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IO Outlook: Bavencio Leads PD-1/L1 Pack In Ovarian Cancer

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The ovarian cancer market will experience significant growth over the next five years as novel therapies complete pivotal trials and make their way through regulatory agencies; the value of the US market is expected to expand at the fastest rate.

According to forecasts from Datamonitor Healthcare, combined ovarian cancer drug sales in the US, Japan, and five major EU markets (France, Germany, Italy, Spain and the UK) will increase from $121m in 2014 to $667m in 2023 at a compound annual growth rate of 20.91%.

To date, in the US, only four drugs have been approved for the treatment of ovarian cancer – but the development pipeline presents promising drug candidates. Poly ADP-ribose polymerase (PARP) inhibition remains an attractive target for drugs in this indication – with three PARP inhibitors already approved – but developers are also assessing newer immunological pathways.

"With about 22,000 diagnosed patients and about 15,000 deaths annually, there is a clear need and opportunity for innovation in advanced ovarian cancer," Sankalp Sethi, manager at ZS, a global sales and marketing firm, told *Scrip*. He noted that the next big wave in ovarian cancer treatment after PARP inhibition monotherapy is combination therapy – which is spurring development of other cancer immunotherapies in this space.

"PARPs alone are currently in Phase I/II trials in combination with anti-PD-L1, anti-CTLA-4, VEGF inhibitors, MEK inhibitors and chemotherapy, to name a few," he said. "By 2019, we will likely have approvals for combination regimens – with PARPs as the backbone – that continue to improve survival for ovarian cancer patients, especially HRD-negative and platinum-resistant patients where the unmet need is substantial."

AFTER PARP COMES PD-L1

Outside the PARP space, all five programmed cell death protein-1 (PD-1) or PD-ligand 1 (PD-L1) therapies already on the market for other cancers are being tested in clinical trials in various ovarian cancer settings.

Sethi noted that there is "ample potential in this market for new therapies and combinations, especially those aimed at the up-to-half of patients not substantially benefitting from the current wave of PARP targeted therapies."

Merck KGAA and **Pfizer Inc.**'s jointly developed PD-L1 inhibitor *Bavencio* (avelumab) is positioned to be the first of this class to win approval in ovarian cancer. The drug is in Phase III trials for the treatment of advanced ovarian cancer patients in the first-line and maintenance settings, as well as the platinum-resistant/refractory setting.

Bavencio is slightly ahead of its closest competitor, **Roche**'s PD-L1 drug *Tecentriq* (atezolizumab), in ovarian cancer but Roche's drug is snapping at the Merck KGaA/Pfizer drug's heels and is already in Phase III. Tecentriq is targeting the same patient populations as Bavencio – addressing first-line and maintenance indications – but Roche does not have a late-stage trial ongoing in the platinum-

CONTINUED ON PAGE 7

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

from the editor

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Our front-page story this week takes a look at immuno-oncology options being explored for ovarian cancer. This cancer type has not been at the forefront of IO development, not least because it had not previously been thought to be immunogenic. However, with both Merck KGaA/Pfizer and Roche conducting Phase III trials of their flagship PD-L1 inhibitors for ovarian cancer, that assumption could soon be challenged (or validated).

The article is the latest in *Scrip*'s IO Outlook series, which has drilled down into the R&D pipeline for a range of cancer types, always through the prism of immuno-oncology. Check out previous issues of Scrip and our website for separate overviews of IO development programs in kidney, head and neck, brain, gastric and cervical cancer. As the expected next wave of filings expands the potential IO treatment landscape beyond the already impressive inroads into melanoma, lung, bladder, kidney and head and neck cancers and Hodgkin's lymphoma with the likelihood of multiple new and combined therapy options reaching the market, our writers are monitoring the pipelines to bring you timely and analytical updates.

In other IO news, Roche's *Tecentriq* has been given a positive opinion by the EU's CHMP, setting it on course for lung and bladder cancer monotherapy approvals in Europe by the third quarter (its first indications in the EU after receiving prior approvals in the US). See p10. Meanwhile, AstraZeneca is keeping its cards close to its chest on the outcome of the CHMP's consideration of *Imfinzi* for accelerated assessment in lung cancer (p16).

Scrip

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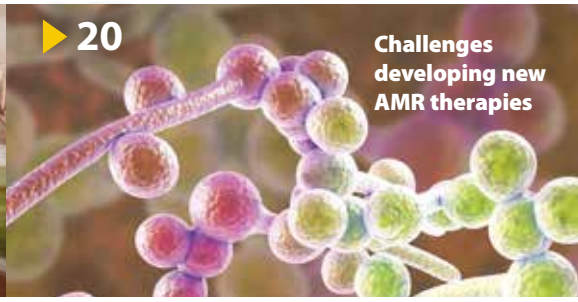

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Deal Watch: Gilead And Spring Bank Set Second Trial Collaboration In HBV
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Analyst speculates that Gilead could move to acquire Spring Bank if combo trial yields promising data for functional cure of hepatitis B. Eisai in-licenses PARP inhibitor with potential in breast cancer from Oncology Venture, while Sunovion out-licenses three corticosteroid products to Covis.

Infographic: Trends In Korean Gene And Stem Cell Therapies
http://bit.ly/2uoUugI
South Korea has opened a new era with the recent granting of approval to the country's first gene therapy, for Kolon Life Science's osteoarthritis drug *Invossa*. *Scrip* takes a graphical look at the current state of the country's wider gene and stem cell therapy sector, one of the key biotech areas the government is nurturing.

Celltrion Healthcare IPO To Accelerate Celltrion's Global Biosimilar Expansion
http://bit.ly/2vB7MFy
Celltrion Healthcare's initial public offering, which is seen as the most anticipated biotech IPO in South Korea's Kosdaq market this year, is set to speed up Celltrion's expansion of its global market presence as well as the development of biosimilars and novel drugs.

Spanish Biotech Star Oryzon Slumps After Roche Rejection
http://bit.ly/2us7i4i
Barcelona-based Oryzon Genomics remains upbeat about the prospects for 'a first-in-class, best-in-class LSD1 inhibitor' for cancer even though Roche has walked away from what was a potentially lucrative partnership.

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Novartis CEO Sees Recovery Ahead, Fueled By Pipeline And Alcon Growth

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Novartis AG, apparently en route to recovery, is forecasting a return to growth next year driven by newly launched drugs, a bulging late-stage pipeline of promising therapies, and growth of new potential products.

That was the message from the Swiss group's second-quarter update on July 18, which also saw a rebound in sales by heart drug *Entresto* (sacubitril/valsartan) and a return to growth by its troubled eye division Alcon.

"Our innovation flow is stronger than ever and our results in Q2 give us confidence that our next growth phase is coming and expected to begin in 2018, once we're out from under the patent expiration of [former blockbuster] *Gleevec*," CEO Joe Jimenez told reporters. "The trajectory of current growth drivers reinforces our confidence in our next growth phase," the CEO added.

And Alcon finally delivered a quarter with clear sales growth in its two main sub-divisions, following a long period of retrenchment and heavy investment. The Vision Care division for contact lenses and accessories saw sales grow by 2%, while the more problematic Surgical area which includes intraocular cataract lenses grew by 3%. Noting this was the first quarter where Alcon had shown sales growth since 2014, Jimenez said: "We're starting to think this is the beginning of the turn for the [Alcon] business."

The generics division Sandoz however saw quarterly net sales decline 4% at constant exchange rates from a year earlier to $2.45bn, due largely to pricing pressures in the US market. This was partially offset by biosimilar growth.

DRUG DRIVERS

Drivers underpinning the overall group's strong second quarter included *Cosentyx* (secukinumab), Entresto, *Promacta* (eltrombopag), MEK inhibitor *Mekinist* and BRAF inhibitor *Tafinlar*, *Jakavi* (ruxolitinib), *Tasigna* (nilotinib), *Gilenya* (fingolimod) and the cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor *Kisqali* (ribociclib 200 mg tablets), as well as Biopharmaceuticals and sales growth generally in emerging markets.

Entresto generated sales of $110m in the second quarter versus $32m a year earlier. Jimenez said the company expects Entresto's sales to continue to recover and reach $500m for the full-year. *(Also see "Can Slow Selling Heart Drug Entresto Perk Up In 2017? Novartis Hopes So" Scrip, 25 Jan, 2017.)*

Cosentyx, which is in the lead in the ankylosing spondylitis and psoriatic arthritis areas, giving the group first mover advantage in the IL-17 space, saw sales of $490m in the second quarter, 90% higher than the year-ago quarter. Jimenez said the company now projects *Cosentyx peak* sales of around $3bn, but didn't give a time frame.

ANALYSTS APPLAUD RESULTS

Analysts generally agreed that the latest quarter suggests Novartis is on the way up.

Eric Le Berrigaud of Bryan Garnier & Co said in a reaction note that "we were expecting Alcon and Entresto to show signs of an inflexion point and we can say that those signs are indeed present in today's release."

Analysts at Berenberg said Novartis "enjoyed a productive period from the pipeline and, with good commercial execution, should now be on a sustainable growth trajectory."

CEO Jimenez told journalists the second quarter of 2017 "was probably the strongest innovation quarter that we've had in our history."

PIPELINE HEADLINERS

No R&D update was given during the presentation. But Jimenez did highlight three pipeline assets which had read-outs in the second quarter and which have significant commercial potential for Novartis.

He said Novartis's CAR T-cell therapy CTL019 will likely get US FDA approval by October for the small indication of pediatric acute lymphocytic leukemia (ALL) after winning unanimous FDA adcom backing earlier this month.

Jimenez said that Novartis is "also making progress on what could become the next indication," that being the bigger commercial opportunity, diffuse large B cell lymphoma (DLBCL). He noted that The JULIET study showed that CTL019 delivered a 37% complete response rate at three months. The company thus plans to file CTL019 in DLBCL in the US and in Europe during the fourth quarter of this year. "This [DLBCL] could be a significant platform for the company, but it's too early to project possible sales," the Swiss company's American CEO said.

Another pipeline promise he highlighted was the biologic, *RTH258*, a single chain antibody fragment that binds vascular endothelial growth factor (VEGF). It is designed to treat wet AMD (wAMD) and have long duration of activity in the eye. The HAWK and HARRIER trials proved that RTH258 is as effective as market leader *Eylea* (aflibercept), and allows for less frequent maintenance dosing. *(Also see "Novartis' Brolucizumab Shows Dose Advantage Over Eylea In nAMD Trials" Scrip, 20 Jun, 2017.)* This market is already worth over $8bn in sales globally and RTH258 could take 35% of the market at peak, according to analysts at Berenberg. Details of the HAWK and HARRIER evaluations will be presented at the American Academy of Ophthalmology meeting in November, Jimenez said.

CANTOS STUDY

The third asset singled out for praise by the CEO was Novartis' IL-1β inhibitor antibody *ACZ885* (canakinumab), which unexpectedly showed positive top-line results from a trial called CANTOS in which the Phase III cardiovascular disease study using canakinumab met the primary endpoint in atherosclerosis. Canakinumab is an interleukin-1 beta blocker, already approved in the US as *Ilaris* for treating cryoporin-associated periodic syndrome and active systemic juvenile idiopathic arthritis. Full details from the CANTOS the trial will be presented on August 27 at the European Society of Cardiology congress in Barcelona, Spain. Jimenez said an analyst presentation would also take place that day "and that's when we'll reveal our plans for Ilaris in cardiovascular," he said.

The CEO said the positive second quarter meant "we are on track for the full year guidance," which was left unchanged, meaning Novartis expects group net sales broadly in line with those of 2016 and core operating income to be broadly in line to a low single-digit decline, both measured at constant exchange rates. In the second quarter net sales were flat when measured at constant exchange rates at $12.24bn. Core operating income for the latest three months was also flat in constant currency terms at $3.23bn.

M&A BOLT-ONS ONLY

Speaking later on an analyst call, Jimenez reiterated that Novartis isn't interested in mega mergers, adding that "we're still very focused on our strategy of bolt-on acquisitions - anywhere from $2bn to $5bn would be our sweet spot … We are still focused on the strategy that we strengthen either oncology or the pharmaceutical business or differentiated generics business and that's where we're going to invest." He said the better performance by Alcon has strengthened the company's menu of options for it.

"We said when announcing the Alcon review that we were going to consider all the options, ranging from keeping the business to making a capital markets exit, and obviously a business that has turned and is showing quarterly improvement in growth rates, it just increases the options that we have," Jimenez said. He added that a rebounding business "makes a capital markets exit a possibility, because you've got a growing business with presumably margins that will grow over time. We're going to give an update at the end of the year in terms of what our plans are or where we stand in terms of the carve [of Alcon]."

Jimenez said artificial intelligence will be playing a big role in future drug discovery and development. He said Novartis made significant investment in upgrading the group's IT infrastructure. "This allows us to better leverage advanced analytics in drug development."

ARTIFICIAL INTELLIGENCE

Asked by *Scrip* what use of artificial intelligence will play a significant role in the company going forward, he replied: "We have data from hundreds of thousands if not millions and patients and we're using artificial intelligence to help draw links between certain genetic mutations that will allow us to identify new targets in oncology for targeted therapy.

"And on the development side, we have ten years of data for clinical trials – very, very clean and tight data and we're beginning to use artificial intelligence in ways that will help us improve the probability of success of a late stage clinical trial by using patient identification and based on our historical data as well as predicting something as simple as which centers in the world should we go to for a particular type of clinical trial that will also allow us to reduce our total cost."

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Merck's Lantus Copy Lusduna Poised For US Market Pending Litigation

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Merck & Co. Inc. and development partner **Samsung Bioepis Co. Ltd.** could bring the second copy of **Sanofi**'s blockbuster long-acting insulin *Lantus* (insulin glargine) to the US market now that the product has been tentatively approved by the FDA. Merck announced the tentative approval of *Lusduna Nexvue* on July 20, setting the company up to launch the drug following the resolution of ongoing patent litigation.

The FDA's tentative approval designation means a drug has met the regulatory standards for approval, but it is subject to an automatic stay of approval due to patient infringement litigation. Sanofi filed a patent infringement suit against Merck over the product in September 2016, resulting in an automatic 30-month stay of action.

While Lusduna is not technically a biosimilar, because of the regulatory standards around which insulin is approved in the US, it is expected that it would effectively be marketed as one, basically a more affordable alternative to the originator. The entry of a third product would enhance the competitive market for Lantus-like products in the US and could create more pricing competition. **Eli Lilly & Co.** and **Boehringer Ingelheim GMBH** already have launched a Lantus copy in the US, *Basaglar*. The drug launched in December 2016 following a similar regulatory process that also included a tentative approval in August 2014.

Sanofi and Lilly reached a settlement agreement on their patent dispute in 2015, paving the way for the launch of Basaglar in December 2016. *(Also see "FDA Makes It Official With Basaglar Approval For Diabetes" Pink Sheet, 16 Dec, 2015.)* The terms of the settlement were not disclosed, but Lilly agreed to pay Sanofi royalties on sales of the product. *(Also see "Sanofi Settlement With Lilly Paves The Way For Biosimilar Lantus" Scrip, 28 Sep, 2015.)*

It's possible that Merck and Sanofi could reach a similar agreement on Lusduna, though Merck would not comment on the status of the proceedings.

Some insurers have given Basaglar preferred status on their commercial formularies this year, excluding Lantus, citing competitive pricing. *(Also see "UnitedHealthcare Prefers Basaglar Biosimilar At Lantus' Expense" Scrip, 22 Sep, 2016.)* The drug generated $46m worldwide in the first quarter, $22m of which came from the US.

Sales of Lantus took a hit in the first quarter, falling 14.1% to €1.23bn, with sales impacted by competition from Sanofi's own newer insulin glargine formula *Toujeo* and biosimilar competition in Europe and the US. Sales of both glargine products in the US were down 15.5% in the quarter to €805m, which the company attributed to exclusion from CVS formularies.

Sanofi has been hoping to transition patients on Lantus to Toujeo to protect its all-important franchise, but more competition and potentially even lower prices will only make the market more challenging.

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Teva 'Pay-For-Delay Case Will Keep Courts Busy For Years'

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The marketing activities of drug companies are in the headlines again as European regulators have accused **Teva Pharmaceutical Industries Ltd.** of breaching antitrust rules over its sleep disorder therapy but it will be years before any judgment will be made.

The case is going to be a very long one, given that the European Commission has only just sent Teva a statement of objections, informing the Israeli company of its preliminary view that an agreement signed in 2005 with Cephalon (itself acquired by Teva in 2011) was in breach of antitrust rules. Following a lawsuit, Teva, along with Barr Laboratories, (which Teva also acquired), **Ranbaxy Laboratories Ltd.** and **Mylan Pharmaceuticals Inc.** committed not to market a cheaper generic version of Cephalon's *Provigil* (modafinil) in the European Economic Area until October 2012.

The Commission argues that in exchange, Teva received "a substantial transfer of value from Cephalon through a series of cash payments and various other agreements." In its preliminary view, it argues that the deal "served as a significant pay-for-delay inducement for Teva not to compete with Cephalon's modafinil worldwide."

'SUBSTANTIAL HARM' TO PATIENTS AND BUDGETS

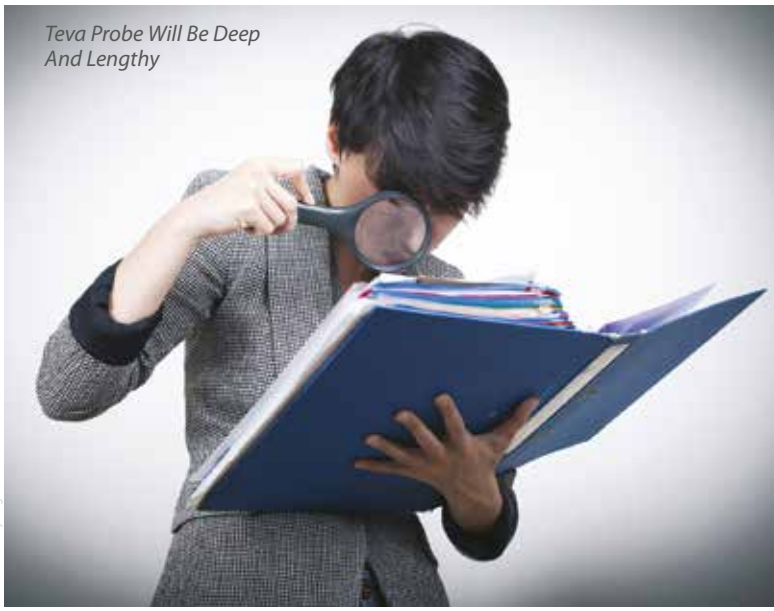
The statement of objections alleges that the patent settlement agreement between Cephalon and Teva "may have caused substantial harm to EU patients and health service budgets," by delaying the entry of a cheaper generic. The Commission argues that "this behavior, if confirmed, would infringe Article 101 of the Treaty on the Functioning of the European Union that prohibits restrictive business practices."

Margrethe Vestager, EU commissioner in charge of competition policy, said: "Market entry and competition by generic drugs is an essential element to improve the affordability of healthcare. In this case, our preliminary finding is that Teva and Cephalon broke EU antitrust rules by agreeing on Cephalon paying Teva to keep its cheaper generic version of Cephalon's sleep disorder drug modafinil out of the market. It's now up to the companies to respond to our concerns."

The emphasis here is very much on preliminary findings and Gustaf Duhs, head of the competition and regulatory team at UK-based law firm Stevens & Bolton, told *Scrip* that this is the beginning of what could be a very long process. He explained that Teva can now examine all the documents on the Commission's investigation file and will then reply in writing - the company can then request an oral hearing.

There is no legal deadline for the Commission to complete antitrust inquiries and the duration of the Teva investigation will depend on the complexity of the case. The original deal with Cephalon will be under the spotlight and Duhs said that patent infringement cases can be settled "perfectly legitimately in normal circumstances" even when rather than fight and maybe win, companies "take the easier and ultimately more profitable and certain route" and come to an agreement.

However, the Commission believes this is a case where the money paid does not reflect what Cephalon would have got in ordinary circumstances. As for the part in the statement of objections which talks about "substantial harm" to patients and health services, Duhs noted that the Commission "will never go there, they will never try to quantify exactly what the loss might be...they don't have to prove the loss, just that Article 101 has been infringed and is it restrictive to competition."



Teva Probe Will Be Deep And Lengthy

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TEVA DENIES ANTI-COMPETITIVE CLAIM

For its part, Teva said it needs time to consider the statement of objections "but we do not believe that Cephalon and Teva entered into any anti-competitive behavior and we will co-operate fully with the authorities with their inquiries." The company added that it "strongly disagrees with the way the commission analyses patent settlements in the pharmaceutical sector."

There is a precedent from across the Atlantic in this specific case as the Federal Trade Commission filed an antitrust action against Cephalon in 2008. In May 2015, Teva reached a settlement ending litigation with the FTC and agreed to pay $1.2bn.

The Commission has probed 'pay-for-delay' agreements involving **Lundbeck Inc.** (2013), **Johnson & Johnson** (also 2013), **Servier SA** (2014) and a number of generic companies. In September last year, the General Court rejected an appeal by Lundbeck *(Also see "EU Pay-For-Delay Ruling Against Lundbeck Sends Signal To Others, Including UK Competition Body" Pink Sheet, 13 Sep, 2016.)* and proceedings concerning an appeal by Servier and others over their €427.7m fine *(Also see "Servier and generics firms to appeal EU verdict on perindopril 'sweetheart' deals" Scrip, 11 Jul, 2014.)* are still pending.

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CONTINUED FROM COVER

resistant/refractory setting. Tecentriq is being trialed as a treatment for recurrent, platinum-sensitive patients.

If Bavencio and Tecentriq successfully make it through regulatory processes and are approved for use in ovarian cancer, the treatments face competition not only from each other but from established therapies like Avastin and the PARP inhibitors, as well as new therapies being tested. Tecentriq and Bavencio share some weaknesses, including the possibility treatment may be limited to PD-L1-positive patients only, intravenous delivery and potentially hefty price tags that could slow or block uptake.

Other drugs in Phase III for ovarian cancer include: **Eisai Co. Ltd.**'s farletuzumab, **PharmaMar SA**'s lurbinectedin, **ImmunoGen Inc.**'s mirvetuximab soravtansine, AstraZeneca's *Recentin* (cediranib), **AbbVie Inc.**'s veliparib, **Gradalis Inc.**'s *Vigil* vaccine and Mateon Therapeutics' *Zybrestat*.

Datamonitor Healthcare analysts expect Bavencio to receive approval in relapsed platinum-resistant/refractory ovarian cancer patients in the US in the third quarter of next year and in Japan and five major EU countries in 1Q 2019.

Further back in the pipeline, other PD-1 inhibitors are being tested in ovarian cancer settings. **Merck & Co. Inc.**'s *Keytruda* (pembrolizumab) is in Phase II, while **AstraZeneca PLC**'s *Imfinzi* (durvalumab) and **Bristol-Myers Squibb Co.**'s *Opdivo* (nivolumab) are in Phase I/II.

The development pipeline presents promising drug candidates

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CHALLENGES IN OVARIAN CANCER

One major hurdle for the development of immunotherapies in this oncological space is that IO drugs have limited efficacy data in ovarian cancer. "Late phase trials that show immunotherapies are efficacious and safe are needed to better establish their place in the treatment paradigm," Datamonitor Healthcare analyst Zachary McLellan told *Scrip*.

Additionally, the development of immune checkpoint inhibitors has lagged behind in the ovarian cancer treatment space in comparison with other indications like melanoma and non-small cell lung cancer.

McLellan said this is likely because ovarian cancer has traditionally been considered non-immunogenic. "More recent early-phase studies have shown certain immunological pathways could be effective in treating ovarian cancer, including the PD-1 pathway. There is still more development and validation to be done," he highlighted.

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At A Glance: PD-1/PD-L1 Inhibitors In Development For Ovarian Cancer

DRUG	TRIAL PHASE	TARGET PATIENT POPULATION IN MOST ADVANCED TRIAL	BIOMEDTRACKER'S LIKELIHOOD OF APPROVAL RATING
Bavencio	Phase III	The Phase III pivotal study JAVELIN Ovarian 100 is testing Bavencio in combination with or following chemotherapy in first-line epithelial ovarian cancer.	39% (4% above average for development stage)
Tecentriq	Phase III	The Phase III ATALANTE trial is testing Tecentriq in patients with late relapse of epithelial ovarian, fallopian tube or peritoneal cancer that has previously been treated with platinum-based chemotherapy.	35% (average rating)
Keytruda	Phase II	The Phase II KEYNOTE-100 study uses monotherapy Keytruda in patients with advanced, recurrent ovarian cancer.	16% (6% above average for development stage)
Imfinzi	Phase I/II	Imfinzi is being trialed as a monotherapy in patients with advance solid tumors that are refractory to standard therapy, including ovarian cancer patients. This trial will report topline data in 2017.	10% (average rating)
Opdivo	Phase I/II	Opdivo is being used in three combination trials targeting advanced solid tumors, including ovarian cancer: ECHO-204, which is pairing BMS's drug with **Incyte Corp.**'s epacadostat an indoleamine dioxygenase (IDO) inhibitor; ORION-01, a combination of Opdivo and **Quest PharmaTech Inc.**'s OvaRex; and a Phase I/II trial in combination with **Celldex Therapeutics Inc.**'s anti-CD27 antibody varlilumab.	10% (average rating)

Source: Scrip & Biomedtracker

Remicade: Biosimilars And Pricing Pressure Wear On J&J's Blockbuster Brand

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Johnson & Johnson's top-selling power brand *Remicade* (infliximab) is beginning to show cracks in its veneer, taking a revenue hit in the second quarter, in part because of a one-time headwind but also because of pricing pressure and a biosimilar rival.

US sales of Remicade declined 13.9% in the second quarter to $1.06bn, while worldwide sales declined 14% to $1.53bn.

A big portion of the US revenue decline was due to a favorable price adjustment in 2016 that has created a headwind in 2017 across the pharmaceutical portfolio, and particularly impacted Remicade, *Procrit*, *Stelara* and *Simponi*, according to the company.

But the launch of the first biosimilar competitor to Remicade last year – **Celltrion Inc.**'s *Inflectra* – and pricing pressure in the crowded market was also a factor. **Pfizer Inc.** launched the lower-priced Inflectra in the US in November 2016 and thus far the impact on Remicade has been minimal. A second biosimilar, **Samsung Bioepis Co. Ltd.**'s *Renflexis*, was approved in April but hasn't yet launched.

Excluding the 2016 pricing headwind, US sales of Remicade in the second quarter were down 5%, chief financial officer Dominic Caruso said. The decline was due to some share erosion, some impact on price and the conversion of some Crohn's disease patients on Remicade to Stelara (ustekinumab), which was approved by the FDA for the indication last year.

Caruso insisted the impact from biosimilars remains moderate and less than the company had forecast.

"A roughly 5% decline is much lower than I think us and any of you had expected for erosion of Remicade, which we all targeted to be somewhere between 10% and 15%," he said. "We haven't seen much impact for now."

The launch of a second biosimilar could hasten the erosion, but it is not clear when Samsung's commercial partner, **Merck & Co. Inc.**, might launch Renflexis.

"In terms of what impact that might have, I think that all depends on the degree to which they discount that product," Caruso added. "For this year, we have our contracting in place with all the managed care organizations, so we feel pretty good that Remicade erosion overall, even with the entrance of a new biosimilar, will be less than we previously expected."

Nonetheless, one analyst, Leerink's Danielle Antalffy, noted in a same-day note, "Remicade generics appear to be starting to have an impact, albeit seemingly still relatively modest."

Remicade remains an essential cornerstone for J&J, generating $6.97bn in sales last year, even as the company advances new growth drivers in immunology and oncology.

During a pharma business review earlier this year, management said immunology will remain a significant growth driver for the company in the near-term, driven by two new launches and line extensions for Stelara and *Simponi* (golimumab).

The first of those new launches was approved by the FDA on July 13, *Tremfya* (guselkumab), a first-in-class IL-23 blocker for plaque psoriasis. The second anticipated new launch is the IL-6 inhibitor sirukumab, pending at the FDA for rheumatoid arthritis.

Sales of Stelara were strong in the second quarter, up 22.3% to $983m worldwide, driven by new indications. Sales of Simponi declined 2%, however, to $439m. Sales in immunology overall declined 2.6% to $2.96bn.

Oncology was a bright spot, with worldwide sales up 17.2% to $1.73bn, driven by the blood cancer drugs *Darzalex* (daratumumab), which generated $299m and *Imbruvica* (imbrutinib), which generated $450m.

Worldwide pharmaceutical sales decreased 0.2% to $8.6bn in the second quarter, a performance that isn't likely to impress investors though consolidated sales increased 1.9% to $18.8bn and adjusted net earnings grew 3.1% to $5bn.

Management is anticipating a strong second half of the year, however, and the company raised its sales and earnings guidance for the full year.

J&J closed the roughly $30bn acquisition of **Actelion Pharmaceuticals Ltd.** in June, giving the company a new foothold in respiratory disease and particularly pulmonary arterial hypertension. *(Also see "J&J's $30bn For Actelion Buys Immediate And Longer-Term Value" Scrip, 26 Jan, 2017.)*

"We see great opportunities with this business, starting with the treatment of the disease itself, addressing PAH earlier, producing better outcomes and expanding into new patient populations," CEO Alex Gorsky said. "For existing medications, we want to explore how combination therapies can improve patient outcomes. For the business itself, we want to expand its global footprint."

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'Potential Blockbuster' Dupixent Set For EU Eczema OK

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Already approved in the US for the condition, **Sanofi** and **Regeneron Pharmaceuticals Inc.'s** biologic *Dupixent* (dupilumab) looks set for approval also in the 28-nation European Union for treating adults with moderate-to-severe atopic dermatitis – but analysts say its therapeutic - and commercial - prospects go much further than that.

Dupixent is an injectable human monoclonal antibody designed to specifically inhibit overactive signaling of two key proteins, IL-4 and IL-13, which are believed to be major drivers of the persistent underlying inflammation in atopic dermatitis, also known as eczema. If approved, as is expected, by the European Commission in coming months, Dupixent will be available in the region as a 300 mg solution for injection.

The London-based European Medicines Agency said its Committee for Medicinal Products for Human Use (CHMP) at its latest meeting backed use of Dupixent due to its "ability to improve the skin condition as measured by improvements in the IGA and EASI-75 scales and to reduce itching in patients with atopic dermatitis."

THE 'NEXT HUMIRA'?

Worldwide sales forecasts for Dupixent in atopic dermatitis are currently around $150m. But many analysts believe the therapy's potential revenues could be significantly higher should it gain approval in other indications.

Analysts at Bernstein in a report issued July 17 said Dupixent could be "the next Humira" [AbbVie Inc.'s adlimumab], implying it is substantially under-modeled because it could work in many more indications that are not in current analyst forecasts.

"This is not a crazy idea; in atopic dermatitis, some NMEs that could pose a competitive threat need to be monitored, but these are generally only in mid-stage development and none share the same mechanism of action," the analysts said, adding that Dupixent "is becoming increasingly critical" to Sanofi's share price performance going forward. Other indications Dupixent could eventually get approval for include asthma, food allergies, esophagitis, and nasal polyposis, according to Informa's Biomedtracker.

> Dupixent could be 'the next Humira' and is becoming 'increasingly critical' to Sanofi's share price

Sanofi's management remains optimistic about growing the number of indications. A Phase III study in pediatric atopic dermatitis in patients aged 6-11 is scheduled for the second half of this year, while top-line Phase III data in adults with asthma are likely in the fourth quarter, with subsequent regulatory submission by year-end. A Phase III for asthma in children aged 6-11 is also planned to start this year. Phase III trials in nasal polyps and Phase II trials in eosinophilic esophagitis are underway, analysts say.

ECZEMA: A HIGH UNMET NEED

There have been few therapeutic advances for atopic dermatitis in the past decade. However, the therapy area is expected to become a blockbuster-sized drug market. New drugs are also expected to command considerably higher prices over today's treatments, which are mainly topical corticosteroids and calcineurin inhibitors. Higher prices will fuel growth but could also raise alarms with payers.

Barclays sees peak sales of more than $1bn across all indications by the early 2020s. Analysts there noted that with Dupixent, Sanofi is focused on the 300,000 adult atopic dermatitis sufferers in the US with the highest unmet medical need, and the 7,000 physicians there who both regularly treat atopic dermatitis and have experience with biologics. Sanofi secured coverage at launch with both Express Scripts and CVS with just one step-edit; discussions with other payers remains ongoing.

Datamonitor Healthcare analyst Christina Vasiliou said "dermatologists eagerly anticipate this biologic as it has the potential to address a high burden in the treatment of atopic dermatitis by providing a targeted therapy suitable for severe patients who are not adequately controlled on topical corticosteroids."

Another positive is that Dupixent has displayed efficacy as a steroid-sparing monotherapy, as the FDA label allows for both monotherapy and combination therapy.

"Some patients are unwilling to take steroids or give them to their children who may suffer from the disease, and they can't be taken for long periods of time because of side effects such as skin atrophy, so having a therapy which can be steroid-sparing in patients with severe disease is a plus," Vasiliou said. Key opinion leaders interviewed by Vasiliou suggested that Dupixent would be used in combination with steroids in most patients, because the response rates are still better with combination therapy.

Dupixent is an anti-IL4/-13 MAb that comes to Sanofi through its collaboration with Regeneron. Sanofi's head of global R&D Elias Zerhouni recently told *Scrip* that Dupixent is representative of its approach to drug discovery going forward, shifting from small molecules to biologics, and going from a single targeting molecule to dual or multi-targeting molecules. Dupixent is a case in point as the biologic works through two independent mechanisms; interleukin-4 and interleukin-13 inhibitors.

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Roche's Tecentriq Gets The Double At The EU CHMP

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The EU's CHMP has recommended approval of **Roche/Genentech Inc.**'s anti-PD-L1 product *Tecentriq* (atezolizumab) for use in lung cancer as well as in second-line bladder cancer, despite its recent disappointment in the IMvigor211 study.

At its latest meeting, the committee recommended that the product be approved for use as a monotherapy for locally advanced or metastatic urothelial carcinoma (UC) and locally advanced or metastatic non-small cell lung cancer (NSCLC). Specifically, the indications are:

- The treatment of adult patients with locally advanced or metastatic UC after prior platinum-containing chemotherapy or who are considered cisplatin ineligible; and
- The treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy. Patients with EGFR activating mutations or ALK-positive tumour mutations should also have received targeted therapy before receiving Tecentriq.

These will be the first indications for Tecentriq in the EU and mean Roche will gain a foothold in the lucrative lung cancer market and also shore up its bladder cancer indication after the surprise failure in the confirmatory Phase III IMvigor211 study.

In lung cancer, Tecentriq is already approved in the metastatic NSCLC setting in the US and a number of other countries. In the EU, Tecentriq is set to compete with **Merck & Co.** Inc.'s *Keytruda* (which has the broadest label in NSCLC including first-line and second-line use in monotherapy, and second-line use), and **Bristol-Myers Squibb Co.**'s *Opdivo* (nivolumab), which is approved for second line use.

In future, analysts are looking to first line use in NSCLC as a potential honey pot for Tecentriq. Jefferies analysts said in a recent research note (July 12), "We remain focused on IMpower150 for Tecentriq in 1L NSCLC, expected in Q3'17. We believe Roche is given little credit for this opportunity despite the positive Phase II Keytruda KN-21(G) study. Recall, KN-21(G) failed to show an OS benefit and if IMpower150 delivers, which we think it will, it is likely to be viewed as superior to Keytruda in this setting."

But **AstraZeneca PLC** is also awaiting data from the MYSTIC study combining its anti-PD-L1 product Imfinzi (durvalumab) with its CTLA-4 inhibitor tremelimumab in first-line NSCLC.

The EU go-ahead in bladder cancer will be of some comfort for Roche. Tecentriq, which had US breakthrough therapy status for bladder cancer, first received accelerated approval in May 2016 – four months ahead if its PDUFA date – for patients with disease progression during or following platinum-containing chemotherapy and for those whose disease progressed within 12 months of neo-adjuvant or adjuvant treatment with platinum-containing chemotherapy. The approval, which was the first for an immunotherapy in bladder cancer, was based on the single-arm Phase II IMvigor 210 study, which tested atezolizumab every three weeks in 310 patients with second-line urothelial cancer.

Two CHMP hurdles cleared for Tecentriq

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> 'Probably the most important thing is to restate our expectation that we will reach double-digit earnings per share growth at constant currencies'

But then came a shock when the confirmatory IMVigor211 study failed to show a survival benefit this May. The setback was all the more disappointing as Merck & Co's rival product Keytruda (pembrolizumab) had already shown an OS benefit in its Keynote-045 study.

Meanwhile, other competitors had also entered the fray: *Bavencio* (avelumab), **Merck KGAA/Pfizer Inc.**'s PD-L1 inhibitor, was granted US accelerated approval in second-line advanced or metastatic urothelial cancer on May 9, shortly after AstraZeneca's Imfinzi gained its first approval, for the same indication on May 1, again in the US. Keytruda was approved on May 18 in the US for first-line patients who are ineligible for cisplatin-containing therapy, and (with a breakthrough designation) patients with disease progression on or after platinum-containing chemotherapy. The product also received a CHMP positive opinion for expanded approval for the same indications in UC at its July meeting. Roche said the CHMP positive opinion was based on results from IMvigor211 as well as cohorts 1 and 2 from IMvigor210 study.

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UCB's Bimekizumab Could Struggle With Saturated Psoriasis Market

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UCB Group is preparing to take its psoriasis therapy bimekizumab into a large Phase III trial on the back of "striking" Phase IIb data – but the drug will be a latecomer to a packed disease space with high efficacy standards.

Analysts have also highlighted that bimekizumab's market entry is unlikely to offset challenges the Belgian drug developer faces in the coming years because of impending patent expiries for its established medicines.

Bimekizumab met its primary objective in the Phase IIb BE ABLE study, with up to 79% of patients achieving at least 90% skin clearance in the psoriasis area and severity index (PASI90) at week 12. Also, up to 60% of patients achieved complete skin clearance at week 12 as measured by PASI100, a secondary efficacy variable.

UCB believes bimekizumab – a monoclonal antibody designed to neutralize both IL-17A and IL-17F, two key pro-inflammatory cytokines involved in the pathophysiology of psoriasis – could offer psoriasis patients a promising new therapeutic option.

The company plans to present and publish the full results of BE ABLE in early 2018; it is also ready to advance bimekizumab into Phase III.

In BE ABLE, bimekizumab, the first humanized monoclonal IgG1 antibody to target both IL-17A and IL-17F, showed a favorable safety profile with no new safety signals observed. The most common adverse events observed were runny nose (nasopharyngitis) and common cold (upper-respiratory tract infection).

Kim Papp, lead investigator of the study and president of Canadian clinical research company Probity Medical Research, said: "The results with bimekizumab are striking, especially because a stringent PASI90 primary efficacy threshold was used."

By comparison, most previous trials in psoriasis have used the proportion of people who achieve a 75% improvement in the skin affected (PASI75), as the primary threshold for evaluating psoriatic skin clearance. Papp added that a "remarkably high" number of patients treated with UCB's therapy achieved clear skin quickly in the trial. "Rapidly achieving clear or almost clear skin is of critical importance for positively impacting patient lives," he said.

Bimekizumab is also in Phase II trials for psoriatic arthritis, axial spondyloarthritis and rheumatoid arthritis.

> 'It seems that an attractive pricing strategy could help newer biologics penetrate the market and compensate for their late market entry'

A SATURATED MARKET

Bimekizumab is similar to **Novartis AG**'s blockbuster psoriasis drug *Cosentyx* (secukinumab) but it is designed to have potentially superior efficacy. "Although details from the trial are limited, the results seem to support potential for this differentiation," Deutsche Bank analysts said in a July 21 note.

However, they were skeptical about the prospects for UCB's psoriasis drug "given the highly competitive environment for new drugs for severe psoriasis and bimekizumab's expected late entrance (unlikely before 2021/2022)."

They also noted that while the Phase IIb data were promising, the individual dose cohorts in the BE ABLE trial were relatively small (approximately 40 patients per arm). "Thus, it is difficult to gauge comparative efficacy," they said, adding that although bimekizumab's mechanism may be differentiating, **AstraZeneca PLC**'s *Siliq* (brodalumab) also inhibits both IL-17A and IL-17F and was not associated with meaningfully better efficacy than IL-17A inhibitors. The bar for new entrants onto the psoriasis market is already set high because current IL-17 inhibitors and other biologics, like **Johnson & Johnson**'s *Tremfya* (guselkumab) are "exceptionally effective treatment options," Deutsche Bank analysts noted. Furthermore, by the time bimekizumab reaches the market, Novartis' Cosentyx will have had six to seven years to establish itself as a go-to psoriasis treatment.

Datamonitor Healthcare analyst Ines Mihel also highlighted that the growing availability of anti-tumor necrosis factor (anti-TNF) biosimilar products has upped the ante for new agents in psoriasis. "Therefore, bimekizumab is likely to be relegated to the post-TNF setting and compete with the interleukin inhibitors," she said.

There are also several other options for psoriasis coming up through the development pipeline. The use of newly launched interleukin inhibitors is likely to be restricted as the market is becoming saturated.

However, Mihel highlighted that the cost of biologics is the most prominent unmet need in psoriasis. "It seems that an attractive pricing strategy could help newer biologics penetrate the market and compensate for their late market entry," she said.

GENERICS ENCROACH

Meanwhile, future potential sales of bimekizumab are unlikely to be enough to offset the challenges UCB faces from patent expiries over the next few years.

UCB's best-selling medicines in 2016 were its immunology product *Cimzia* (certolizumab pegol), epilepsy drugs *Vimpat* (lacosamide) and *Keppra* (levetiracetam), and Parkinson's disease transdermal patch treatment *Neupro* (rotigotine).

Generic versions of Keppra are abundant on the market; the product was UCB's top earner until it lost patent protection around 2011. Now, Vimpat is also facing a battle for market share against generic options and Neupro is soon to lose exclusivity.

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Ablynx Adds Sanofi To Its List Of Big Pharma Partners

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Sanofi is paying €23m upfront to Belgium-based **Ablynx NV** for access to the latter company's Nanobody-based therapeutic platform; the pair will develop novel treatments for various immune mediated inflammatory diseases.

Under the agreement, Ablynx will receive research funding of around €8m for preclinical development of the initially selected targets. Sanofi will be responsible for the clinical development, manufacturing and commercialization of any products resulting from the agreement.

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The deal holds a lot of potential for Ablynx as the company is eligible to receive development, regulatory and commercial milestone payments from Sanofi of up to €2.4bn, as well as tiered royalties up to low double digits on the net sales of any products originating from the collaboration.

Ablynx told *Scrip* it would re-invest the €23m upfront fee in its own research programs and technology. The company's lead compound, for which it is the sole developer, is caplacizumab; the drug is currently in Phase III trials for thrombotic thrombocytopenic purpura (TTP), a rare blood disorder. Caplacizumab has been filed for EU conditional approval for TTP, and a US regulatory submission is expected for the Nanobody product in the first quarter of 2018. Ablynx also recently initiated a Japanese safety study for the drug and has ongoing preclinical research in a new indication, stroke reperfusion injury.

Data from Ablynx's Phase III HERCULES study for caplacizumab in TTP are expected to readout in 3Q 2017. Its Nanobody platform uses therapeutic proteins based on single-domain antibody fragments, which Ablynx believes combine the advantages of conventional antibody drugs with some of the features of small-molecule therapeutics.

Jefferies analysts called Ablynx's research deal with Sanofi "impressive," and said in a July 20 note that the agreement "represents another example of Ablynx crystallising the value of its tech platform."

The deal allows Sanofi access to Nanobodies in Ablynx's current portfolio that are in the preclinical phase and allows for the development of up to eight Nanobody products.

The companies have not yet disclosed specific indications they will target but said they would all be immunological conditions. Examples of immune mediated inflammatory diseases the due might target are: ankylosing spondylitis, psoriasis, psoriatic arthritis, Behçet's disease, arthritis and inflammatory bowel disease.

OTHER ABLYNX PARTNERS

Sanofi is number nine on Ablynx's list of major pharma partners. The Belgian biotech already has alliances with **AbbVie Inc.**, **Boehringer Ingelheim GMBH**, **Eddingpharm International Holdings Ltd.**, **Merck KGAA** of Germany, **Merck & Co. Inc.**, **Novartis AG**, **Novo Nordisk AS** and **Taisho Pharmaceutical Co. Ltd.**

In the field of immunology, Ablynx has a licensing agreement with AbbVie for vobarilizumab, which is currently in a Phase II study in patients with systemic lupus erythematosus, with data expected in the first half of 2018. The company's collaboration with Merck KGAA is for a bi-specific anti-IL17A/F Nanobody in psoriasis, for which positive Phase Ib data were presented earlier this year. Finally, Ablynx has a licensing agreement with Taisho and with EddingPharm for its anti-TNF Nanobody in rheumatoid arthritis in Japan and Greater China, respectively.

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Touchstone Plays Tough As IP Group Ups Bid

A number of UK biotech start-ups and university researchers are watching with interest a revised takeover offer from IP Group to merge with fellow intellectual property group **Touchstone Innovations**.

The revised all-share offer, worth in the region of £490m, values each Touchstone share at 304p, a premium of around 11% to the latter's closing price of 273.6 pence on July 17. Touchstone shareholders would own about 34% of the combined company, 1% higher than the previous £466m offer in June from IP Group which says it has received support for the improved offer from shareholders representing about 89.7% of Touchstone's share capital.

Access to London's IP

One of the key benefits of the deal for IP Group is that it wants to tap into Touchstone's access to IP developed at Imperial College London and University College London, adding to existing partnerships it has with other leading UK research universities. What has helped the latest bid considerably has been a direct appeal to the endowment board of Imperial (Touchstone was formerly called Imperial Innovations) which says it is willing to accept the improved offer.

Touchstone's portfolio includes Oxford-based immuno-oncology company **PsiOxus Therapeutics Ltd.** and its lead oncolytic virus enadenotucirev. The latter is in Phase I/II trials in a variety of tumor types and as a combination therapy with both checkpoint inhibitors and convention chemotherapeutics.

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Read about Touchstone's Strong Links With Imperial here: **http://bit.ly/2uQ4ZdE**

Gilead Completes HCV Clinical Development With Vosevi Approval

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Gilead Sciences Inc. obtained US approval – about three weeks ahead of an Aug. 8 user fee date – for its final hepatitis C product incorporating the nucleoside polymerase inhibitor sofosbuvir as the US FDA okayed *Vosevi* (sofosbuvir/velpatasvir/voxilaprevir) on July 18 as a treatment for HCV-infected patients who have failed prior therapy with a direct-acting antiviral regimen.

With the Foster City, Calif.-based firm earlier this year slashing sales guidance for its HCV franchise, the Vosevi approval can be seen as virtually the end of an era for the virology powerhouse, which has not quite figured out its future direction. Its declining HCV revenues are offset somewhat by HIV franchise growth powered by new combination therapies incorporating tenofovir alafenamide (*Vemlidy*, also known as TAF), but with Gilead sitting atop a $34bn stack of cash as of the end of the first quarter, the company is the subject of frequent speculation on whether it might try to buy out Vertex or Incyte in order to establish a franchise in cystic fibrosis or hematology. *(Also see "Gilead's CEO Gives Glimpse Of Strategic Opportunities As HCV Sales Slide Continues" Scrip, 3 May, 2017.)*

Roughly a week ahead of its second quarter earnings call on July 26, however, Gilead can begin factoring Vosevi – which combines the nuc sofosbuvir and second-generation NS5A inhibitor velpatasvir (components of *Epclusa*) with the novel protease inhibitor voxilaprevir – into its HCV business prospects going forward. *(Also see "Gilead Coming To The End Of HCV Road With Triple-Drug Regimen" Scrip, 2 Nov, 2016.)*

Gilead set the wholesale acquisition cost of Vosevi at $74,760 for a 12-week course of treatment.

Vosevi's label recommends a single tablet daily for 12 weeks for patients with genotypes 1, 2, 3, 4, 5 or 6 of the virus who have failed a previous DAA regimen including an NS5A inhibitor – such as Gilead's Epclusa or its predecessor *Harvoni* (sofosbuvir/ledipasvir), **Merck & Co. Inc.**'s *Zepatier* (grazoprevir/elbasvir) or **AbbVie Inc.**'s *Viekira Pak* (dasabuvir/ombitasvir/paritaprevir/ritonavir) – or patients with genotype 1a or 3 infections who failed therapy with a previous sofosbuvir-containing regimen that did not incorporate an NS5A inhibitor. The regimen received breakthrough therapy designation for retreatment of genotype 1 HCV-infected patients who previously failed an NS5A inhibitor-containing course of therapy and the NDA was accepted for priority review.

Like the other HCV combination products that include NS5A inhibitors, the Vosevi label includes a black box warning about the risk of hepatitis B reactivation in HCV/HBV co-infected patients. *(Also see "Direct-Acting Antivirals Slapped With Black Box On Hepatitis B Risk" Pink Sheet, 4 Oct, 2016.)* It recommends that physicians test patients for current or prior HBV infection before starting treatment and monitoring co-infected patients for hepatitis flare or HBV reactivation during and after treatment with Vosevi.

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The approval was based on the POLARIS-1 and POLARIS-4 studies, in which roughly 97% (340/353) patients treated with Vosevi for 12 weeks achieved and maintained sustained virologic response (SVR) 12 weeks after the end of therapy.

The POLARIS-2 and POLARIS-3 studies, which tested an eight-week course of therapy against a comparator regimen of Epclusa, also were included in the filing. Gilead had hoped Vosevi would demonstrate non-inferiority to Epclusa in those trials, but fell short of that mark.

Datamonitor Healthcare analysts have projected that the failure to demonstrate non-inferiority to Epclusa and enable a standardized eight-week, pan-genotypic course of therapy likely indicates narrow utilization for Vosevi. *(Also see "AbbVie's New Hep C Drug Will Break Gilead's Dominance If Approved In EU" Scrip, 21 Jun, 2017.)*

During Gilead's first quarter earnings call on May 2, CEO John Milligan said the main purpose of Vosevi was to ensure that "we'd have an answer for every patient in our portfolio." Two weeks later, addressing the Bank of America Merrill Lynch Healthcare Conference on May 18, Gilead chief operating officer Kevin Young conceded that the product would serve a "small group, but we think it's the right thing to do for hepatitis C."

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US FDA Sends Amgen/UCB Evenity Back With BRIDGE Request

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Amgen Inc./UCB SA's investigational therapy for osteoporosis *Evenity* (romosozumab) could still bring in sales of more than half a billion dollars despite delays to market and concerns over its adverse event profile, say analysts as the product received a Complete Response Letter from the US FDA.

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Bridge over Evenity's troubled waters

Hopes for a swift approval for the first-in-class sclerostin inhibitor died when a cardiovascular safety signal overshadowed positive efficacy data from the 4,000-patient ARCH study in May. The product was filed in 2016 largely on the basis of the somewhat mixed FRAME study *(Also see "Amgen/UCB Poised For Osteoporosis Drug Filing On Back Of Mixed PhIII" Scrip, 23 Feb, 2016.)*, but Amgen had already agreed with the agency that the ARCH data should be considered in the regulatory review prior to the initial marketing authorization.

The disappointment was all the more acute as it left their major rival **Radius Health Inc.**'s newly approved *Tymlos* (abaloparatide) with a clearer run of the novel anabolic osteoporosis drugs market. *(Also see "Radius Prices Osteoporosis 'Blockbuster' Tymlos To Compete, Grow Market" Scrip, 1 May, 2017.)*

Amgen and UCB say the FDA has now asked that the efficacy and safety data from ARCH be integrated into the application. It also wants to see the efficacy and safety data from the BRIDGE study, a Phase III trial evaluating EVENITY in men with osteoporosis. The companies said the agency's requests will be addressed in the form of a resubmission, which will be an extension of the current review.

"During our interactions with the FDA, we agreed that the ARCH data should be considered in the regulatory review prior to the initial marketing authorization and, as a result, anticipated this request," said Sean E. Harper, Amgen's executive vice president of research and development.

Data from the 245-patient BRIDGE study presented at the ACR meeting last November showed that the patient incidence of positively adjudicated cardiovascular serious adverse events was 4.9% in the romosozumab group and 2.5% in the placebo group, although for cardiovascular death, the incidence was just 0.6% in the romosozumab group and 1.2% in the placebo group.

SEMI-BLOCKBUSTER

Analysts at Jefferies said the letter was no surprise given the ARCH data but they are still hopeful of an approval in 2018-19, albeit with a narrower label than currently sought. "Ultimately based on a label that fits the right risk/benefit population and based on conversations with Amgen, we still think the drug could be a $500m+ franchise given **Eli Lilly & Co.**'s *Forteo* (teriparatide) is over $2bn and daily injections and had theoretical safety concerns, and Romo is very potent and monthly injections and would be an option for patients with high risk of fracture and no prior or material CV risk."

Their optimism is based in part on the fact that, despite the CV imbalance in ARCH, no such safety signal was apparent in the larger 7,180-patient FRAME study. "So since neither of these studies are powered to show significant differences in CV events and preclinical and genetic data hasn't suggested anything target related, it would seem to be just a numerical imbalance and bad luck and if the two studies were pooled, unlikely to see any major difference either."

> 'Ultimately based on a label that fits the right risk/benefit population and based on conversations with Amgen, we still think the drug could be a $500m+ franchise'

Analysts at Barclays were more circumspect, saying that any safety warning on any label might discourage some prescribers despite the fact that both Radius Health's Tymlos and Lilly's Forteo have black box warnings. "Still, the approval of both competitors prior to Evenity is likely to blunt some of the drug's uptake – at least initially. Evenity may yet prove to be a major contributor to Amgen's *Prolia/Xgeva* bone health franchise, but we are continuing to exclude it from our model (vs. consensus of ~$300MM in 2020) pending greater clarity into potential launch timing and label composition."

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Spark Sets Sights On Bringing First Gene Therapy To Market In 2018

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Spark Therapeutics Inc. could bring the first gene therapy to the US market in 2018, after the company said a biologic license application (BLA) for the drug has been accepted by the FDA for priority review with an action date of Jan. 12. The launch of a potential one-time treatment that could represent a cure for vision loss due to a certain inherited retinal disease (IRD) will pose new questions for the industry related to cost, reimbursement and the value of medicines.

The company announced on July 17 that the FDA has accepted its BLA for the gene therapy, voretigene neparvovec, with the proposed trade name of *Luxturna*. The treatment has the potential to be the first therapy for vision loss due to biallelic RPE65-mediated IRD. The company has not said when it might be prepared to launch the drug following approval.

As Wedbush Securities analyst David Nierengarten put it in a May 10 research note, "Approval is expected, but then comes the hard part."

Jefferies analyst Michael Yee has a more positive outlook for Luxturna and Spark more generally. He forecast in a July 10 research note that the therapy could generate as much as $600m in peak worldwide revenue in IRD, an umbrella term that encompasses several rare genetic blinding conditions.

Spark's Luxturna marks a milestone in the budding field of gene therapy as it is the first gene therapy to be filed in the US. **UniQure NV** holds the title for being the first company to get a gene therapy approved in Europe; the firm won EU approval for *Glybera* (alipogene tiparvovec) in 2012 for an ultra-small indication, familial lipoprotein lipase deficiency (LPLD) and set a commercial price of $1m per treatment. But only one patient was ever treated with the therapy commercially and the company ultimately decided not renew the drug's marketing authorization, citing the small indication and limited use restrictions. *(Also see "White Flag Raised: UniQure Gives Up On Glybera, But Not Gene Therapies" Scrip, 21 Apr, 2017.)*

HOW TO PAY $1M PRICES?

UniQure's experience points to the serious challenges for drug makers looking to develop gene therapies, because the manufacturing process is complex and administration is just one time, which creates a new dynamic for the drug payment system: a hefty initial payment for savings that are born out over many years, or a lifetime.

Express Scripts Holding Co.'s chief medical officer Steve Miller raised the issue of gene therapy pricing during a discussion at the Biotechnology Innovation Organization's annual meeting in June, pointing to Spark's therapy for blindness as a specific issue for payers. *(Also see "Gene Therapy Reimbursement: Is Blindness A Bad First Test?" Scrip, 29 Jun, 2017.)*

Some analysts expect Spark's Luxturna could, like Glybera, cost upwards of $1m for treatment, although the company hasn't disclosed its pricing strategy. The Institute for Clinical and Economic Review (ICER) recently announced plans to develop a clinical effectiveness assessment of the drug to help payers develop policies for covering the drug.

Spark said it is willing to work with ICER, payers and others to consider different pricing models, and believes there are options for therapies that offer a high value.

EXPLORING ALTERNATIVE PRICING

"While we await the FDA's decision, we will continue to work collaboratively with all stakeholders, including ICER, to talk about the unique value of gene therapies, as well as explore pricing, distribution and reimbursement models that could accommodate one-time therapy options," the firm said in an email.

"We're engaging in productive conversations with payers, both private and public, and are encouraged by the discussions so far," the company said. "Spark is exploring potential payment, distribution and reimbursement models where the company might address budgetary concerns or be paid for performance to further align with the potential long-term benefits of Spark's investigational therapies."

Aside from the obvious pricing challenge, Spark will also have hurdles to overcome in the commercial market, like successfully identifying and screening patients with the genetic mutation and establishing a commercial presence targeting centers that specialize in IRD treatment.

FILING BASED ON PHASE I AND PHASE III TRIALS

Inherited retinal diseases are a group of rare blinding conditions caused by one of more than 220 different genes. Patients with IRD due to biallelic RPE65 gene mutations often experience night blindness in childhood or early adulthood, and the vision loss can become more serious as the disease progresses, until some patients lose their vision entirely.

Spark's BLA filing is based on two open-label Phase I trials in patients who received Luxturna between 2007 and 2012 and a Phase III trial in patients who received Luxturna between 2013 and 2015. The clinical trial program included 41 participants with vision loss age four to 44. The results showed a statistically significant and clinically meaningful difference in treated patients and control subjects. *(Also see "Spark Restores Vision In Phase III; CEO Hopes To Lead Gene Therapy Field" Scrip, 6 Oct, 2015.)*

The Philadelphia-based company is developing a range of gene therapies across multiple rare indications, including IRDs, hematological and neurodegenerative diseases.

Spark had a strong IPO in 2015, raising $161m from the sale of stock at $23 per share. *(Also see "Spark ignites investors; one of year's first five biotech IPOs" Scrip, 2 Feb, 2015.)* Its stock opened with a 3.7% one-day gain at $61.54 on July 17 based on the news that FDA accepted the Luxturna BLA for priority review.

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Speedy EU Assessment On Cards For AZ's Durvalumab

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AstraZeneca UK Ltd. will find out this week whether its key immuno-oncology drug, *Imfinzi* (durvalumab), will be granted speedy assessment in the EU for the treatment of Stage III lung cancer.

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The European Medicines Agency's drug evaluation committee, the CHMP, will consider at its July meeting which is taking place this week the company's request for accelerated assessment of durvalumab for the treatment of patients with locally advanced, unresectable Stage III non-small cell lung carcinoma (NSCLC) whose disease has not progressed following platinum-based chemoradiation therapy.

AstraZeneca has not yet filed for approval – the EMA advises companies to submit their requests for accelerated assessment two to three months before they submit their marketing authorization application – but it seems the company is moving quickly to capitalize on the early and positive results that it reported in May from its Phase III PACIFIC study of durvalumab – the newest PD-L1 blocker on the market – in Stage III lung cancer.

In terms of near-term direct competition, there is nothing in this space. It therefore seems likely speedy approval will be granted. This would mean the assessment timetable for durvalumab being reduced from 210 to 150 days. This mechanism is used for medicines that are of major interest for public health or can be considered a therapeutic innovation. AstraZeneca said at the time of the PACIFIC results that it would work with regulatory agencies to make Imfinzi available quickly to unresectable Stage III lung cancer patients. Analysts have suggested that PACIFIC's success could bring an extra $1.7bn in sales for the product.

AstraZeneca received its first approval for Imfinzi in May – in the US under the Food and Drug Administration's accelerated approval pathway for the treatment of advanced bladder cancer. Imfinzi, which the company describes at the "cornerstone of our extensive immuno-oncology programme," is in development across many tumor types, as monotherapy and in combination.

The CHMP's July meeting started on 17th July and runs until 20th July. Among many other things, the committee is expected to decide whether a dozen or so new medicines that are in the final stages of the evaluation process should be approved for marketing across the EU.

Editors Note/Update: the CHMP is understood to have discussed the drug, but AstraZeneca is not commenting on the outcome, and the EMA won't say until it publishes the minutes in September.

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Indian Tax Turbulence Dents Alembic

Alembic Pharmaceuticals Ltd., reported a 36% decline in net profit to INR650m ($10.1m) for the first quarter ended June, with net sales down by 12% to INR6.48bn, primarily due the transitional provision of India's new Goods and Services Tax (GST) regime and price erosion in the US.

GST, dubbed as the biggest tax reform since India's independence, replaces most indirect taxes currently in place and is expected to eliminate multiplicity of taxes and their cascading effect in the country.

R K Baheti, Alembic's director (finance) and chief financial officer, said that while the firm's internal GST preparedness, was "perfectly on dot" and the company commenced the new billing on July 1, the external situation seemingly went from "bad to worse."

"Lot of key clarifications were coming from the government in the last minute," he said at a post results investor call on July 20. Baheti referred to destocking across the sector and noted that some reports suggested that inventory levels in trade was down from almost 45-50 days to less than 15 days. He, however, indicated that prescription generation continues to be healthy and that Alembic hopes to recover lost ground.

"The trade channel may re-fill inventories little slowly, but I don't think there is any structural change."

Alembic's India formulation business dropped 21% to INR2.36bn due to the transition related to GST; the firm's acute products business declined by 22%, while the specialty business ended 23% lower in the first quarter ended June.

Uncertainty in the trade channels due to the implementation of the GST from July 1 was quite expected, although seen as temporary, but Alembic's result is perhaps indicative that the initial hit may be quite material.

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Shire Aims To Stay On Top In Hemophilia With Novimmune Pact

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Amid growing competition from **Roche**, **Shire PLC** is looking to consolidate its position at the top of the hemophilia tree, having inked a licensing pact with Switzerland's **Novimmune SA** to develop a bispecific antibody for the rare bleeding disorder.

The deal with Novimmune centers around a fully human, bi-specific IgG antibody targeting FIXa and FX for hemophilia A, designed to imitate the body's natural mechanism of Factor VIII-driven coagulation. The product is at the preclinical stage but Shire says the aim is deliver a treatment that is "highly efficacious with fewer side effects that improves upon the strong and long-term record of efficacy and safety that has been set by the class of clotting factor treatments."

'While further development and clinical trials are needed to fully evaluate this antibody, we are encouraged by the potential of the data'

Although very early-stage, the link-up takes on extra significance given the spat Shire became embroiled in with Roche last week concerning the latter's late-stage hemophilia A bi-specific monoclonal antibody emicizumab which binds to both Factors IXa and X. Following the publication of positive data from the Phase III HAVEN 1 study on emicizumab, which has been positioned as a convenient, once-weekly subcutaneous therapy and alternative to frequent intravenous injections and infusions, Shire obtained a preliminary injunction against Roche, charging that the company made misleading statements about adverse events in the aforementioned study.

Back to the Novimmune pact and Fritz Scheiflinger, Shire's head of global research, acknowledged that "while further development and clinical trials are needed to fully evaluate this antibody, we are encouraged by the potential of the data that we have seen in early discovery and the promise it may hold for hemophilia A patients and patients with inhibitors."

Shire added that it has been "steadily building its MAb research capability," which now includes programs in hereditary angioedema, diabetic macular edema, antibody-mediated autoimmune disease and anti-thrombotic therapy - "all signatures of Shire's new Rare Diseases Innovation Center coming to Cambridge, Massachusetts."

Staying with innovation and Shire chief executive Flemming Ornskov has told the *Financial Times* that he believes the company's product portfolio and pipeline are undervalued by investors.

The firm's stock has fallen by over 11% since the start of the year, not least as a result of concerns in the investment community about how the successful Shire's acquisition of Baxalta will prove successful. In response to whether he thought Shire was under-appreciated, Ornskov told the *FT* that he "made it a principle not to comment on the share price because my judgment is a biased judgment...but if I look at the growth, the profitability, the improving margin, the history of the company and the pipeline, it's certainly a question I would ask."

In an interview with the newspaper, Ornskov added that the Baxalta merger had gone "better than I anticipated," confirming the company was on track to achieve $700m in annual cost synergies.

The deal, the financials for which were not disclosed, is clearly good news for Novimmune which has been collaborating with Shire since 2015. The privately-held biotech also has partnerships in place with Roche and **Tiziana Life Sciences PLC**, while its most advanced monoclonal antibody, emapalumab, is currently in Phase II trials for the rare blood disorder hemophagocytic lymphohistiocytosis.

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Uphill Climb For Cariprazine After Delayed EU OK

Gedeon Richter PLC 's antipsychotic cariprazine – which has EU approval following a positive regulatory assessment in May – is expected to start launching across the EU on a country by country basis from mid-2018 when pricing and reimbursement has been finalized, analysts say. But to drive its uptake, Hungary-based Gedeon and its European market partner **Recordati Industria Chimica & Farmaceutica SPA** of Italy will need to differentiate their product from other well-established – and genericized – antipsychotics, which are already capable of addressing the disease's positive symptoms.

Datamonitor Healthcare analysts believe commercial success for cariprazine therefore "hinges on its potential to treat schizophrenia's negative symptoms," and note that earlier trials suggested the therapy benefits schizophrenia patients with predominantly negative symptoms. Confirmation of these benefits would be a clear competitive advantage in a saturated market, they add.

EU approval of Gedeon's drug followed its recommendation May 18 by the CHMP to treat schizophrenia. The CHMP at the time said that the benefits of cariprazine, which is called *Reagila* in Europe, "are its ability to improve psychotic symptoms." The most common side effects are akathisia and parkinsonism." The drug is a potent dopamine D(3)/D(2) receptor partial agonist with preferential binding to D(3) receptors.

Its European application for the treatment of schizophrenia included results from three placebo and partly active controlled positive trials in over 1,800 patients and one long-term trial, using the change from baseline in the scale, assessing the severity of schizophrenia symptoms using the Positive and Negative Syndrome Scale (PANSS) total score and the time to relapse as primary efficacy endpoints, respectively.

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Vertex Triple-Data Combos Live Up To High Hopes In Early Studies

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Vertex Pharmaceuticals Inc. is moving forward as fast as it can with the development of next-generation correctors as part of triple-drug combination therapies that may expand treatment to new cystic fibrosis patients, according to newly revealed efficacy in early clinical trials. The company plans to rapidly complete Phase II trials and start one or two pivotal studies in 2018.

Vertex will move from Phase I and II studies into a Phase III program in less than a year now that it has data showing that each of its three newest compounds for cystic fibrosis (CF) improved lung function and decreased sweat chloride in combination with the company's first approved CF therapy *Kalydeco* (ivacaftor) and the soon-to-be-submitted compound tezacaftor (VX-661).

Executives said during a July 18 conference call that Vertex is talking with regulators about the fastest way to bring a new triple-drug combo to CF patients, but the company will complete Phase II studies for each of its three-drug regimens first to determine the best one or two combinations to take into Phase III studies.

There are 75,000 people with CF in North America, Europe and Australia, according to Vertex, and only about 30,000 of them can be treated with Kalydeco and the company's other approved drug *Orkambi* (ivacaftor/lumacaftor), but the number of patients eligible for treatment with a Vertex drug is expected to grow to 44,000 with the approval of tezacaftor in combination with Kalydeco and new indications for the company's two approved therapies. Triple combinations could push the number of patients in those three regions who could be treated with a Vertex drug to 68,000.

"Today, we've provided new hope for those still awaiting a therapy," Vertex CEO Leff Leiden said during the company's conference call, adding later that, "we will not stop until we develop a medicine for all people with this disease."

Vertex revealed its triple therapy results after the stock market closed and rose 25.5% in after-hours-trading to $165.85 per share on July 18. The company's stock has risen 79.4% year-to-date based on enthusiasm for the Kalydeco-tezacaftor Phase III results revealed in March and these hoped-for positive early data for the three-drug combinations.

"This is an extremely important event for Vertex and consistent with our positive thesis on Vertex as they now have very clear visibility on going from 50% of the CF market ($2bn-$4bn) to capturing 80%-90%+ of the CF market ($4bn-$6bn+) in time," Jefferies analyst Michael Yee said in one of three July 18 reports on the triple-therapy data.

In his final note of the night, Yee revised the top end of his Vertex annual CF sales forecast to $6bn to $7bn-plus, adding to his and other analysts' expectations that the company is an attractive target based on its leading cystic fibrosis portfolio. *(Also see "Cystic Fibrosis Drug Sales Should Soar; VX-661/Ivacaftor To Lead Way" Scrip, 29 Sep, 2016.)*

EXPANDING CF DOMINANCE TO MORE PATIENTS

CF is caused by a defective or missing cystic fibrosis transmembrane conductor regulator (CFTR) protein due to mutations in the CFTR gene. Kalydeco is a CFTR potentiator for patients with at least one mutation in the CFTR gene; it was first approved in the US in 2012 for individuals with a G155D mutation, but other mutations have since been approved. *Orkambi*, which combines Kalydeco with a CFTR corrector, is approved for patients who are homozygous for the F508del mutation in the CFTR gene, meaning they have two copies of that mutation.

Tezacaftor also is a CFTR corrector for which Vertex reported positive Phase III results in March in combination with Kalydeco for the treatment of patients with two F508del mutations or patients with one F508del mutation and another mutation that results in residual CFTR function. The two-drug treatment will be submitted to the FDA and European Medicines Agency (EMA) during the third quarter of this year.

The combination of Kalydeco and tezacaftor is the backbone for the four triple-drug regimens that the company is testing in Phase I and II studies. In each of those combinations – Kalydeco and tezacaftor plus VX-445, VX-440, VX-125 or VX-659 – the third drug is a next-generation CFTR corrector.

Vertex reported data from separate Phase II studies for Kalydeco and tezacaftor in combination with VX-440 and with VX-152 on July 18 as well as preliminary Phase I results for Kalydeco and tezacaftor plus VX-659 that showed forced expiratory volume in one second (FEV1) improvements ranging from 9.6% to 12% at 15 days or 29 days, depending on the study, in patients with one F508del mutation and a minimal function mutation (F508del/Min). These three-drug regimens were the first therapies to ever show potential for treating the underlying genetic cause of CF in this population.

"Patients with minimal function mutations have been waiting for a medicine to treat the underlying cause of their disease, which makes these data showing pronounced improvements in lung function particularly important," University of Alabama at Birmingham (UAB) Doctor and Professor Steven Rowe said in a statement from Vertex.

"It's also encouraging to see that the addition of a next-generation corrector may lead to substantial additional benefits for patients with two copies of the F508del mutation, who were already receiving tezacaftor and ivacaftor," said Rowe, who is the director of UAB's Gregory Fleming James Cystic Fibrosis Research Center.

When added on to Kalydeco and tezacaftor in homozygous F508del mutation patients – individuals with two F508del mutations who qualify for treatment with Orkambi – treatment with three-drug combinations containing VX-440 and VX-152 provided FEV1 increases of 9.5% and 7.3%, respectively, on day 15 of triple therapy.

Jefferies analyst Yee said the data in homozygous patients represent "a substantial doubling of improvement over what

patients have now [with Orkambi] and with [tezacaftor] (2%-4% benefit)."

He added in a second report that data in homozygous CF patients look more robust than in F508del/Min patients, because "the 7.3%-9.5% FEV benefit in homozygous is against the [tezacaftor] combo (not placebo) and on top of the benefit of perhaps around 4% … so total new homozygous FEV is as much as 13%-14%."

"These numbers are close to what was seen for Kalydeco in G551d mutation patients (10.6%-12.5% in Phase III), and numerically stronger than the change from baseline for the combination drug Orkambi in homozygous F508del patients (the values for the Phase IIa study of Orkambi were difficult to interpret due to an initial decline in the monotherapy phase; values in Phase III were 2.6%-4%)," BioMedTracker said in a July 18 analysis of the data for the three next-generation correctors.

Sweat chloride reductions also were significant and consistent across the three Phase I and II studies. Defective and absent CFTR protein causes poor flow of salt and water through cells in multiple organs, resulting in a buildup of thick, sticky mucus in the lungs that leads to chronic lung infections, progressive lung damage and death in the mid-to-late 20s.

"What strikes us is the consistency of the data," Leiden said during the Vertex conference call. "The magnitude of the FEV1 and sweat chloride responses is remarkable."

In terms of safety, the majority of adverse events were described as mild or moderate. The most common side effects across the Phase II studies for VX-440 and VX-152 were infective pulmonary exacerbation, cough, sputum increases and diarrhea. Side effects observed in more than 10% of patients also included productive cough and fatigue for those treated with VX-152. Cough, infective pulmonary exacerbation and productive cough were the most common side effects for patients treated with VX-659 in Phase I.

One patient who received VX-440 discontinued treatment due to elevated liver enzymes and elevated liver enzymes were reported for another individual treated with VX-440 on the final day of dosing, but levels returned to normal for both patients after stopping or completing therapy. A patient in the placebo arm of the Phase II study for VX-440 triple therapy discontinued participation in the trial due to abnormal respiration and increased sputum.

FEV1 Changes In Phase II VX-440 And VX-152 And Phase I VX-659 Studies In F508del/Min Patients

VX-440 PLUS KALYDECO/TEZACAFTOR (MEAN ABSOLUTE WITHIN-GROUP CHANGE FROM BASELINE THROUGH DAY 29; P-VALUES REFLECT THE AVERAGE OF DAY 15 AND 29 RESULTS)
Triple placebo (n=11) +1.4% (p=0.4908)
VX-440 200mg plus tevacaftor 50mg or 100mg and Kalydeco 150mg, all given every 12 hours (n=18) +10% (p<0.0001)
VX-440 600mg plus tevacaftor 50mg and Kalydeco 300mg, all given every 12 hours (n=18) +12% (p<0.0001)
VX-152 PLUS KALYDECO/TEZACAFTOR (OBSERVED MEAN ABSOLUTE WITHIN-GROUP CHANGE FROM BASELINE THROUGH DAY 15)
Triple placebo (n=5) –0.9% (p=0.6245)
VX-152 100mg every 12 hours plus tevacaftor 100mg once-daily and Kalydeco 150mg every 12 hours (n=6) +5.6% (p=0.0135)
VX-152 200mg every 12 hours plus tevacaftor 100mg once-daily and Kalydeco 150mg every 12 hours (n=10) +9.7% (p=0.0017)
VX-659 PLUS KALYDECO/TEZACAFTOR (OBSERVED MEAN ABSOLUTE WITHIN-GROUP CHANGE FROM BASELINE THROUGH DAY 15)
Triple placebo (n=3) –0.4%
VX-659 120mg every 12 hours plus tevacaftor and Kalydeco (n=9) +9.6%

FEV1 Changes In Phase II VX-440 And VX-152 Studies In Homozygous Patients

VX-440 PLUS KALYDECO/TEZACAFTOR (MEAN ABSOLUTE WITHIN-GROUP CHANGE FROM BASELINE THROUGH DAY 29; P-VALUES REFLECT THE AVERAGE OF DAY 15 AND 29 RESULTS)
Placebo plus tevacaftor 100mg once-daily and Kalydeco 150mg every 12 hours (n=6) –2.5% (p=0.2735)
VX-440 600mg plus tevacaftor 50mg and Kalydeco 300mg, all given every 12 hours (n=20) +9.5% (p<0.0001)
VX-152 PLUS KALYDECO/TEZACAFTOR (OBSERVED MEAN ABSOLUTE WITHIN-GROUP CHANGE FROM BASELINE THROUGH DAY 15)
Placebo plus tevacaftor 100mg once-daily and Kalydeco 150mg every 12 hours (n=4) –1.4% (p=0.2773)
VX-152 200mg every 12 hours plus tevacaftor 100mg once-daily and Kalydeco 150mg every 12 hours (n=10) +7.3% (p=0.0354)

THE PATH TOWARD PHASE III AND APPROVALS

While triple-therapy regimens with VX-445, VX-440 and VX-152 already are in Phase II studies, the three-drug combination with VX-659 will move into Phase II in early August. Vertex expects to have the Phase II results from all four Phase II studies – including higher doses than already tested – in early 2018. The company will review all four drugs' mid-stage studies to determine which one or two of the next-generation correctors to move into Phase III pivotal trials during the first half of 2018 in combination with Kalydeco and tezacaftor.

The company is talking to regulators and a steering committee it has assembled with CF experts from around the world to advise the Phase III program's design. UAB's Rowe co-chairs the steering committee with Jennifer Taylor-Cousar, a pulmonologist at National Jewish Health and an associate professor at the University of Colorado, Denver. Taylor-Cousar is the director of the CF Therapeutics Development Network, Adult CF Program, at National Jewish Health.

It remains to be seen whether or not a three-drug regimen can be approved based on the strength of Phase II data in hand or yet to come, but Leiden said, "We feel the strength of these data do make it possible to talk to regulators about the most expedited path to approval."

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The Need For Patient Perspectives To Reinforce Urgency Of Antimicrobial Drug Development

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Shutterstock: Kateryna Kon

Antimicrobial resistance (AMR) is a global, life-threatening problem, but, unlike cancer and rare diseases, there is not a large community of patients advocating for new antibiotics or antifungal treatments.

During the BIO International Convention last month in San Diego, *Scrip* moderated a roundtable discussion about the challenges of developing these new therapies, including the need for more patients to tell their stories about surviving potentially deadly infections and the need for others who've lost family members to help define the importance of new medicines.

The roundtable included two members of the Antimicrobials Working Group (AWG) – Ciara Kennedy, president and CEO of the Phase I antifungal developer **Amplyx Pharmaceuticals Inc.**, which is in Phase I with the antifungal APX001, and Ted Schroeder, president and CEO of **Zavante Therapeutics Inc.**, which is preparing to seek US FDA approval for the EU-approved intravenous antibiotic *Zolyd* (fosfomycin). The third participant was Joe Larsen, acting deputy director at the Biomedical Advanced Research and Development Authority (BARDA), who leads BARDA's initiative on combating antibiotic-resistant bacteria and the BARDA-backed antibiotic accelerator CARB-X.

(The transcript of the discussion below has been lightly edited for clarity and length.)

SCRIP: *Besides additional incentives to spur investment in and development of new antibiotics and antifungals, what else could help this space?*

JOE LARSEN: There is no patient advocacy group for this at all, because when grandma who has Alzheimer's and has to go to a long-term care facility and gets MRSA and dies, the family says, "She died of Alzheimer's." Because usually you have something happen to you that lands you into this health care system that exposes you to one of these infections.

TED SCHROEDER: But if you take even a young person with an infection – with a pneumonia, with an abscessed abdomen – and you treat them effectively with an effective antibiotic, you give them decades of life; you give their whole life back to them. But if you treat them with the latest oncology product, and you give them back six months or a year, it's not very compelling, but we'll pay $200,000 for those six months, and we won't pay $2,000 for decades. The reimbursement model is a little bit backwards. [But Larsen is] right – there's no patient group and it's not as emotional.

CIARA KENNEDY: There's no face. [It's not like] cystic fibrosis, where you think about the little girl who can't breathe.

You think about Duchenne muscular dystrophy and it's the 10-year-old boy in a wheelchair who can't walk and is likely going to die in a few years. There's not that face [to show] the impact of these infections.

SCRIP: *How do you think you can put together a group like that, because obviously there are people whose lives have been saved?*

LARSEN: Pew Charitable Trust has done some work with a group called Supermoms Against Superbugs. They're not just super moms – there's men in there, too. One [program they did was about] parents of a soldier who contracted an infection overseas and succumbed to it. [Another example is] Chris Linaman and he had an article just recently in *Time* that said, "A MRSA infection cost me $300,000 – and nearly killed me." He was a normal guy that injured his knee and went in and got a surgery and ended up getting MRSA.

These stories are out there, [but] there's not anybody out there that is collecting them and publicizing them in a way that [would raise awareness of antimicrobial resistance].

KENNEDY: I think that the biggest challenge is that infections are acute. You either die or you recover. And if you recover, you kind of move on. You don't really identify as a bacterial infection survivor. But at the same time, when I talk to people – random people – I hear stories all the time like, "Oh, a friend of mine had AML and ended up dying from a fungal infection." Or, "I know this guy who had to have half his lung resected, because he had [a fungal infection]." All these stories are there, but they don't come together, because it's not chronic. You're not thinking it's something you're going to face again in your life, with the exception of MRSA – that's a little different; that can reoccur.

One of the things that the AWG is working on is trying to put that patient voice and that patient face, which is so impactful in terms of regulatory discussions, in terms of payer discussions, to put something more concrete around these patients and the cost of these infections.

One of the things that dawned on me at one point was many patients who have an invasive mold infections, they typically are hematology-oncology patients. They've gone through multiple rounds of chemotherapy. Maybe they've had a bone marrow transplant. Think about the health care resource dollars that have been put into that pa-

tient to get them through this condition. And then, because of those treatments, they're immune-compromised, they're neutropenic, they become susceptible to an infection, and many of them don't make it.

I have to find a way to say this that doesn't sound so callous, but you're making an investment in a patient's recovery, and then you're leaving them hanging off the edge of a cliff [without new antibiotics and antifungals] and saying, "Well, we'll see what happens." It really is counterintuitive to the value we're [creating by helping] people recover from these conditions that they have.

SCHROEDER: When someone like that gets an infection, it's seen as a failure of the system, right?

KENNEDY: Right. It's someone's fault.

SCHROEDER: But, in fact, the evidence would say that it's a fairly normal occurrence. It's part of the disease and …

SCRIP: *It should be anticipated and probably is anticipated.*

KENNEDY: Right; it is.

SCHROEDER: I actually think one of the worst things that ever happened was a few years ago when we decided that infections were 100% preventable. And that drove a lot of behaviors at the institution level and at the physician level that really didn't do anything to help the problem. It just was, "Just don't blame me for the infection, and make sure I get paid for my effort [to treat it]."

When you have a mobile society that's moving all over the world and these pathogens are being moved from community to community, it's naive to believe that the hospital can stamp it all out just because people wash their hands more often. It helps, and it's a good place to start, but I'm just saying that doesn't solve the problem.

Every antimicrobial ultimately depends on an immune system to support its activity. And the more compromised your immune system is, the less chance you have of an antimicrobial to actually work, so the most at-risk patients are going to get infections. Everything infects them.

SCRIP: *And not even in the hospital setting. Patients who have arthritis and other autoimmune conditions often are on some kind of immune-compromising medication and they frequently get all kinds of infections.*

KENNEDY: And when you listen to the TV ads for those medications, for the Enbrels, the Humiras, the anti-TNF therapies, you hear: "Tell your doctor if you've been to an area where fungal infections are common." It's part of the biology; it's not a failure on the part of a hospital's infection control.

It's interesting – Candida auris is a now hospital-acquired fungal infection, which typically didn't happen before. Fungal infections are transmitted in a very different way than bacterial infections, and the people who are associated with hospitals where they're having an outbreak or cases of candida auris, they really don't want to talk about it. They don't want to be labeled as that hospital that has candida auris. But the reality is, those kinds of behaviors are going to diminish patient care.

SCRIP: *With that in mind, the WHO recently put out their list of pathogens to try and spur drug development. Do you think that's helpful? If all these other incentives we discussed previously aren't in place, how will people will be compensated for investing in treatments for those infections? (Also see "WHO Publishes List Of Pathogen Threats To Rouse Drug Developers" - Scrip, 1 Mar, 2017.)*

LARSEN: My perspective is anything that's put out helps guide the thinking about where the priorities are to be making these investments. If you look at the list in terms of the difference between what the [Centers for Disease Control and Prevention (CDC)] put out in 2013, which previously we had been kind of aligning to, there's really not a lot of difference. There's a couple of pathogens – Pseudomonas, Acinetobacter – that were elevated, and it was just a difference of looking at morbidity versus mortality. WHO favored mortality more than morbidity, where CDC favored morbidity. Gonorrhea's high on the CDC list; not as high on WHO's.

But at the end of the day, we think about things in terms of pathogens and making investments, but I think it's more important to think about indications and unmet need in terms of making investments. For example, right now we really need an oral formulation for Gram-negative infections, because there are resistant infections for [urinary tract infections (UTIs)] – just a normal, uncomplicated UTI – for which women are having to get a [peripherally inserted central catheter (PICC) line] in their arm to treat. That just further exposes them to a health care setting unnecessarily where they can contract all these [other] resistant infections.

We think in terms of opportunity for new formulation development, opportunities for trying to address new indications like hospital-acquired and ventilator-associated pneumonia [(HAP) and (VAP)], where there's really not a lot of products being developed right now. The typical market strategy right now is to get in the market for complicated urinary tract infection, which is understandable. It's easy to enroll patients, the endpoints are reproducible and robust, and it's not as costly as doing something in HAP/VAP, but we need things for HAP/VAP too.

KENNEDY: And I think that it's important that the FDA [Qualified Infectious Disease Product (QIDP)] list also mirrors [the WHO or CDC priority pathogen lists] and they're all pretty close.

LARSEN: QIDP's almost too expansive, but yeah, it's pretty large – but that's fine. It was kind of a catch-all for everyone to benefit from [the Generating Antibiotic Incentives Now (GAIN) Act].

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View the roundtable focused on government incentives and commercial investment for antibiotics and antifungals here: **http://bit.ly/2vSVoA8**

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Selected clinical trial developments for the week 14–20 July 2017

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
Phase III Results Published			
Spark Therapeutics Inc.	*Luxturna* (voretigene neparvovec)	biallelic RPE65 mediated inherited retinal dystrophy	301-LCA2; *The Lancet* online, July 13, 2017.
Beta Pharma Inc.	icotinib	non-small cell lung cancer	BRAIN; *The Lancet Respiratory Medicine* online, July 19, 2017.
ViiV Healthcare	*Triumeq* (dolutegravir, abacivir, lamivudine)	HIV/AIDS, previously untreated women	ARIA; *The Lancet* online, July 17, 2017.
PTC Therapeutics Inc.	*Translarna* (ataluren)	Duchenne muscular dystrophy	ACT DMD; The *Lancet online*, July 17, 2017.
Roche	*Perjeta* (pertuzumab)	breast cancer	APHINITY; *NEJM*, July 13, 2017.
Updated Phase III Results			
Aerie Pharmaceuticals Inc.	*Roclatan* (netarsudil/ latanoprost)	glaucoma	MERCURY-1; positive 12-month safety profile.
Phase III Interim/Top-line Results			
Theravance Biopharma Inc./ Mylan NV	revefenacin (a once daily nebulized LAMA)	chronic obstructive pulmonary disease	Well tolerated in a 12-month safety study.
Nektar Therapeutics	NKTR-181 (the first full mu-opioid agonist)	chronic pain	SUMMIT-HAL; less abuse potential than oxycodone.
Paratek Pharmaceuticals Inc.	omadacycline	skin and skin structure infections	OASIS-2; the third positive Phase III study.
Phase III Initiated			
Incyte Corp.	itacitinib	graft-versus-host disease	GRAVITAS-301; a JAK1 inhibitor, as first-line therapy.
Axsome Therapeutics Inc.	AXS-05 (bupropion and dextromethorphan)	Alzheimer's disease with agitation	ADVANCE-1; treated for five weeks.
Phase III Announced			
SynCore Biotechnology Co. Ltd.	SB-05 (EndoTAG-1)	pancreatic cancer	In Taiwan, with gemcitabine.
BrainStorm Cell Therapeutics Inc.	*NurOwn* (adult stem cells)	amyotrophic lateral sclerosis	US clinical centers recruited.
DelMar Pharmaceuticals Inc.	VAL-083 (dianhydrogalactitol)	glioblastoma multiforme	STAR-3; overall survival the primary endpoint.
AbbVie Inc./Boehringer Ingelheim GMBH	risankizumab	plaque psoriasis	M16-177; compared to methotrexate.
Novartis AG/MorphoSys AG	VAY736	autoimmune hepatitis	A dose-ranging and confirmatory trial.
Forsee Pharmaceuticals Co. Ltd.	LMIS (leuprolide mesylate) 25 mg three-month injection	prostate cancer	Previous Phase III of 50 mg dose completed Jan. 2017.

Source: Biomedtracker

TR-PHARM Sees Early Success In Mediterranean Fever Antibody

AHMET SEVINDIK

Turkish pharma company **TR-PHARM** has disclosed it is working on a new biological molecule for the treatment of familial Mediterranean fever (FMF), with Phase I studies expected to be officially completed in September.

According to chair Tuygan Goker, TR-PHARM has been developing the new monoclonal antibody, RPH-104, with the Pharmaceutical Development and Application R&D Center of Ege University in Izmir. The first phase of clinical studies of the biologic, which is patented by R-PHARM, is being conducted in volunteers aged 18-35 and the primary outcome is positive. Phase II studies are planned to start later this year or at the beginning of 2018.

Goker estimated that in a few years the company would complete development and licensing processes and launch it as a commercial product. FMF is an inherited condition characterized by recurrent episodes of painful inflammation in the abdomen, chest, or joints, often accompanied by fever and sometimes rash or headache. Although the disease may affect any ethnic group, it usually occurs in people of Mediterranean origin including Sephardic Jews, Arabs, Greeks, Italians, Armenians and Turks.

It is thought to affect around one in 1,000 of the Turkish population, where one in five people carry the mutation that causes the disease.

OTHER R&D PLANS

TR-PHARM was established in 2014 as an equal partnership between R-PHARM and Goker, an ex-member of Roche's global management team.

He also underlined that TR-PHARM has been planning another R&D project to develop a treatment for Behcet's disease, and pointed out that producing biosimilar oncology drugs in Turkey will be another priority area for the company. Last year, TR-PHARM started construction of a biotechnology production facility in Cerkezkoy, near Istanbul.

R-Pharm CJSC, to which TR-PHARM is affiliated, is one of the leading pharmaceutical companies in Russia. Founded by Alexey Repik, R-PHARM had a turnover in RUB74bn ($1.25bn) in 2015 and is the largest supplier of medicines to state organizations in Russia (RUB35.6bn; 11% market share).

Japanese Corporation Mitsui disclosed an agreement with Alexey Repik in April this year to acquire 10% of R-Pharm's shares for $200m. In the course of the transaction, Mitsui will have the option to expand its share to 20% under the same conditions until the end of July 2017. The transaction is expected to close in September 2017.

From the editors of *PharmAsia News*.

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APPOINTMENTS

GlaxoSmithKline Plc. has named ***Karenann Terrell*** chief digital and technology office – effective Sept. 4, 2017. Terrell will be responsible for developing the company's digital, data and analytics strategy. She was previously chief information officer for Walmart, where she focused on the company's use of data, analytics and digital engagement with customers. Before this she was chief information officer at Baxter International Inc.

Meghan FitzGerald has joined **Arix Bioscience**'s board of directors as non-executive director and will also be a member of the board's audit committee. FitzGerald is a partner of L1 Health and associate professor of strategy and health policy at Columbia University. Before L1 Health, she was executive vice president of strategy and health policy at Cardinal Health.

CTI BioPharma Corp. has named ***Laurent Fischer*** director of the company. With over 20 years' experience developing and commercializing medicines in the biopharmaceutical industry, Fischer is currently senior vice president, head of liver therapeutic area, at Allergan. He was formerly CEO of Tobira Therapeutics, before the company was acquired by Allergan. Fischer has been a senior advisor on the Frazier Healthcare Partner's life sciences team since March 2017 and was previously chair and CEO of Jennerex Inc.

Julie Cooke has joined **Neurocrine Biosciences Inc.**, a company focused on neurological and endocrine disorders, as chief people officer. Cooke joins the company from Sanford Burnham Prebys Medical Research Institute, where she was senior vice president for human resource and a member of the executive management team.

Cue Biopharma, a company focused on cancer and autoimmune diseases, has appointed ***Mary Simcox*** vice president of translational biology. Simcox joins the company with over 20 years' experience in cancer cell biology and most recently she was vice president of biology at Tarveda Therapeutics. She has previously held leadership positions at Roche, where she led various small molecule and antibody projects into clinical development.

BenevolentAI, one of the world's largest private AI companies, has appointed ***Nathan Brown*** head of cheminformatics following the promotion of Mark Davies earlier this year from head of cheminformatics to VP, biomedical informatics. Brown has experience as a software designer and joined the institute of Cancer Research, London, in 2007.

Milestone Medical has appointed ***James Dwyer*** vice president of technical operations and ***Janet Moy*** vice president of human resources. Previously, Dwyer was director of technical services at Mangar.

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