high rates of virologic suppression and a clean tolerability profile.

In contrast, Gilead is not expected to market its integrase inhibitor bictegravir as a standalone agent, so the drug will not be well positioned if payers shift to generics after Descovy’s patent expiry, Datamonitor predicts.

**ViiV’s Ascendancy**

ViiV’s position in the HIV market is being driven by Tivicay as well as new combination regimens.

Tivicay and Merck & Co. Inc.’s integrase inhibitor Isentress (raltegravir) have achieved strong uptake and play an important role in the HIV treatment algorithm. This class is now recommended for first-line use in US and EU treatment guidelines, whereas protease inhibitors are less preferred due to the need for use with a boosting agent, which increases the risk for drug-drug interactions as well as cardiovascular events, the report explains.

Key opinion leaders interviewed by Datamonitor called Tivicay the drug of choice among most physicians. One described it as “almost a perfect drug.” ViiV’s new two-drug regimens, Juluca (dolutegravir/rilpivirine) and Tivicay/Epivir, may experience slow uptake compared to Gilead’s Biktarvy and J&J’s Symtuza, because of physicians’ concerns regarding long-term resistance generation with two-drug regimens versus the standard-of-care three drug regimens, the report says.

Juluca was approved in the US in November 2017 and brought in initial sales of £5m during the fourth quarter of 2017. With the Juluca regimen, there is little room for error in terms of drug levels, so compliance is very important, prescribers say.

“Although Juluca and Tivicay/Epivir have displayed promising virologic suppression rates in the Phase III SWORD studies and Phase II ACTG A5353 trial, respectively, long-term virologic data will be essential to promote uptake and reassure physicians regarding the risks of emergence of resistance and/or virologic failure,” the report states.

Also, the safety advantage of a two-drug regimen over three-drug TAF-based regimens is difficult to prove with physicians, especially compared with the newer three-drug combos that offer improved bone and renal safety.

Nonetheless, Datamonitor expects Juluca and Tivicay/Epivir to reach blockbuster status by 2026. The analysts also expect ViiV’s investigational cabotegravir/rilpivirine combination – the first long-acting injectable (given once every four to eight weeks) – to be a hit.

“Key opinion leaders also stressed their preference for prescribing the LAI [long-acting injectable] over the oral two-drug regimens developed by ViiV Healthcare due to the reduced risk of non-adherence and subsequent lower likelihood of emergent treatment resistance,” the report says.

**Overall Market Contracts**

In addition to Truvada, Atripla and Descovy, patents for other key HIV brands are expiring during Datamonitor’s forecast period of 2017-2026, including J&J’s Prezista (darunavir), Bristol-Myers Squibb Co.’s Reyataz (atazanavir) and Merck’s Isentress.

In its Feb. 6 earnings report, Gilead said that HIV and hepatitis B product sales for 2017 reached $14.2bn compared to $12.9bn in 2016. The increase was due primarily to the strong uptake of regimens that include TAF, which now account for 62% of Gilead’s total HIV prescription volume in the US, the company explained. (TAF solo therapy, marketed as Vemlidy for HBV, also contributed to those sales figures.) Performance of TAF-based HIV products helped to offset large declines in the company’s hepatitis C virus franchise.

GSK reported that its HIV sales in 2017 were up by 22% to £4.3bn (almost $6bn), driven by increases in market share for Truvada and Tivicay, which brought in about £3.8bn, helping to partially offset losses related to the impact of generic competition for other brands.

Despite the success of new products, Datamonitor projects that the HIV market will start to contract from a peak of £22.7bn in sales for 2024, declining to £21.1bn in 2026.

Gilead’s HIV sales in the US and five major EU markets are expected to decline from $9.7bn in 2017 to $6.1bn in 2026. However, these figures do not include sales for HIV prevention – most US sales of Truvada currently fall into this category – or products that were not considered to have a major impact in the market during the forecast period, like Viread (tenofovir disoproxil fumarate). Also, Gilead’s overall market share will be aided by the launch of J&J’s TAF- and cobicitstat-inclusive Symtuza, which will bring significant royalty income Gilead’s way.

*Published online 18 April 2018*
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.

### Selected clinical trial developments for the week 13–19 April 2018

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*Source: Biomedtracker*
Struggling Fibrocell To Consider All Strategic Options From Business As Usual To Full Sale

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Cell-based therapy company Fibrocell Science Inc. filed an 8-K with the US Securities and Exchange Commission on April 18 saying that it is conducting a comprehensive review of strategic alternatives for the future direction of the company.

Formerly known as Isolagen, the Exton, PA-based biotech focuses on developing autologous regenerative fibroblast therapies for aesthetic and medical indications – an expensive and difficult development track.

Although the company will keep advancing its candidates, the strategic review could lead to a merger or reverse merger with another company (seeking Nasdaq listing), a strategic investment in Fibrocell, a sale, out-licensing or other disposition of corporate assets, or continuation of the firm's current direction.

Fibrocell has FCX-007 in Phase I/II for recessive dystrophic epidermolysis bullosa (RDEB) and obtained US FDA approval of an investigational new drug (IND) application on March 6 to begin clinical study of FCX-013 in localized scleroderma. Both candidates are partnered with Intrexon Corp. under a deal signed in 2012 and expanded several times since. The company has experienced R&D delays over the past few years.

According to Biomedtracker, Fibrocell plans to initiate an open-label, Phase II/III study of FCX-013 in moderate-to-severe scleroderma during the third quarter of 2018. FCX-007, a gene-modified autologous fibroblast injection that encodes collagen 7, will move into the Phase II portion of a Phase I/II study begun in 2016. The biotech notes that following interim data from three adults in the Phase I portion of the study showing the drug was safe and well-tolerated, with positive early trends in pharmacology and wound healing, it obtained the FDA's okay to initiate enrollment of pediatric patients in the Phase II portion, slated for the third quarter.

Fibrocell pointed out that both candidates have received rare pediatric disease designations from FDA, meaning the company could earn a priority review voucher for the FDA's okay to initiate enrollment of pediatric patients in the Phase II portion, slated for the third quarter.

Fibrocell also cited continued developments unless and until the board decides on a specific action.

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Novartis has appointed Dr. John Tsai as head of global drug development (GDD) and chief medical officer, effective May 1. He will be based in Basel, Switzerland, will report to CEO Dr. Vas Narasimhan, and become a member of the executive committee. Tsai joins Amgen where he has been chief medical officer and senior vice president of global medical since May 2017. He succeeds Narasimhan who became CEO of Novartis on February 1. Dr. Rob Kowalski, who has led GDD ad interim since February 1, will resume his responsibilities as head of global regulatory affairs for GDD.

GlaxoSmithKline has appointed Kevin Sin as senior vice president and head of worldwide business development for pharmaceuticals research & development. He will join GSK in July from Genentech, where he is currently vice president and global head of oncology business development. He has worked within the pharmaceutical and life sciences industry for over 20 years in roles spanning business development, legal and research. Before joining Genentech in 2006, Sin was an attorney advising private and public life sciences companies on business development and strategic partnering transactions. He will report to Hal Barron and be based in San Francisco.

Dr. Gilla Kaplan, Celgene’s long-standing director, is retiring from the board and will not stand for re-election at the upcoming annual stockholder meeting on June 13. Patricia “Pat” Hemingway Hall and Hans Bishop have been elected to Celgene’s board. Kaplan has served as director since April 1998 and is currently director of the global health program for tuberculosis at the Bill and Melinda Gates Foundation. Hemingway Hall has more than 30 years of experience with a focus on the US health insurance market. Bishop was most recently president and CEO of Juno Therapeutics, which he co-founded in 2013 and led until Juno was acquired by Celgene in March.

Vectura Group’s chief financial officer and executive director Andrew Derodra has decided to leave the group to take up a new role as chief financial officer at Unilabs, the private-equity owned medical diagnostics company. Derodra will remain in his position at Vectura and on its board until the end of July and a search for his replacement is underway. Vectura has also appointed Anne Whitaker as an independent non-executive director with effect from June 1. Whitaker has more than 25 years’ experience in the life science industry, with experience in the US respiratory sector. Until recently she was president and chief executive officer of KNOW Bio, LLC and its wholly owned subsidiary, Novodlem Therapeutics Inc, and before that was executive vice president and group chairman at Valeant Pharmaceuticals.
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