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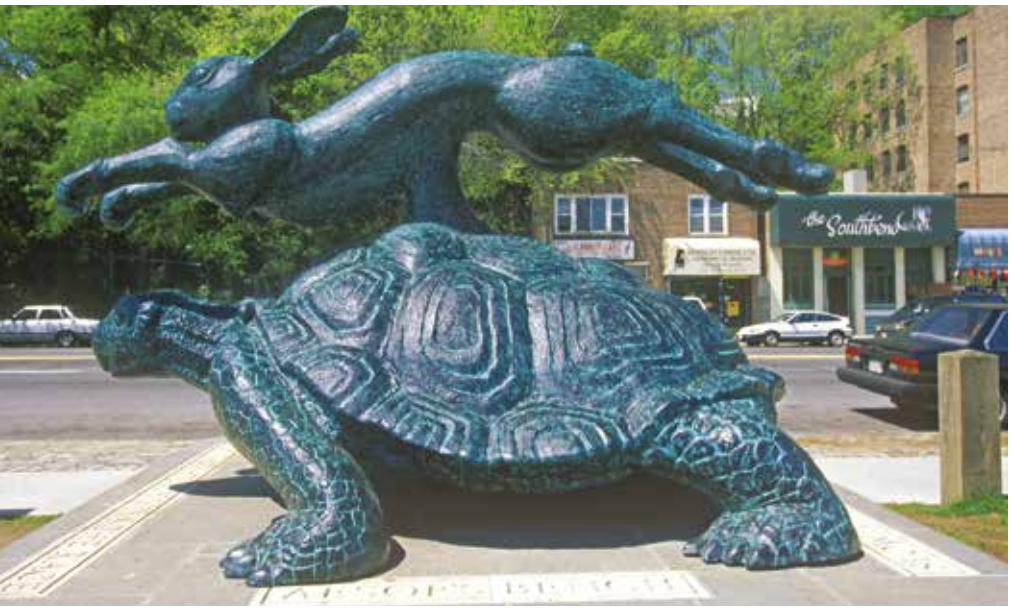

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Genfit May Be Gaining An Edge In NASH Race

JOSEPH HAAS joseph.haas@informa.com

Genfit SA may now hold the clearest path to market of the four companies in Phase III for non-alcoholic steatohepatitis (NASH), due largely to the misfortunes of its competitors. Those setbacks, and the progress being made in NASH, were discussed on the sidelines of the American Association for the Study of Liver Diseases annual meeting.

Presumed leader **Intercept Pharmaceuticals Inc.** has battled safety issues for its candidate *Ocaliva* (obeticholic acid) due to real-world treatment experience with the drug in primary biliary cholangitis (PBC), and **Gilead Sciences Inc.** and **Allergan PLC** recently have unveiled data for their candidates that could be called mixed at best. But Genfit chugs along with its strategy to advance elafibranor to an anticipated 1,000-patient interim look at its ongoing Phase III RESOLVE-IT study in 2019.

Genfit R&D Director Dean Hum told *Scrip* during the just-ended AASLD meeting that his firm believes elafibranor – a peroxisome proliferator accelerator receptor (PPAR) alpha/delta agonist – offers an efficacy and safety profile that will position it as a first-line NASH monotherapy and a potential backbone agent in combination therapy. Behind the four that have reached Phase III, dozens of other biopharmas are developing candidates employing a host of mechanisms and targeting numerous pathways to potentially treat NASH, which has no approved drug therapy.

Hum noted that elafibranor has demonstrated the ability to resolve NASH without worsening of fibrosis – one of the surrogate endpoints accepted by US FDA for registrational trials in NASH – and has indicated the potential for cardiometabolic benefit in biomarker findings.

He declined to say, however, whether Genfit will seek a labeling claim for cardiometabolic protection. The company's belief that elafibranor can offer such a benefit is based on measuring risk factors of cardiometabolic disease, such as lipid levels. "For example, elafibranor significantly decreases LDL cholesterol, decreases triglycerides and significantly increases HDL," Hum noted. "We also confirmed in a Phase IIb study that it has a beneficial impact on glucose homeostasis and it's clearly insulin-sensitized."

"If you look at the whole landscape of NASH programs, and more particularly the late-stage programs in Phase III, elafibranor is the only drug that is able to resolve NASH without worsening fibrosis, combined with that benefit on cardiometabolic risk factors," he said. "It has a very clean safety profile, no toxicity issues, no tolerability issues, so when you take all of these things together, you can see why we think elafibranor is a very strong candidate to be first-line therapy."

GILEAD APPEARS TO TRAIL

Intercept and Genfit both are on track to produce Phase III data for their candidates in 2019. Gilead – which has three NASH candidates in mid-stage development or later, including Phase III selonsertib, an apoptosis signaling kinase 1 (ASK1) inhibitor – has been less clear about timelines. On Oct. 23, the Foster City, Calif.-based company unveiled Phase II data for its acetyl-coA-carboxylase

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Express Scripts sees Amazon opportunity (p21)

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Immuno-neurology in sight as pipeline bar rises (p12-13)

Q3 Highlights
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from the editor

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Non-alcoholic steatohepatitis, or NASH, has burgeoned into a hot target for pharma companies, and no wonder. Rates of non-alcoholic fatty liver disease (NAFLD) have risen to around 25% in many developed countries alongside the rise in obesity, and nearly a fifth of those cases are of the more severe form, NASH – which involves inflammation and liver cell damage that can lead to cirrhosis and hepatic cancer. With NASH affecting about 5% of the population and rates likely to rise as growth in obesity continues, it is clear that the commercial opportunity is large for any pharmaceutical company with an effective treatment.

This is reflected by the R&D activities of major players like Gilead Sciences, Allergan, Novartis, Bristol-Myers Squibb, Boehringer Ingelheim and others, and by the dogged commitment of a host of smaller firms including, most notably, Intercept Pharmaceuticals. However, challenges that have affected some of those companies are now enabling smaller rival Genfit, of France, to move into poll position in the race to market (see cover story).

As Genfit emerges as an increasingly dominant contender in the space, bolstered by the additional attraction of its research into non-invasive biomarker-based NASH diagnostic technology, it might be viewed as a warmer target for larger firms on the hunt for acquisitions. Remember, though, that rumors swirled earlier this year that Novartis was on the verge of buying it without this coming to pass, and Genfit more recently raised €180m in a bond sale that provides it with independent means to develop its late-stage products. It's one to watch, in any case.

Scrip

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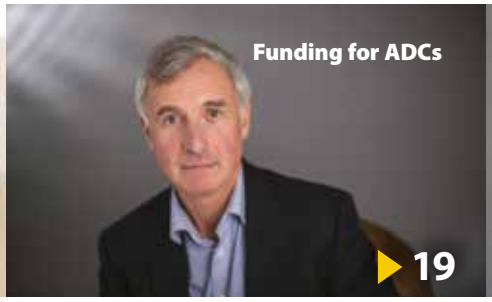

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Alexion Seizes On New Soliris Indication, Business Development For Growth
http://bit.ly/2hqWwGt
Alexion will target Soliris to about 3,000-8,000 US patients with ultra-rare generalized myasthenia gravis (gMG) following FDA approval. Meanwhile, the company has hired a new head of business development.

AZ Licensing Deal Boosts Mereo Orphan Disease Model
http://bit.ly/2iixiJL
UK group Mereo BioPharma is paying a very reasonable $5m to get its hands on AstraZeneca's Phase II compound for the rare genetic disorder AATD.

Xarelto Is The Pharma Watchword In Bayer's 3Q Update
http://bit.ly/2h0teBj
Despite Bayer AG's third quarter earnings call being heavily dominated by talk of the company's ongoing Monsanto acquisition and its recent deconsolidation of material science company Covestro, *Xarelto* stood out as the hot topic within the German firm's pharma division

BioInvent CEO To Step Down And Seek Scientific Successor
http://bit.ly/2hrxarl
With its focus firmly on oncology, the Swedish biotech, and its outgoing chief, believe the company now needs someone with more scientific skills in the CEO role.

Is Triple Phase III Triumph for AbbVie's Risankizumab In Psoriasis Good Enough?
http://bit.ly/2A4qwQe
AbbVie's investigational monoclonal antibody therapy risankizumab has triumphed against its competitors in three Phase III trials in psoriasis, but will it be too late to the party to enjoy the full commercial benefits?

Finance Watch: NDA-Ready Impact Gets Commitment For Another $90m
http://bit.ly/2gYXMDR
Start-up Impact's new structured financing – its second fundraising event this month – will pay out in increments as fedratinib nears the market. Also, Ablynx closed its $200m US IPO; Chi-Med follow-on brings in $262m; and VCs gives Cydan $34m to launch new companies.

inside:

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Celgene Admits It Messed Up Otezla Estimates

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CEO Mark Alles started **Celgene Corp.**'s third quarter earnings call with a mea culpa, admitting that the company's estimates for *Otezla* (apremilast) – the cornerstone of its inflammation and immunology franchise – "did not adequately anticipate" psoriasis and psoriatic arthritis market realities.

Confidence in Celgene's forecasting abilities was understandably shaken on Oct. 26, since just three months earlier executives spent a good part of the company's second quarter call reassuring analysts and investors that a quarter-over-quarter dip in Otezla sales during the first quarter had been corrected. *(Also see "Celgene Eases Angst Over Otezla, Sets The Stage For Growth" Scrip, 27 Jul, 2017.)* Celgene's share price plunged as a result of the company's third quarter total revenue and Otezla sales performance, coupled with lowered expectations for the PDE4 inhibitor's sales and a decrease in earnings guidance for 2017 and 2020. The stock closed down 16.4% at $99.99.

Third quarter total revenue increased 10% on a year-over-year basis to $3.29bn, versus analyst consensus of $3.43bn, including $308m in Otezla sales versus consensus of $411m.

"Let me start by just admitting that we're very disappointed with the results of the quarter and are committed to rebounding very quickly with respect to Otezla and our overall performance," Alles told the call.

Terrie Curran, Celgene's president of inflammation and immunology (I&I), provided more color about the market miscalculations that led the company – and, as a result, its investors – to believe that Otezla would perform better than it did in the third quarter.

"In the past two years, the US market for psoriasis and psoriatic arthritis grew strongly, posting [prescription] growth rates in the high teens versus previous years. This was fueled by new launches, including Otezla, which expanded the total pool of patients on treatment. We assumed that category growth rates would maintain these historical levels in setting our 2017 targets," Curran said.

"However, year-to-date through September, both markets have experienced a significant slowdown in growth as a result of increasingly restrictive [pharmacy benefit manager (PBM)] formulary control," she continued. "While Otezla demand continues to outpace the overall market, we are seeing lower-than-expected revenue due to market deceleration, increases in gross-to-net discounts to drive [treatment authorization without requiring a prior biologic failure] and inventory fluctuations."

REBOUND A WAYS OFF

The rebound Alles alluded to apparently won't be immediate, however, since Celgene said it now expects 2017 revenue to total $13bn versus prior guidance of $13bn to $13.4bn. The Otezla forecast for the year is now $1.25bn compared with the earlier estimate of $1.5bn to $1.7bn – a remarkable pair of revisions, since the company is known for beating consensus and raising guidance on a regular basis.

The shift comes at a tough time for Celgene, which took a hit less than a week earlier when it discontinued development of GED-0301 (mongersen) in Crohn's disease – a Phase III program for a drug acquired from **Nogra Pharma Ltd.** for $710m up front in 2014. Ulcerative colitis will be assessed after completion of a Phase II study. *(Also see "1Q EARNINGS: Celgene boosts sales, bets big on Crohn's drug" Scrip, 25 Apr, 2014.)*

"The discontinuation of GED-0301 in Crohn's disease exacerbates Celgene's negatively revised outlook, and PharmaVitae has revised its 2017 top-line forecast to $13.2bn" from $13.5bn, said PharmaVitae analyst Edward Thomason, a division of Datamonitor Healthcare. The late-stage blowup in Celgene's I&I franchise was a disappointment not only because of the investment in the asset, but also because it was one of just a few expected blockbusters acquired to help diversify Celgene's portfolio beyond its dominant hematology and oncology franchise. The firm's revenue is driven by sales from the multiple myeloma powerhouse *Revlimid* (lenalidomide); Revlimid sales jumped 10% to $2.08bn in the third quarter versus consensus of $2.11bn.

The GED-0301 failure in Crohn's disease and Otezla's muted growth trajectory contributed to Celgene's revised guidance, but the firm is also lowering expectations for oncology and new hematology products. The company now expects to bring in $19bn to $20bn in 2020 revenue versus a prior estimate of more than $21bn (*see table below*), which also includes a boost in the forecast for established hematology products – namely Revlimid and the newer multiple myeloma therapy *Pomalyst* (pomalidomide).

"Celgene has had disappointing quarter, but out to 2021, Celgene will still grow at a strong mid-teen [compound annual growth rate (CAGR)], driven primarily by the continued uptake of Revlimid and Pomalyst," Thomason said. "PharmaVitae expects the company to resume a policy of aggressive deal-making to bolster its pipeline, undeterred by the expensive GED-301 failure, given its strong cash flow."

Executive Vice President and Chief Financial Officer Peter Kellogg said the CAGR between 2017 and 2020 will be 14.5%. Kellogg also noted repeatedly during Celgene's earnings call that the company has the financial wherewithal to do deals, including $11.8bn in cash as of Sept. 30 and agreements with its creditors to expand its debt

Celgene's Updated 2020 Guidance

	ORIGINAL TARGETS (2015)	NEW TARGETS (2017)
Established hematology indications and products	$13bn	$14.7bn
New hematology indications and products	$1.8bn	$700m to $1.4bn
Total hematology	>$14.8bn	$15.4bn to $16.1bn
Total oncology	>$2.2bn	$1bn to $1.1bn
Total I&I	>$4bn	$2.6bn to $2.8bn
Total net product sales	**>$21bn**	**$19bn to $20bn**

capacity as needed. Alles noted that the company is putting its money to work in both internal research and development as well as business development.

"Our research and early development team continues to discover new molecules at a rapid pace, with five [investigational new drug (IND) applications] filed year-to-date and another three on deck. This tremendous productivity is a result of our multi-year strategy to invest in internal and external transformative technology, drug discovery platforms and paradigm shifting science," the CEO said.

In response to a question about business development later in the call, he said: "Celgene's track record of doing aggressive business development and continuing to build our innovation engine will continue. I don't know that the miss on GED-0301 makes us more or less likely to do the kinds of innovative partnerships we've done over the years. It's clear that we have a gap, and it's clear that something we're going to work hard to fill organically. And from an external point of view, we look for opportunity all the time. I've said it many times – wherever there's great science, wherever innovation's happening, whether it's happening here at Celgene or through another start-up or another company, we're interested in following that science to build our company."

Celgene also announced that it would institute an aggressive program to buy back stock in the company from its investors – a move that usually pleases shareholders. However, Jefferies analyst Michael Yee said in an Oct. 26 note that Celgene's investors would rather see the company put the money into deal-making activity that will drive revenue growth.

"Celgene should be aggressive and has plenty of capacity … to buy synergistic oncology companies with FDA-approved drugs," Yee wrote, suggesting that the company consider buying *Nerlynx* (neratinib) developer **Puma Biotechnology Inc.**, *Rubraca* (rucaparib) developer **Clovis Oncology Inc.**, or **Exelixis Inc.** with *Cabometyx* (cabozantinib), *Cometriq* (cabozantinib) and *Cotellic* (cobimetinib).

"This would 'diversify' and add revenues (preferred over buying larger companies)," Yee continued. "At this point, and with negative sentiment, investors prefer lower-risk products rather than higher-risk early-stage stuff, which Celgene has plenty of already."

LATER-STAGE LED BY OZANIMOD

Celgene talked up later-stage drug development programs, including ozanimod – a key asset in the pipeline. Pivotal Phase III results in multiple sclerosis, to be filed with the US FDA later this year, will be presented at the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) Congress in Paris on Oct. 27 and 28.

Both ozanimod – a selective sphingosine 1-phosphate (S1P) 1 and 5 receptor modulator – and Otezla are also being developed for inflammatory bowel disease (IBD). Otezla is in Phase II for ulcerative colitis (UC), while ozanimod is in Phase III for UC and in Phase II for Crohn's disease.

Celgene is enthusiastic about ozanimod's prospects in UC based on Phase II data, but the company said it will take a while longer to report the Phase III results because of the competition for patients among companies running IBD clinical trials. Enrollment in the Phase III TRUE NORTH study won't be complete until the second half of 2018, by current estimates, versus prior expectations of the second half of 2017.

"We are committed to building a leading inflammatory bowel disease franchise now led by ozanimod for the treatment of ulcerative colitis and Crohn's and perhaps Otezla in one or both of these serious unmet need medical conditions," Alles said. "And this immediate shift from GED-0301 to ozanimod and Crohn's disease is a great example of the pipeline optionality and opportunity we have built and continue to build into our research model for hematology/oncology and inflammation and immunology."

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Celgene plots blockbuster course: http://bit.ly/2z89lPl

Amgen Focuses On Pipeline As Mature Products Decline

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Amgen Inc. came to the same conclusion as just about everyone else with a CETP inhibitor and discontinued development of AMG 899, but the company highlighted several other drug candidates during its third quarter earnings call that may eventually offset declining demand for its mature brands.

DalCor Pharmaceuticals is the only company left with a drug targeting cholesterol ester transfer protein (CETP) in the clinic now that Amgen has decided "the value of our CETP inhibitor AMG 899 would be best realized through outlicensing opportunities, which we are now exploring," according to Executive Vice President of Research and Development Sean Harper during the company's third quarter conference call on Oct. 25. Harper's R&D update, which included Phase I assets not previously highlighted, followed a presentation that noted sales declines for multiple products.

Amgen's total product sales fell 1% to $5.45bn versus the third quarter of 2016 and total revenue also dropped 1% to $5.77bn, which was in line with consensus estimates of $5.7bn in revenue.

Chairman and CEO Robert Bradway said the quarter's results "show that we are effectively managing our business in a challenging time."

Amgen decided to no longer pursue CETP inhibition based on **Merck & Co. Inc.**'s announcement in September that it would not seek approval for anacetrapib after it appeared that the drug's LDL cholesterol-lowering mode of action did not provide a big enough cardiovascular outcomes benefit to make it a blockbuster product. AMG 899, which Amgen acquired in the 2015 purchase of **Dezima Pharma BV**, was in Phase II for the treatment of atherosclerosis.

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However, Amgen has other opportunities to add products to its relatively nascent cardiovascular franchise, the first of which could be US FDA approval of a supplemental biologic license application (sBLA) for the PCSK9 inhibitor *Repatha* (evolocumab), which is approved to lower LDL cholesterol for statin-intolerant and certain other hypercholesterolemia patients. The company wants to add positive results from the FOURIER cardiovascular outcomes trial to Repatha's label.

Also, omecamtiv mecarbil, partnered with **Cytokinetics Inc.**, is being tested in a Phase III clinical trial for chronic heart failure. Harper also revealed that the apelin APJ receptor agonist AMG 986 is being tested in a Phase I trial enrolling healthy volunteers and heart failure patients.

COMPELLING MARKETS

In neuroscience, where Amgen is working on multiple R&D programs under a partnership with **Novartis AG**, the company's CGRP inhibitor *Aimovig* (erenumab) is under FDA review for approval to treat chronic migraine headaches.

Amgen Executive Vice President for Global Commercial Operations Anthony Hooper said during the company's call that he recently attended the 18th Congress of the International Headache Society in Vancouver, British Columbia, Canada and heard from doctors there that they've been waiting for a new migraine drug for more than two decades.

Hooper noted that Amgen is "working with migraine bloggers and people who experience migraine to better understand the patient journey" while talking to payers about the potential for reimbursement.

Jefferies analyst Michael Yee pointed out in an Oct. 25 note, however, that some investors are concerned about payers' attitudes toward CGRP inhibitors, which could lead to strict limits on reimbursement for the preventative injection Aimovig.

Amgen sees a lot of potential in the indication, however, and has expanded its migraine portfolio to include the PAC1 receptor inhibitor AMG 301, which will be tested as a monotherapy and in combination with Aimovig – potentially in a bispecific antibody. A Phase II trial under way now is evaluating AMG 301 in both episodic and chronic migraine.

Amgen has made big investments in bispecific antibodies via its bi-specific T cell engager (BiTE) platform, which generated *Blincyto* (blinatumomab), a CD19-directed CD3 T cell engager approved to treat adults and children with relapsed or refractory B cell precursor acute lymphoblastic leukemia (ALL). The BiTE technology is a key element of the company's oncology portfolio and it is being used to develop multiple compounds, including new indications and combination regimens for Blincyto.

Three additional BiTE's now are being evaluated in Phase I studies, including AMG 596 targeting EGFRviii in a glioblastoma study, AMG 673 targeting CD33 in relapsed or refractory acute myeloid leukemia (AML), and AMG 701 targeting BCMA for multiple myeloma. AMG 673 and AMG 701 use Amgen's extended half-life technology for BiTE compounds.

Harper said when asked about Amgen's interest in cell therapies for cancer that the company still is working with its partner **Kite Pharma Inc.**, now part of **Gilead Sciences Inc.**, on chimeric antigen receptor T cell (CAR-T) therapies and learning a lot about the technology.

However, he said Amgen will be more focused on the BiTE platform for the next three to five years for multiple reasons: the efficacy seen to date, including in combination with checkpoint inhibitors and in solid tumors; the off-the-shelf nature of BiTEs versus first-generation autologous CAR-T therapies; and a safety profile that may allow for treatment in earlier lines of cancer treatment.

The company continues to invest in new technology to improve or enhance its BiTE platform, including a recent partnership with **CytomX Therapeutics Inc.** for bispecifics targeting EGFR and CD3.

Additional drugs for cancer and other indications were highlighted in Harper's R&D update.

Bradway said Amgen can't provide any clarity about the launch of its biosimilars, since ongoing patent litigation creates uncertainty about when the copycat products will be allowed on the market. Bradway said, however, that the company will "continue to be transparent on Phase III studies and regulatory submissions."

APPROVALS NEXT YEAR DON'T HELP SALES TODAY

While Amgen is expecting new drug approvals and label expansions later this year and in 2018, sales of products already on the market showed mixed performance in the third quarter. Hooper said during the earnings call that sales volume growth for the osteoporosis therapy Prolia and newer products, including Kyprolis for multiple myeloma and the high cholesterol treatment Repatha, partially offset declines for older drugs.

Prolia sales jumped 22% year-over-year to $464m worldwide, while Kyprolis sales grew 13% to $207m. But while Repatha sales more than doubled from $40m in last year's third quarter to $89m this year, the figure fell below consensus of $109m.

Amgen has had a hard time generating blockbuster sales for Repatha as payers limit utilization. The company hopes that updated treatment guidelines and the addition of positive CVOT data to the antibody's label will increase prescriptions and improve reimbursement.

However, Amgen has not been successful at keeping another PCSK9 drug off the market – Praluent (alirocumab) from **Sanofi** and **Regeneron Pharmaceuticals Inc.** – with a recent patent court decision falling in the competitors' favor.

"The market share we've achieved to date has been in the presence of a competitor," Hooper said. He added that Amgen continues to "work with payers on utilization management criteria" that has limited reimbursement and frustrated prescribers, but the company is working to improve coverage for Repatha in contracts with payers for 2018.

Revenue from Amgen's top-selling product *Enbrel* (etanercept) for rheumatoid arthritis and other inflammatory conditions sank 6% to $1.36bn, which missed consensus estimates of $1.38bn. *Neulasta* (pegfilgrastim), for which the company is beating back biosimilar competitors in the US, also saw sales fall 6% year-over-year to $1.12bn globally, but it beat consensus of $1.08bn.

The company said in its third quarter earnings report that increasing competition and declining demand contributed to lower sales for several mature products, despite price increases for some drugs and discounts for others to either boost revenue or improve reimbursement. Notably for Enbrel, Hooper said declining demand for Enbrel and lower realized net prices for the drug are trends that will continue in 2018.

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To see Additional drugs for cancer and other indications highlighted in Harper's R&D update: **http://bit.ly/2gUltbp**

Lilly Math: Subtracting Employees = Pharma Growth

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Recently launched drugs contributed significantly to **Eli Lilly & Co.**'s third quarter growth, but it remains to be seen whether those assets plus recent job cuts and the proposed sale or spin-out of its animal health business will be enough to offset competitive pressures for pharmaceutical products.

Lilly continues to meet its goal of 5% annual revenue growth through 2020, helped by a 9% year-over-year increase to $5.66bn in revenue for the third quarter, but analysts questioned the company's reliance on new products, many of which face tough competition from therapies in the same drug class. However, any savings generated by laying off 3,500 employees and income from a potential merger, sale or initial public offering for Elanco Animal Health will be used to cut operating costs while reinvesting in Lilly's pharma business.

The company revealed in its third quarter earnings report that it will decide by mid-2018 whether to sell Elanco, spin it out as a separate company via an IPO – like **Pfizer Inc.** did with Zoetis Inc. in 2013 – or retain the animal health business.

Morningstar analyst Damien Conover pointed out in an Oct. 24 note that Elanco provided Lilly with some financial stability while the company dealt with losses of patent exclusivity for key brand-name products between 2011 and 2014. However, that business's growth has become stagnant with the exception of products brought in with recent acquisitions, including the $885m acquisition of **Boehringer Ingelheim GMBH**'s Vetmedica pet vaccines business that closed in January and the $5.4bn acquisition of **Novartis AG**'s animal business as part of a 2014 asset swap that also involved **GlaxoSmithKline PLC**.

"While Lilly needed to lean on the [Elanco] division during the heavy patent loss years of 2011-14, the company's drug group is on much more solid footing now and synergies between animal and human health seem limited," Conover wrote.

However, BMO Capital Markets analyst Alex Arfei questioned the timing of Lilly's decision to seek strategic alternatives for its animal health portfolio in an Oct. 24 note, asking, "Is Lilly doing this because Elanco now has enough scale and there is simply too much trapped value, or because Lilly needs the financial engineering to offset other headwinds [e.g. *Trulicity* vs. (**Novo Nordisk AS**'s semaglutide), *Humalog* biosimilar, regulatory headwinds for baricitinib, *Verzenio*'s potential slow launch]? We suspect its more the latter."

Lilly Chairman and CEO David Ricks said during the company's earnings conference call that a sale of Elanco is being considered now, after the Boehringer and Novartis assets have been integrated into the animal health business, because "over the last many years we have grown this business rather substantially through acquisitions, but also though our own organic actions, and now we have a global business that's highly competitive."

NEW PRODUCTS CHALLENGED OUT OF THE GATE

Selling or spinning out Elanco would allow Lilly to focus entirely on its pharma business, which generated $4.92bn of the company's $5.66bn in third quarter revenue. Sales fell year-over-year for the period for almost all of Lilly's mature products, because of decreased demand that was offset somewhat by price increases as well as generic competition for multiple legacy assets.

The exception was Humalog (insulin lispro) for which sales rose 9% to $696.2m due to increased realized prices and slightly higher demand in the US and higher sales volume in ex-US markets. However, Humalog's dominance will be challenged by Sanofi's biosimilar of the insulin, which the French pharma is expected to launch in 2018 – and which Lilly will not try to stop with patent litigation.

Leerink Swann analyst Seamus Fernandez said in an Oct. 24 research note that "the announcement that Lilly does not have a settlement in place with [**Sanofi** (SNY)] nor does it plan to sue SNY to avail itself of potential Hatch-Waxman protections likely was a partial driver of today's weakness." Lilly's stock closed down 2.3% at $85.17 per share.

The company's sales of new products totaled $1.2bn during the third quarter, which was 141% higher than in the year-ago quarter, including big gains for multiple diabetes drugs. Sales of the glucagon-like peptide 1 (GLP-1) receptor agonist Trulicity (dulaglutide) jumped 117% to $527.7m, while the sodium-glucose co-transporter 2 (SGLT2) inhibitor *Jardiance* (empagliflozin) spiked 168% to $127.2m, and *Basaglar* (insulin glargine) – a copy of Sanofi's *Lantus* (insulin glargine) – surged 650% to $145.7m.

"Although, the launch franchises beat consensus by 3%, they were closely in-line with our forecast," BMO's Arfei wrote. "Basaglar did better than expected in the US, which doesn't bode well for Humalog's prospects after [the second half of 2018] with biosimilar competition."

In new product sales outside of diabetes, revenue from the second-to-market Interleukin-17A (IL-17A) inhibitor *Taltz* (ixekizumab) – approved in the US in 2016 to treat psoriasis, following the Novartis IL-17 inhibitor *Cosentyx* (secukinumab) onto the market – jumped 365% to $151.3m in the second quarter.

However, analyst consensus for Taltz sales was $170m for the third quarter and Arfei described the miss as "concerning." Novartis reported during its earnings call, also on Oct. 24, that Cosentyx sales grew 83% during the third quarter to $556m.

BARICITINIB BACK ON TRACK

Lilly could add another important drug to its immunology franchise in 2018 if the FDA approves the Janus kinase 1/2 (JAK1/2) inhibitor baricitinib for rheumatoid arthritis (RA) following a refiling of the drug's rejected new drug application (NDA) by the end of January. The agency initially rejected the NDA and asked the company for more data regarding thromboembolic events.

Lilly Bio-Medicines President Christi Shaw said during the company's earnings call that the thromboembolic event rates observed to date in clinical trials and in real world use reflects the rates you'd normally see among RA patients.

The drug, which is developed in partnerships with **Incyte Corp.**, has been approved in Europe and Japan as *Olumiant*; if approved in the US it will be the third JAK inhibitor on the market and the second approved for RA after Pfizer's *Xeljanz* (tofacitinib). Baricitinib also is being developed for atopic dermatitis, with a Phase III program starting soon, and is in Phase II for lupus.

With baricitinib's US approval shifted from 2017 to 2018, the CDK4/6 inhibitor Verzenio (abemaciclib) was the ninth drug Lilly's launched since 2014 and the company expects to launch 11 more by 2023.

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GSK Spotlights Three Impending Drug Launches

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GlaxoSmithKline PLC diverted attention from the struggles it faces in some areas of its pharmaceutical portfolio by highlighting the launches of three drug products due in the final quarter of 2017, one of which has been labeled as the savoir of its respiratory business.

GSK is already seeing an impact from the approaching patent expiry of its flagship asthma and COPD drug, *Advair* (fluticasone and salmeterol). The drug will lose patent protection in the majority of markets in 2018, but worldwide sales, which peaked at $8.3bn in 2013, have been in decline since 2014.

"Although GSK reported a respectable third quarter the company is entering a challenging and uncertain period with impending generic competition to Advair in the US and headwinds in its HIV and respiratory portfolio," PharmaVitae lead company analyst Ali Al-Bazergan told *Scrip*.

To pull up the performance of its respiratory portfolio, GSK is banking on strong uptake for its recently approved once-daily, triple combination treatment, *Trelegy Ellipta*. Trelegy (also known as FF/UMEC/VI) is a combination of an inhaled corticosteroid (ICS), a long-acting muscarinic antagonist (LAMA) and a long-acting beta2-adrenergic agonist (LABA), delivered once daily in GSK's Ellipta dry powder inhaler for the treatment of chronic obstructive pulmonary disease (COPD).

The drug was approved in the US in Sept. this year, two months ahead of its expected user fee date of Nov. 21, 2017. The product will be the first LABA/LAMA/ICS triple combination therapy to market in the US. Natixis analysts said at the time of Trelegy Ellipta's FDA approval that GSK had "rescued its respiratory franchise despite the inevitable decline of Advair." Trelegy Ellipta is also the first once-daily, single inhaler triple therapy to be granted a positive opinion by the European Medicines Agency's scientific committee, the CHMP**.** Final EU approval is expected for the drug as a treatment for COPD early next year.

OTHER NEW DRUG LAUNCHES

In the fourth quarter, GSK will also launch its recently approved shingles vaccines, *Shingrix* (herpes zoster vaccine), and its dual combination treatment for HIV, dolutegravir/rilpivirine.

GSK's Q3 Performance

Group sales: £7.84bn (versus £7.54bn in Q3 2016)

Group operating profit: £1.88bn (versus £1.43bn in Q3 2016)

EPS: 24.8p (versus 16.6p in Q3 2016)

Total pharma sales: £4.2bn

Respiratory product sales: £1.61bn

HIV product sales: £1.09bn

Immuno-inflammation product sales: £95m

Establishes pharmaceutical product sales: £1.39bn

The company's FY 2017 guidance remains the same.

Shingrix has been slated as a potential blockbuster product for GSK due to its best-in-class profile. The vaccine was approved in the US this month, in people 50 years and older, as a prevention tool against the painful, blistering rash. Shingles is the result of reactivation of the varicella-zoster virus, which causes chickenpox and remains latent in those who have had that disease. Older people are most at risk of an outbreak of the often-debilitating condition.

Analysts have called Shingrix an important improvement on the existing vaccine option, **Merck & Co. Inc.'s** Zostavax.

Adding to GSK's busy upcoming quarter, the company – through **ViiV Healthcare** – will also look to launch its single-tablet regimen of dolutegravir plus **Janssen Inc.'s** non-nucleoside reverse transcriptase inhibitor rilpivirine in the US by the end of the year.

The dolutegravir/rilpivirine NDA is based on the two Phase III SWORD trials, which enrolled over 1,000 patients who had previously achieved viral suppression on a three- or four-drug antiretroviral regimen. Viiv submitted the drug to the FDA in June this year with a priority review voucher, which should lead to a faster than normal regulatory verdict in December this year.

Walmsley said GSK is prepared for a "rapid launch" of the dual combination HIV treatment if it is successfully approved in the US. Biomedtracker analysts have given the product a likelihood of approval rating of 96%, 8% higher than the average for a similar product at the same stage of development. The combination has also been filed in Europe, where a regulatory decision is expected by the third quarter of next year.

Walmsley noted during the company's Q3 earnings call that GSK is interested in acquiring **Pfizer Inc.'s** consumer health business, should the unit be placed up for sale. Pfizer recently announced it is re-examining the potential sale of its consumer business – though it doesn't expect to make a decision on the future of this unit until 2018.

Walmsley said: "Our capital allocation priorities that were laid out in Q2 go completely unchanged, we did say we would be interested in building up our consumer business. It's a business we like and we are a world leader in consumer healthcare and have a demonstrative track record of successful integration. You would expect us to look at any assets that complement our portfolio."

While GSK's potential overtures during its Q3 earnings call on Oct. 25 for Pfizer's consumer health business were encouraged by the company's track record in demonstrating integration with acquired assets, comments from the company's CEO "cooled when quizzed about a potential dividend risk to finance a bid," Al-Bazergan noted.

GSK's chief exec did mention that other options could be on the card for a deal between Pfizer and GSK, aside from a straightforward acquisition. "They [Pfizer] only announced the process last week so it's a bit premature and not even confirmed for sale. We would be focused as always on driving shareholder value, and it's a conversation we would be having with our partners in the joint venture. One option could be a structured deal but there are other options as well and we will continue to watch this."

GSK agreed a joint venture in 2014 with **Novartis AG,** as part of a mega-deal transaction. The two firms merged their consumer health business units, under the name GSK Consumer Healthcare; and both hold seats on the venture's board.

Pfizer's consumer health business, which includes brands such as the painkiller *Advil* and lip balm *Chapstick*, had revenue of about $3.4bn in 2016. The unit has been valued at around $14bn to $15bn by market spectators.

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Revamped Novartis In Good Shape At Q3 Ahead Of CEO Succession

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Novartis AG's out-going CEO Joe Jimenez said the revamped diversified Swiss group is running smoothly, with growth fueled in the third quarter by new therapies and improved performances by generics division Sandoz and its Alcon unit.

But a decision on either spinning-off or listing of the troubled eye care division would now be decided in the first-half 2019, rather than the fourth quarter of this year as previously promised, that is, once he has gone and his designated successor, chief medical officer Vas Narasimhan, is in charge.

The American CEO was speaking to reporters as Novartis Oct 24 reported net sales in the third quarter of $12.4bn, up 2% measured at constant currencies, allowing Novartis to re-confirm its 2017 outlook of net sales expected to be broadly in line with prior year measured at constant currencies, and core operating income expected to be broadly in line or decline low single digit.

Assessing the update, Berenberg analysts said that, "Novartis delivered a solid set of Q3 numbers primarily driven by good margin performance in Alcon and Sandoz, though full-year guidance remains unchanged."

Notable strong performers included psoriasis-fighting *Cosentyx* (secukinumab) which saw sales rise 83% to $556m measured at constant currencies and showing strong growth across all its indications. Cosentyx is heading for multi-blockbuster status in 2017, Jimenez said.

KYMRIAH ON 'BLOCKBUSTER' PATH

Jimenez noted that the group's CAR-T therapy *Kymriah* (tisagenlecleucel) was recently approved in a small pediatric leukemia indication by the FDA. He confirmed Kymriah's next targeted indication is the bigger commercial opportunity, diffuse large B cell lymphoma (DLBCL). "We are now certifying centers for trials and we are infusing our first patients. We will be filing the second indication for Kymriah in DLBCL during the fourth quarter and that means we will be commercializing Kymriah in DLBCL most likely in 2019. So we're off to a good start with Kymriah."

Shutterstock: TDallas

> 'Novartis delivered a solid set of Q3 numbers primarily driven by good margin performance in Alcon and Sandoz, though full-year guidance remains unchanged'

Although Novartis hasn't yet given a projection on potential peak sales for Kymriah, it is set for big sales.

"We have said that we expect Kymriah, our cell therapy, to be a blockbuster when you include pediatric ALL (acute lymphocytic leukemia) and DLBCL, putting peak sales at something over a billion dollars and as you know we are exploring additional indications even beyond that." He did not identify what those additional indications might be, however.

ENTRESTO RISING

Sales of heart drug *Entresto* (sacubitril/valsartan) rose138% in the third quarter, measured at constant currencies, to $128m, driven by improved patient access and US sales force expansion. Entresto, which had had a slow launch and now has launched in more than 45 countries, is progressing steadily, Jimenez said, with further acceleration expected in 4Q 2017.

"For Entresto, we're still holding to the plus or minus $500m for the year [target]; that will require some acceleration in the fourth quarter," the CEO said. He blamed a slowing of prescriptions over the summer months in the US to physicians not wanting to initiate a new therapy when they or the patients are on vacation. "But the good news is that if you look at the new to brands scripts in the latest weeks we're back up to a level that is higher than it's been in the last 12 weeks so we're still feeling relatively bullish on Entresto."

SANDOZ STABILIZES

Generic division Sandoz grew 1% measured at constant currencies, helped by growth outside the US, fully offsetting price pressure in the US, where US generic sales were down 13%. Sandoz sales in the latest three months of $2.58m were better than market forecasts.

But analysts said this better performance from the embattled copy-cat division appears to be temporary, as full-year guidance

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was slightly downgraded by Novartis' management from "broadly in line" to "broadly in line to a slight decrease".

Jimenez told reporters, "We are taking the Sandoz sales forecast down slightly from a year ago and at the same time we're taking the innovative medicines forecast up slightly and that's why the group is right on its forecast."

He said the strength of innovative medicines was offsetting the issues on pricing within Sandoz. "The good news for Sandoz is that outside the US, the business is growing in almost every region. Its very strong biosimilars launch in Europe has gone well with Rituximab. The US pricing situation continues to not be good. And it's affecting the whole industry." Those pricing pressures in the US retail market for generic drugs prompted Novartis to announce in October it will close a 450-employee Sandoz plant in Broomfield, Colorado, over the next two years.

ALCON DRAMA CONTINUES

Perhaps the biggest surprise contained in the Q3 update was news that Novartis is delaying a possible spin-off of its eyecare division Alcon until the first half of 2019, amid signs of a turnaround in the ailing business.

"Regarding Alcon, we're very encouraged by the results that we're seeing. If you look at the last two quarters we're starting to see the business turn. But we still need to see multiple quarters of sales growth and core operating income growth to get this business to a position where a final decision can be made. Because if we did decide to spin-off this business we'd want to come to the market from a position of strength," Jimenez told reporters. He said that what Novartis was considering now would be a standalone company with a separate listing and that those shares would go to the Swiss group's current shareholders.

"We've always said that this business should generate margins in the low-twenties to the mid-twenties. Right now if you look at the margin in the third quarter it was just under 16%. We do believe that over time this will be a business that will sustain margins that are in the range of the sector average of something of between low- to mid-twenties." He said Alcon's improved performance reflected innovative products and increased customer-oriented service and consequent improved customer satisfaction.

'I am very interested in the intersection point of where biology and technology come together; I'm interested in looking at the industry in a slightly different way in my next phase which would most likely involve health technologies so I plan to return to California where my family is from and get involved in new and exciting things around health tech'

He stressed that no decision has yet been made on what to do with the eye care unit. Whether such a stand-alone entity would be domiciled in Switzerland or the US would largely depend on tax considerations. "We have time on our side to see how the US tax reforms situation plays out, but we're taking everything into consideration," he said.

Management has decided to move the Novartis Ophthalmic OTC products, which in 2016 had sales of $700m, to the Alcon Division effective Jan 1, 2018, where the products will hopefully create most value, as they are complementary to the Alcon Vision Care business, he said. The transfer will allow Novartis' Innovative Medicines Division to focus on delivering the Novartis Rx product pipeline, including RTH258.

JIMENEZ' LEGACY

Jimenez will retire February 1, 2018. Perhaps the biggest legacy he will leave behind will be the multi-asset swap he orchestrated with **GlaxoSmithKline PLC** in 2014 along with GSK's then CEO Andrew Witty under which GSK acquired Novartis' global vaccines business for $5.25bn, divested its oncology business to Novartis for $16bn, and formed a consumer health care joint venture with the Swiss firm. The transaction closed in March 2015.

Jimenez said the process of handing over the CEO reins to Narasimhan was going smoothly. "Vas will take control of the budget from November to ensure a seamless transition here at Novartis."

JIMENEZ' PLANS

Asked by *Scrip* what his plans will be after passing the reins to Narasimhan, Jimenez said "I am very interested in the intersection point of where biology and technology come together; I'm interested in looking at the industry in a slightly different way in my next phase which would most likely involve health technologies so I plan to return to California where my family is from and get involved in new and exciting things around health tech."

Jimenez said Novartis was happy to continue with its consumer health care joint venture with GSK which was launched in early 2015 and in which the Swiss group has a minority stake. *(Also see "'Migraine Experience' Debuts Excedrin Advertising By Glaxo/Novartis JV" Pink Sheet, 18 Apr, 2016.)*

"We have an ability to 'put' that stake back to GSK beginning in March 2018, but we have no intention immediately to do that because the asset is continuing to increase in value as we get more and more synergies out of that venture."

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Bristol's Opdivo Delivers, But CheckMate 227 Clouds

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Bristol-Myers Squibb Co.'s PD-1 inhibitor *Opdivo* continues to deliver impressive sales despite increased competition, but uncertainties about the all-important CheckMate 227 study of combination use with *Yervoy* in first-line non-small cell lung cancer, including the relevance of tumor mutation burden as an emerging immuno-oncology biomarker, cast a bit of a cloud on the third quarter.

Bristol reported sales of about $1.3bn for Opdivo (nivolumab) for the third quarter, up 38% from the same period in 2016. Performance for the company's novel anticoagulant *Eliquis* (apixaban) continued to be strong, with sales of $1.2bn, up 39% year-over-year.

Year-over-year sales of the rheumatoid arthritis drug *Orencia* (abatacept) and oncologic *Sprycel* (dasatanib) were up by 10% and 8%, respectively – which is meaningful growth for products at their lifecycle stage, execs said during an Oct. 26 earnings call. Overall, Bristol reported $5.3bn in sales, up by 7%.

OPDIVO HOLDS ITS OWN

Investors have been carefully watching Opdivo's performance following a number of market shakeups, notably the US FDA approvals of **Merck & Co. Inc.**'s competing PD-1 inhibitor *Keytruda* (pembrolizumab) as monotherapy and in combination with chemotherapy for first-line NSCLC and the market entry of **Roche**'s *Tecentriq* (atezolizumab) in second-line NSCLC. But Opdivo has been holding its position.

Chief Commercial Officer Murdo Gordon noted during the call that Opdivo's share in the second-line NSCLC US market has been stable and that there has been good growth in penetration and reimbursement of the same opportunity ex-US.

Looking beyond lung cancer, the drug continued to hold a very high share in renal cell carcinoma (RCC), despite strong competition from **Exelixis Inc.**'s *Cabometyx* (cabozantinib) in the second-line setting.

Bristol has reported positive overall survival results for the combination of Opdivo with its CTLA-4 inhibitor Yervoy (ipilimumab) in the CheckMate 214 first-line RCC study and Gordon noted during the call that US National Comprehensive Cancer Network guidelines have been updated to reflect those data.

"We're also hopeful that the strong data from the '214 first-line renal cell carcinoma trial – the combination of Opdivo and Yervoy – will be submitted quickly and reviewed quickly … that's another strong catalyst for growth," Gordon said.

The front-line RCC opportunity is roughly twice the size of the second-line market (16,000 vs. about 8,000 treated patients in the US). Opdivo currently has more than a 50% share of the US second-line RCC market. For the next year, the company expects uptake in the first-line setting, if all goes well, and "continuing robust business" in second-line RCC, Gordon said.

The company also noted that it is doing well across its immuno-oncology portfolio in first-line metastatic melanoma as it awaits a decision from FDA on adjuvant use of Opdivo, and that anecdotal feedback suggests that the new launch in liver cancer, an indication approved by FDA in September, is going well.

Execs said that they were optimistic about IO growth going forward, but also acknowledged that there are many new datasets coming from Bristol and competitors, so there are "a wide range of potential scenarios for 2018."

MUM ON '227 STATISTICAL PLAN

Bristol's last big chance for approval in first-line lung cancer – the biggest market segment for IO – rests on the Opdivo/Yervoy combination, and there is still uncertainty about prospects for the CheckMate 227 study of Opdivo with Yervoy in first-line NSCLC.

Execs reaffirmed that they plan to report final results for PD-L1-positive participants of the multi-arm study in the first half of 2018, and Chief Scientific Officer Tom Lynch said that an interim analysis of overall survival may be done at the end of 2017 or early in 2018.

CheckMate 227 used PD-L1 expression as a prospective biomarker, but a new biomarker – tumor mutation burden (TMB) – is becoming increasingly important. Tumor mutation burden refers to the number of mutations in tumor cells; a high mutation burden is thought to be associated with better response to treatment, but more research is still needed to support this hypothesis.

Bristol recently released data from an exploratory analysis of the CheckMate 032 study of Opdivo and Yervoy in small-cell lung cancer showing a strong association between high tumor mutation burden and response.

The company had also previously released a retrospective analysis from the failed CheckMate 026 study of Opdivo in first-line NSCLC showing a strong correlation between response and high tumor mutation burden.

Some analysts have been hoping that the company would change its statistical plan for the primary analysis of CheckMate 227 to incorporate tumor mutation burden.

In an Oct. 25 note, Leerink Swann analyst Seamus Fernandez had commented that given the data from Bristol as well as Merck and **Roche** about tumor mutation burden in immunotherapy, "an increasingly permissive but science-driven FDA may seriously consider allowing a retrospective tissue evaluation using a novel biomarker to prospectively segment an ongoing trial."

The company faced numerous questions about TMB and its analysis in the CheckMate 227 study during the third-quarter earnings call. Execs declined to comment about whether any changes had been made to the statistical analysis of the study, however.

Lynch acknowledged that tumor mutation burden is becoming increasingly important and said that the company is doing as much as it can to retrospectively analyze this biomarker in studies across tumor types, and it is also using TMB prospectively in the Phase III 9LA study.

The 9LA study, which tests Opdivo and Yervoy with chemotherapy versus chemotherapy alone in first-line NSCLC, started in July 2017 and is expected to report in 2019.

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CLICK
To see Bristol's Q3 2017 Sales Highlights click here:
http://bit.ly/2iPFUvB

New AbbVie Guidance Sets Pipeline Bar High

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AbbVie Inc. portrayed high confidence in its biggest revenue generator and in the pipeline of new therapies that will help replace revenue lost when *Humira* (adalimumab) biosimilars launch in five years, though some analysts are skeptical.

However, when the company raised its 2020 guidance for sales of the autoimmune disease therapy Humira to $21bn, it also set a high bar for risankizumab, upadacitinib and other drug candidates in terms of the sales they must generate to fill the revenue gap created by biosimilars. AbbVie CEO Richard Gonzalez said during the company's Oct. 27 earnings call that it will take time for biosimilars to erode Humira revenue, but it remains to be seen if the Chicago-area firm is being overly optimistic about its future.

"Over the next five years, Humira will continue to drive meaningful growth," Gonzalez said. "And following the entry of direct biosimilar competition, whether in the US or internationally, we believe our strategy will enable Humira to maintain its strong and meaningful market share position with a manageable erosion curve. As a result, Humira will remain a significant source of cash flow for the company for many years to come."

Leerink analyst Geoffrey Porges said in an Oct. 27 note that the 2020 Humira guidance of $21bn "is well-above the recent consensus estimate of $19.3bn, but below our 2020 estimate of $22bn."

AbbVie reported third quarter revenue of $7bn, which was 9.5% higher than in the third quarter of 2016 and in line with analyst consensus of $7bn. Humira sales totaled $4.7bn in the third quarter, up 15.8% year-over-year and slightly above consensus of $4.65bn.

Third quarter sales of other key products showed mixed results. While revenue from the lymphoma and leukemia drug *Imbruvica* (ibrutinib) rose 37.3% to $688m, sales from AbbVie's hepatitis C virus (HCV) franchise fell 26.8% to $276m as newly approved *Mavyret* (glecaprevir and pibrentasvir) launched into a highly competitive market with intense pricing pressure from US payers. "The three main products in focus – Humira, Imbruvica and HCV – all came in moderately above our expectations," Credit Suisse analyst Vamil Divan said in his initial Oct. 27 report on AbbVie's earnings.

The company said Imbruvica is on track to meet its 2020 goal of about $5bn in sales, while the HCV franchise is tracking below an estimate of $3bn by 2020.

While praising AbbVie's third quarter performance, BMO Capital Markets analyst Alex Arfaei was skeptical about the company's longer-term forecast.

"It seems impressive, but – in our view – optimistic at best, and unrealistic at worst. The central assumption is that future commercial dynamics, particularly regarding immunology price, biosimilar erosion, and access, will be very similar to today's," Arfaei wrote in an Oct. 27 note. "While we acknowledge that AbbVie's growth profile is excellent until 2021, we remain cautious on longer-term growth prospects."

PROTECTION FOR HUMIRA

However, one thing that improved AbbVie's confidence about Humira's sales is an agreement it negotiated with **Amgen Inc.** during the third quarter, which is expected to protect the product's US sales for another five or so years. Amgen agreed to wait until 2023 to launch its biosimilar that the US FDA approved in September 2016, although the company can launch its copycat product in Europe in 2018.

Two biosimilars have been recommended for approval in the EU: *Imraldi* from **Samsung Bioepis** and *Cyltezo* from **Boehringer Ingelheim GMBH**.

Gonzalez said the Amgen settlement "demonstrates the strength of our Humira [intellectual property] portfolio and further demonstrates our confidence that we will not see direct biosimilar competition in the US until at least the 2022 timeframe. Importantly, this will allow a number of key assets within our robust late-stage pipeline to enter the marketplace and establish a strong growth trajectory."

The company has been trying to build excitement for its immunology and oncology research and development programs for a while. But now that assets like risankizumab and upadacitinib are moving into and completing pivotal trials, AbbVie is getting more specific about how much revenue certain drug candidates may add to the company's bottom line.

TWO NEW BLOCKBUSTERS?

"We're very pleased with the significant progress we've made with several late-stage assets," Gonzalez said. "In particular, the data readouts for upadacitinib and risankizumab illustrates that both of these therapies have the potential to be highly differentiated, best-in-class agents across the range of immune-mediated conditions."

AbbVie reported positive results for risankizumab from three Phase III clinical trials in psoriasis on Oct. 26, which showed the antibody beat both Humira and **Johnson & Johnson**'s *Stelara* (ustekinumab) across multiple measures of skin clearance. The company intends to submit the Interleukin-23 (IL-23) inhibitor for FDA approval in 2018, but when it reaches the market it will face multiple competitors that will have been on the market for a few years.

Similarly, the selective JAK1 inhibitor upadacitinib has yielded positive results in a pair of Phase III rheumatoid arthritis studies, but it is likely to be the third or fourth JAK inhibitor approved for that indication in the US by the time it hits the market in 2019. The company plans to initiate Phase III studies for upadacitinib in atopic dermatitis in the first half of 2018, having recently reported positive results in a Phase II trial.

Gonzalez said in a lengthy presentation during the earnings call that AbbVie's non-Humira products should generate $9.6bn in 2017 sales with 2025 non-Humira revenue estimated at $35bn. The long-term forecast includes $5bn from risankizumab in psoriasis, psoriatic arthritis (PsA), ulcerative colitis (UC) and Crohn's disease (CD), and $6.5bn from upadacitinib in PsA, rheumatoid arthritis (RA), ankylosing spondilytis (AS), atopid dermatitis (AD), UC and CD.

BMO's Arfaei disputed those numbers as well as AbbVie's expectation for a relatively slow erosion of Humira sales following the introduction of biosimilars after 2022.

"This assumes no progress in interchangeability for the next five years, which we believe is unrealistic given the single

switch data, and efforts by BI and Sandoz," the analyst wrote. "If interchangeable, biosimilars will no longer compete for just ~20% of the volume, and as 5 to 6+ enter the market [around] 2023, price and share erosion is unlikely to be moderate. Anticipating this, companies with JAKs, i.e. **Pfizer Inc.**, will likely price accordingly to compete."

Arfaei also noted that "by 2023, we believe the access dynamics will change and prevent branded companies from blocking cheaper biosimilars with rebates."

However, when asked about **Celgene Corp.**'s commentary a day earlier regarding its psoriasis and psoriatic arthritis drug *Otezla* (apremilast) and the competitive market for those indications, Gonzalez said AbbVie has a different view of the market, because of Humira's success in patients with moderate to severe versions of those diseases.

"If you think about when Otezla entered the market, it really drove a number of patients, particularly the more mild patients into the market," he said. "And if you recall correctly, we saw the psoriasis market rate grow very rapidly over that period of time [and] what we're seeing now is that that product is no longer gaining traction."

"But if you strip that out," he continued, "because we really compete in more of the moderate patient population where the biologics tend to compete – moderate to severe – that rate has stayed the same or accelerated. In fact, it actually accelerated a bit, because you'll have patients that don't get adequate response [with] Otezla that then move on to a biologic. And psoriasis is one of the fastest-growing segments we operate in."

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AbbVie Goes Boldly Into Immuno-Neurology

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Now that the potential for harnessing the immune system to attack cancer has been well validated, drug makers are looking to the next big therapy area in which to explore the power of the immune system. One area that is getting attention, based on encouraging preclinical data, is neurodegenerative disease.

AbbVie Inc. made a big commitment to immuno-neurology with an announcement Oct. 24 that it will partner with immune system-focused start-up **Alector LLC** to develop and commercialize drugs to treat Alzheimer's disease and other neurodegenerative disorders. AbbVie agreed to pay $205m up front and offered a potential future equity investment of $20m to access Alector's technology. The two partners will research a portfolio of antibody targets, with AbbVie getting a global option to develop and commercialize two targets.

Given all the roadblocks drug developers have hit studying beta amyloid antibody approaches to treat Alzheimer's disease, there is a lot of enthusiasm for novel approaches that could present an entirely new path to explore and re-energize the field of Alzheimer's R&D. Alector insists there is growing rationale from human genetic analyses and animal studies that immune deficiencies in the central nervous system play an important role in the progression of neurodegenerative disease.

"We have been seeing exciting results with our immuno-neurology approach in preclinical animal models – and with that said, the real test will come once we are in clinic and working with patients," Alector's Chief Operating Officer Sabah Oney said.

Big biotechs like **Celgene Corp.** and **Biogen Inc.** have been talking more recently about their interest in exploring immune approaches to target neuro-degenerative diseases. Alector, which launched in 2013 following a Series A round funded by investors Orbimed and Polaris Ventures, has created an immuno-neurology technology platform that simultaneously can address multiple pathologies associated with neurodegeneration, according to the company. The company's founders offer a track record for developing companies and selling them to big pharma. CEO Arnon Rosenthal co-founded **Rinat Neuroscience Corp**, which was sold to **Pfizer Inc.** in 2006 for $500m.

Alector has raised a total of $80m in several financings, including some pharma investors: **Amgen Inc.Merck & Co. Inc.** and **AbbVie Inc.**

AbbVie said its early investment in Alector led to a broad appreciation for the technology platform. "We recognized the potential of Alector's research first as an AbbVie Ventures portfolio company and are now eager to partner with them to further develop this platform into meaningful advances for patients," AbbVie VP-Pharmaceutical Discovery Jim Sullivan said in a statement. Alector's Oney also said the early collaboration helped to foster the eventual partnership. "We have developed a great working relationship with AbbVie over the last few years and have a well aligned scientific philosophy," Oney said. "Together, we know how to best develop these drugs and get them to patients as quickly as possible."

The company was also impressed with AbbVie's commercial experience. "AbbVie is one of the best, if not the best, in commercializing blockbuster biologics in the market – as evidenced by their success with *Humira*," he said.

But AbbVie is better recognized for its experience in inflammation and oncology than neuroscience, where it does, however, boast a budding pipeline. The company is developing an anti-tau antibody for Alzheimer's disease and progressive supranuclear palsy in Phase II.

Alector's top priority now is pushing drug candidates into the clinic. The company has a goal to move five portfolio programs into the clinic within two years, with the first to be in patients within about one year from now.

Alector is responsible for conducting the exploratory research, drug discovery and development for the lead programs up through completion of proof-of-concept. AbbVie will be responsible for leading development and commercialization activities for the drugs it options. The companies will co-fund development and commercialization and will share global profits equally.

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Merck Stresses OS In Keytruda/Chemo '189 Trial Revamp

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Any change to the design of the immuno-oncology combination trials in lung cancer attracts enormous attention. Just one day after **Bristol-Myers Squibb Co.** was grilled over the CheckMate 227 study of its PD-1 inhibitor *Opdivo* (nivolumab) with the CTLA-4 inhibitor *Yervoy* in non-small cell lung cancer, **Merck & Co. Inc.** came under fierce questioning as it announced a delay and endpoint change to the eagerly awaited KEYNOTE-189 study of its PD-1 inhibitor *Keytruda* (pembrolizumab) with chemotherapy in first-line NSCLC. *(Also see "Bristol's Opdivo Delivers, But CheckMate 227 Uncertainties Cloud Quarter" Scrip, 26 Oct, 2017.)*

EMPHASIS ON OVERALL SURVIVAL

Keytruda has accelerated approval for use in combination with **Eli Lilly & Co.**'s *Alimta* (pemetrexed) and carboplatin chemotherapy in first-line non-small cell lung cancer (NSCLC) in the US, based on results from the KEYNOTE-021 Cohort G study. KEYNOTE-189 is a confirmatory study that previously had progression-free survival (PFS) as a primary endpoint and overall survival as a secondary endpoint. These are now dual co-primary endpoints, the company said as part of its third-quarter earnings report on Oct. 27.

"This revision has been reviewed and accepted by the FDA. The timeline for completion of KEYNOTE-189 has therefore been extended to capture longer-term survival data, with an estimated completion date depending upon the underlying event rate in February of 2019. The study is fully enrolled as we announced in the second quarter, and the opportunity exists to conduct interim analyses again depending upon the underlying event rates that we observe," Roger Perlmutter, president of **Merck Research Laboratories**, said during the earnings call. The trial had been expected to have an assessment at the end of 2017.

The company also announced at the close of business on Oct. 27 that an application for Keytruda with Alimta and carboplatin in first-line treatment of metastatic non-small cell lung cancer, based on the 021G trial, has been withdrawn in Europe.

"Merck is confident in the clinical data from this rigorously conducted trial, which demonstrated significant improvements in overall response rate (ORR) and progression-free survival (PFS) for the Keytruda combination regimen compared to chemotherapy alone. Additionally, the company's broad clinical development program includes a number of studies evaluating Keytruda in combination with chemotherapy in the first-line NSCLC setting. Merck looks forward to sharing data from these studies with regulatory authorities and the medical community as they become available," the company said in a statement.

Merck's filing for the chemo combo in Europe based on the 021G data "was a long shot – it would be highly unusual for European regulators to approve an application like this based on Phase II data," Bernstein analyst Tim Anderson said in an Oct. 27 note, adding that "the bar to FDA approval in oncology is lower, and the US approval is very highly likely NOT in jeopardy."

The 021G study had only 16 patients per arm. With the improved power of the '189 study, the company will be following event rates very closely and is hoping to see a meaningful separation in overall survival curves, Perlmutter said.

The company aims to preserve the overall survival results in the '189 study. Those who don't respond will have the option of crossing over to treatment that includes Keytruda. There will be opportunities for interim analyses but the company is going to be "careful to preserve the integrity of the study," Perlmutter said.

BMO Capital Markets analyst Alex Arfaei commented in an Oct. 27 note that the KEYNOTE-189 update is positive in that the company added overall survival to the primary endpoint. KEYNOTE-189 is probably "Merck's best chance at hitting overall survival as the PD-1s become the standard of care in second-line non-small cell lung cancer," Arfaei said.

Perlmutter acknowledged that in the '189 study, everybody in the comparator chemotherapy arm is permitted to get Keytruda after treatment failure.

"And what that means is you either got Keytruda at the beginning or you got it late, and because there's such a dramatic decline in PFS, with a median PFS of less than nine months in the chemotherapy arm, everybody gets Keytruda pretty quickly," Perlmutter said.

Allowing patients to cross over, however, can make it harder to show a survival benefit.

How Keytruda performs as an early versus late treatment is very important and the company wants to make sure it understands this and obtains solid data in the '189 study, because ultimately "that's practice-changing," Perlmutter said.

KEYTRUDA SALES ALMOST DOUBLE

Keytruda was a bright spot for the company, as global human health sales declined by 4% to $9.2bn, due to the loss of exclusivity of several products. But Adam Schechter, executive vice president and president of global human health at Merck, exec said that the company continues to see "strong underlying growth" from launched products, including Keytruda, *Zepatier* (elbasvir/grazoprevir) and *Bridion* (sugammadex) (*see box*).

Keytruda posted about $1bn in sales during the third quarter – almost 200% growth, aided by increased use in first-line lung cancer, Morningstar analyst Damien Conover pointed out in an Oct. 27 note, although this was shy of analyst expectations. Opdivo reported sales of about $1.3bn for the third quarter, up 38% from the same period in 2016.

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Merck's Q3 2017 Sales Vs. Consensus Expectations

Keytruda (pembrolizumab): $1,047m vs. $1,066m
Zepatier (hepatitis C virus combo): $468m vs. $544m
Januvia/ Janumet (sitagliptin/metformin): $1,525m vs. $1,489m
Zetia (ezetimibe): $320m vs. $317m
Vytorin (ezetimibe/simvastatin): $142m vs. $171m
Remicade (infliximab): $214m vs. $191m
Gardasil (human Papillomavirus 9-valent vaccine, recombinant): $675m vs. $776m
Isentress (raltegravir): $310m vs. $304m
Source: Jeffrey Holford, Jefferies

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Scrip's Executive of the Year Award is designed to acknowledge excellence in the leadership of large pharmaceutical and biotechnology companies.

Said Darwazah, chair and CEO of Hikma Pharmaceuticals

Under Said's leadership, Hikma grew by 35% to reach revenues of around $2bn in 2016. The year was transformational for the company as it re-balanced and strengthened its business. Hikma has a clear strategy for growth, centred on optimising its portfolio, developing people, deepening R&D investment, expanding manufacturing capabilities and looking for new M&A opportunities.

David Meek, CEO of Ipsen

Since joining as CEO in July 2016, Meek has guided Ipsen to become a leader in specialty care, focused on oncology, neurosciences and rare diseases. In Q1 2017, sales grew 19.1%, with Ipsen's specialty care business driving top-line growth at a rate outpacing peers. Meek also oversaw the company's largest transaction to date: the acquisition of Merrimack's *Onivyde*.

Flemming Ornskov, CEO of Shire

Under Ornskov's leadership, the close of the acquisition of Baxalta has cemented Shire's position as the leading global rare disease-focused biotechnology company and created a strong environment for growth. With around 40 programs in the clinic and about 20 in the later stages of development, Shire now has the deepest and most innovative pipeline in its history.

Jan van de Winkel, CEO of Genmab

Genmab enjoyed a fourth year of profitability in 2016, under van de Winkel's leadership, and a significant increase in valuation as its anticancer *Darzalex* was approved in additional indications. Genmab's pipeline grew, with a new program, HuMax-AXL-ADC, entering its first clinical trial as the company further secured its reputation as an antibody innovation powerhouse.

James Ward-Lilley, CEO of Vectura Group

Ward-Lilley played a critical role in what was a transformational year for the Vectura Group as it undertook a £441m merger with Skyepharma to create an international inhaled airways disease-focused powerhouse with improved near-term cash flows and an enhanced mid to long-term pipeline. The Group is now in a strong position to create significant sustained value.

Elias Zerhouni, president of global R&D at Sanofi

Under Zerhouni's leadership, Sanofi has transformed its development activities. He was instrumental in creating Sanofi's R&D strategy, rebuilding the late-stage pipeline, and then revamping early-stage research. As a result, Sanofi has shortened development timelines and increased pipeline productivity, and in 2017, it received US FDA approval for two innovative drugs, *Dupixent* and *Kevzara*.

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Gilead Data Suggest Role For ACC Inhibition In NASH

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Gilead Sciences Inc. presented data at the American Association for the Study of Liver Diseases annual meeting indicating a potential role for acetyl-coA-carboxylase (ACC) inhibition in the treatment of non-alcoholic steatohepatitis (NASH), as the higher of two doses tested in a Phase II study showed a statistically significant reduction in the buildup of fat in the liver compared to placebo after 12 weeks of treatment.

Presented as a late-breaking abstract on Oct, 24, the last day of the conference in Washington, DC, GS-0976 reduced hepatic steatosis by a mean 28.9% from baseline in a 49-patient cohort receiving 20 mg daily of the oral ACC inhibitor. The compound – one of three in development by Gilead for NASH – was licensed by the California biopharma in 2016 from Nimbus for $400m up front and up to $800m in milestones. *(Also see "Gilead Buys Nimbus NASH Drug To Dominate Another Liver Disease" Scrip, 5 Apr, 2016.)*

The study also investigated a 5 mg dose of GS-0976, with Gilead reporting that dose did not produce statistically significant differences versus placebo for the primary endpoint of hepatic steatosis reduction or any of the other measures in the study, which also tested a set of biomarkers for potential in non-invasive diagnosis and prognosis of the disease. At present, NASH not only lacks an approved drug therapy but also can only be diagnosed with a liver biopsy.

The primary endpoint was measured using a non-invasive histological scan process called MRI-PDFF (proton density fat fraction). The 5 mg daily dose of GS-0976 yielded a 13% reduction in liver fat after 12 weeks, compared with 8.4% in the placebo arm.

In a secondary measure, the 20 mg dose also demonstrated statistical significance in yielding a 30% or greater reduction in hepatic steatosis from baseline, as 48% of patients in this arm achieved that level of reduction. Twenty-three percent in the 5 mg treatment arm achieved 30% or greater reduction in liver fat, compared to 15% in the placebo group. For a biomarker measuring fibrosis – called TIMP-1 (tissue inhibitor of metalloproteinase-1) – the 20 mg dose also demonstrated statistical significance compared to placebo, producing a 7.9% mean reduction in this score versus a 1.5% reduction for placebo (and 2.9% for the 5 mg dose of study drug.)

Gilead contends that these data indicate potential for GS-0976 to play a key role in treating NASH, as ACC inhibition can address a pathway associated with disease progression. ACC catalyzes the first step of new liver fat accumulation – hepatic de novo lipogenesis – a synthesis of fatty acids that can lead to hepatic steatosis.

> 'Payers are a bit nervous. They see NASH as, perhaps, a very large indication, [that] would cost them a lot of money'

The GS-0976 Phase II were among 18 abstracts that Gilead presented at the AASLD meeting – another abstract unveiled preclinical data indicating that GS-0976 and the firm's most-advanced NASH candidate – ASK1 (apoptosis signal-regulating kinase 1) inhibitor selonsertib – provide greater anti-fibrotic and fat-reducing effects in tandem than either agents does on its own. Gilead currently is advancing selonsertib (GS-4997) as monotherapy in the Phase III STELLAR trial for NASH patients with advanced fibrosis (scores of F3 or F4).

GILEAD ADVANCING COMBO THERAPY STRATEGY

In addition to those two candidates, Gilead also has a non-steroidal farnesoid X receptor (FXR) agonist in Phase II monotherapy investigation for NASH. GS-9674 was obtained in a 2015 deal that could bring back as much as $470m to **Phenex Pharmaceuticals AG**. [See Deal] The smaller firm already has earned an undisclosed upfront payment and a $100m development milestone under the agreement. *(Also see "Gilead Pays Phenex $100m Milestone As NASH Candidate Progresses" Scrip, 5 Jan, 2017.)* Beyond development of the three candidates as monotherapies, Gilead is conducting clinical studies testing two or all three of its candidates in combination therapy for NASH. *(Also see "Combination Strategies A Common Thread In NASH R&D" Scrip, 21 Nov, 2016.)* The company says its strategy involves addressing NASH through multiple core disease pathways – metabolic dysregulation, inflammation and fibrosis.

At the Citi Biotech Conference on Sept. 6, Gilead Chief Operating Officer said the Phase III focus for selonsertib monotherapy is on sick patients because the companies believe that approach will play well with payers who are wary of the coming wave of NASH therapies and the potential for expensive, chronic therapy for a broad patient base.

"Payers are a bit nervous," Young noted. "They see NASH as, perhaps, a very large indication, [that] would cost them a lot of money. I think the very fact that our development program is in the sicker patients is reassuring to them in the F3 and F4 – It's a narrow population. They're in very, very high need. So I think they're encouraged that we're targeting the whole development program. These are patients that often need a lot of help in many other respects. In terms of lifestyle, they're often diabetic. They've got high blood pressure."

"So, I think we can have a very, very good conversation with plans and potentially the PBMs around how we can do compliance programs, how we can do general health care programs that would include the delivery of a drug for NASH that would be sort of a win-win-win," he continued. "It would be a win for the health plan; it would be a win for patients; and I think a win for Gilead."

Gilead Chief Scientific Officer Norbert Bischofberger then added that studying selonsertib in sicker patients also should yield outcomes data that will reassure payers. STELLAR uses a 48-week histological endpoint but as Gilead gathers 96-week follow-up data, he suspects it will accumulate incidents of hepatic decompensation that will bolster a health economics argument for these therapies.

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CONTINUED FROM COVER

(ACC) inhibitor GS-9076 showing the ability to reduce buildup of fat in the liver, but otherwise the data largely showed no statistical benefit compared with placebo.

In an Oct. 24 note on the GS-9076 data, Jefferies Equity Research analyst Michael Yee said general expectations are that Gilead will read out Phase III data for selonsertib in 2019 or 2020. Overall, he posited Gilead's NASH program may be underappreciated by investors, whose immediate focus is more on HIV and immuno-oncology, given Gilead's $11.9bn buyout of **Kite Pharma Inc.** in August.

Yee said Gilead doesn't get much credit for its program "because data is challenging to interpret and compare." Specifically, he noted that the Phase II data for GS-9076 were based on biomarker and imaging findings rather than biopsy data and that the Phase II data for selonsertib came from a small study.

Allergan sustained a likely significant setback to its NASH hopes in September when a Phase II trial for cenicriviroc, its dual C-C chemokine receptor 2/5 (CCR2/5) inhibitor, showed no meaningful difference compared to placebo in reducing fibrosis scores in NASH patients. Allergan gained cenicriviroc as part of its $1.7bn acquisition of **Tobira Therapeutics Inc.** in 2016.

Based on those top-line, two-year data from the CENTAUR study, on Sept. 22 Credit Suisse removed any potential revenues from cenicriviroc from its modeling for Allergan, although analyst Vamil Divan said the drug might still hold potential in sicker NASH patients or combination regimens. Allergan is continuing with the Phase III AURORA study of cenicriviroc with a composite endpoint of reducing fibrosis score by at least one stage with no worsening of NASH. It plans to talk with regulators to see if protocol changes to AURORA are advisable based on the Phase II data.

Intercept, meanwhile, was the first company to initiate a Phase III trial in NASH and says the REGENERATE study remains on track to yield data in 2019, following a decision this past April to revise the primary endpoint. Lowering the bar for success, the endpoint was changed from resolving NASH without worsening of fibrosis and reduction of fibrosis without worsening of NASH to require only either of those measures. In September, however, FDA issued a safety communication that due to excessive dosing of Ocaliva in PBC patients, patients' risk of increasing liver injury or death was increased. Nineteen deaths had been reported in PBC patients taking Ocaliva, a farnesoid X receptor (FXR) agonist, and of the eight with a known cause of death, seven were attributed to worsening of PBC and one to cardiovascular disease.

PBC DOCTORS HAPPY WITH OCALIVA, INTERCEPT SAYS

In an email exchange during the AASLD meeting, Intercept CEO Mark Pruzanski said physicians have been citing positive experiences using Ocaliva, which was approved to treat PBC in 2016. Intercept also reported successful Phase II data for the drug in primary sclerosing cholangitis (PSC) during the conference.

Pruzanski said the AESOP data add to "a robust and growing evidence base for OCA in progressive non-viral liver diseases where there is high unmet need. Specifically, AESOP represents a powerful proof-of-concept for OCA in a second cholestatic liver disease with no approved therapies." Intercept also has Ocaliva in Phase II study in biliary artresia, a rare cholestatic liver disease in infants that has no approved drug therapy.

The exec said Intercept has ongoing talks with FDA about Ocaliva's use in PBC and that no label change has been made for the product in the US or elsewhere.

"Intercept's efforts to reinforce appropriate dosing in PBC patients with advanced PBC (Child Pugh B and C cirrhosis) have reached thousands of physicians through direct engagement and we have mailed more than 40,000 'Dear Healthcare Provider' letters," Pruzanski noted. "Our internal market research and interactions at the Liver Meeting have given us confidence that these initiatives are resonating with physicians and we are committed to continuing our efforts to reinforce the dosing recommendations for Ocaliva in patients with advanced disease."

WHO'S LEADING THE RACE?

Following Genfit's recent second quarter earnings call, analyst Jean-Jacques Le Fur of France's Natixis Equity Research said Intercept's safety issues suggest Genfit may hold the strongest position in the NASH race right now.

"Certainly, the most positive [news] for Genfit is what is happening at its direct competitors," Le Fur wrote Sept. 26. "A number of them are clearly experiencing difficulties which could see Genfit take the lead (assuming positive Phase III results) more comfortably in the treatment of NASH. Intercept has encountered problems with Ocaliva which led to 19 deaths in its primary biliary cirrhosis indication. It is true that NASH is not the same disease, but this product's safety is clearly at issue for a chronic treatment."

"More generally, there is the question of the safety profile of the whole class of FXR agonists (to which Ocaliva belongs) being studied by a number of Genfit's competitors, such as **Novartis AG** or Gilead," the analyst continued. "Also, rival Allergan published underwhelming clinical results for cenicriviroc."

Intercept has enrolled more than 1,300 patients so far in its Phase III REGENERATE study in NASH and anticipates data from an interim analysis cohort during the first half of 2019, he said. The company also intends to investigate Ocaliva in NASH patients with cirrhosis, he added, as data indicate 40%-60% of these patients will advance to liver failure within five to seven years, with one-third dying or requiring a liver transplant.

Pruzanski contends that Ocaliva holds the upper hand in the NASH race because of its activity in multiple aspects of the multifactorial disease.

"Intercept has the largest and most advanced clinical development program in NASH," he said. "The Phase II FLINT trial remains the most robust NASH clinical trial completed to date and [Ocaliva] is the only investigational NASH therapy to demonstrate significant and clinically meaningful improvement in all key histologic features of the disease: fibrosis, together with the three key features of the underlying disease, inflammation, ballooning and steatosis. Fibrosis is the only histologic feature of NASH that has been associated with long-term clinical outcomes."

Genfit's Hum said his firm is on the way to getting authorization to initiate a Phase II study of elafibranor in pediatric NASH and also is investigating the drug in PBC, with Phase II data expected during the second half of 2018.

Genfit's aim, he explained, is to differentiate elafibranor as the only late-stage candidate that can resolve NASH while providing a cardiometabolic-protective benefit.

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Ablynx Ups Profile Stateside With $200m Nasdaq Listing

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Fresh from its clinical success with caplacizumab, **Ablynx NV** has priced its initial US public offering totaling $200m, propelling the company's market capitalization over the €1bn mark.

The Belgium-headquartered group has listed on the Nasdaq after selling 11.4 million American Depositary Shares (ADS) priced at $17.50 each. Ablynx had previously planned to offer $150m worth of shares in the US and concurrently offer $25m worth of stock in a European private placement.

However, Ablynx chief executive Edwin Moses told *Scrip* that investors, including the European backers, decided to focus on the US IPO, noting that "everybody wanted to get the ADSs." Trading of Ablynx shares in Europe, where they are listed on Euronext Brussels, were suspended at the request of the company Oct. 25 but the Ghent-based group made clear that the halt was a precautionary measure to allow the underwriters to communicate allocations to investors "and to facilitate a debut open" on the Nasdaq.

INTERESTING TIMES

In addition, Ablynx has granted the underwriters an option to purchase up to an additional 1.7 million ADSs, which could add another $30m to its coffers. BofA Merrill Lynch, JP Morgan and Jefferies acted as joint book-running managers for the offering, while Baird, Bryan, Garnier & Co and Ladenburg Thalmann were co-managers.

These are interesting times for Ablynx, which has enjoyed a successful month following the publication of positive top-line HERCULES Phase III data for caplacizumab in patients with acquired thrombotic thrombocytopenic purpura (aTTP), a rare blood disorder. The data, which add to positive proof-of-concept data from the Phase II TITAN study, will be used to push forward the firm's filings for the first-in-class anti-von Willebrand factor Nanobody medicine.

In February 2017, based on TITAN, caplacizumab was submitted to the European Medicines Agency and in July this year, Ablynx received fast-track designation from the US Food and Drug Administration – a biologics license application filing is planned for 2018 and if approved, caplacizumab would be the first therapeutic specifically indicated for aTTP.

Ablynx estimates the total market opportunity of aTTP in North America, Europe and Japan to be in excess of €800m and intends to market the drug on its own. October has also seen the company set up a US subsidiary and appoint Daniel Schneider, formerly manager of the specialty pharmaceuticals business unit at BTG International, to lead the commercialization of caplacizumab.

The proceeds from the IPO will come in handy for the build-up to launches of caplacizumab, Moses said, as the company sets up commercial operations, with around fifty staff added in Europe and another fifty hired in the US.

Ablynx is also eyeing a more lucrative market with a second wholly-owned drug for respiratory syncytial virus (RSV) infections. The company believes that the drug, codenamed ALX-0171, illustrates an advantage of Nanobodies over monoclonal antibodies in that the former can be nebulized, and therefore inhaled, while retaining their biological activity.

Moses noted that some of the IPO proceeds will be used on a Phase IIb trial currently being conducted in 180 infants hospitalized with a RSV infection and the firm expects top-line data in the second half of 2018. Ablynx claims that with only one drug currently indicated for RSV in infants, **AstraZeneca PLC**'s *Synagis* (palivizumab), ALX-0171 represents a greater than €1.0bn opportunity in the big three markets of North America, Europe and Japan.

Moses told *Scrip* that if the trial goes well, it will look to partner ALX-0171 and is interested in a co-development and co-commercialization deal. "We do not want to be a single product company," he stressed, noting that Ablynx has considerable funds to build up the pipeline.

With regards to the Nasdaq listing specifically, he said that the strong caplacizumab data meant this was the perfect time to go to the US. Its investor base already consisted of around 35% of backers based across the Atlantic and "they told us again and again that they could not invest in euros and wanted to see more liquidity."

"They want to invest big when they come in," Moses added, noting that the sums that can be raised in the US still dwarf those in Europe. However, he pointed out that "it is not easy money," investors do their homework on a company's projects and are "positively critical…they challenge you but when they like the idea, they pile in in spades."

When asked about the different environments for fundraising, Moses said one street in New York has as many specialist healthcare investors as there are in the whole of Europe, they manage bigger funds and their pockets are deeper. He noted that investors had claimed that if Ablynx had been on the Nasdaq when the caplacizumab data was published, the company's share price would have gone up a lot more than the €2-€3 it rose in Europe.

DUAL LISTING MAKES SENSE

Nevertheless, Moses stressed that the investment community in Europe has been very supportive and "we are lucky to be on Euronext, it has served us well." Now though, as the company bids to become a fully-integrated biopharmaceutical company, a dual listing makes sense.

Formed back in 2001, Ablynx has about 45 wholly owned and partnered programs and has been successful in getting funds to progress the pipeline. To date, it has received nearly €454m from its collaborations and claims to have the potential to receive more than €10.6bn in additional milestone payments, plus royalties.

Key partnerships include a recently-inked deal with **Sanofi** to develop novel treatments for various immune mediated inflammatory diseases. It also has partnerships in place with the likes of **Boehringer Ingelheim GMBH**, **Merck KGAA**, **Merck & Co. Inc.** and **Novartis AG**, and a closely-watched collaboration with **AbbVie Inc.** for vobarilizumab, which is currently in a Phase II study in patients with systemic lupus erythematosus – data expected in the first half of 2018 and if successful, AbbVie will have an opt-in right to license vobarilizumab upon payment of $25m.

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Antibody-Drug Conjugates Attract Hefty Funding To ADC Therapeutics

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Having a realistic view of the amount of funding required to take a potential medicine through clinical trials could be thought a prime requirement of a biotech company, one being exhibited by Lausanne, Switzerland-based biotech **ADC Therapeutics SARL**, that has just raised $200m to take two of its novel antibody-drug conjugate anticancers into and through registrational clinical trials.

The financing is one of the largest private fundraisings for a European biotech over the past couple of years, and saw both existing and new investors supporting the private placement, that comes after early clinical data for its lead compounds was released in the middle of the year. Further clinical data will be presented at the forthcoming American Society of Hematology (ASH) meeting at the end of 2017.

Chris Martin, CEO of ADC Therapeutics

ADC Therapeutics

"We will have six programs in clinical development within six months, and that needs funding," said ADC Therapeutics CEO Chris Martin in an interview on Oct. 23. "We want to progress two lead products into registrational trials, continue the development of two other clinical programs, and put two more drugs into clinical trials in the next six months," Martin noted.

The $200M haul this time around brings to $455m the amount the company has raised since it was set up in 2012, including $105m in a private financing round in Oct. 2016; the company still has part of the 2016 funding in hand, Martin said. In the current financing, existing shareholders including Auven Therapeutics, the family office of flavors billionaire Hans-Peter Wild, **AstraZeneca PLC** and new investors such as the San Francisco-based investment firm Redmile supported the round, that was oversubscribed.

Although most of the funds are destined to support clinical trials, the company will also expand its clinical development team, in areas such as clinical trials, pharmacovigilance and regulatory affairs, Martin reported. The company might also consider partnering discussions. "Given that we will have six drugs in clinical development in the next six months, we probably won't be taking all these to market ourselves, so in some regions we will be looking for collaborations," he noted.

ADC Therapeutics's antibody-drug conjugates use a novel cytotoxic warhead, based on highly potent pyrrolobenzodiazepine (PBD) dimer toxins, that don't distort the structure of DNA and so are nearly invisible to DNA repair mechanisms. "They don't stick out," according to Martin. This stealth-like property is expected to lead to medicines which have better efficacy and a lower propensity for resistance to emerge in tumor cells than other anticancer agents.

The antibody-drug conjugates bind to specific targeted tumor cell surface antigens, are taken inside cells, and the PBD dimers released. These bind to the minor groove of DNA, forming DNA interstrand cross-links that block cell division and kill the cells. The small UK biotech, **Spirogen Ltd.**, that was acquired by AstraZeneca's MedImmune subsidiary in 2013, was involved in developing this PBD technology, that ADC Therapeutics has exclusively licensed to cover certain targets.

"People are getting more confident that PBD technology could outperform other types of antibody-drug conjugate technology," Martin commented. Other companies including **Seattle Genetics Inc.** are also developing the use of pyrrolobenzodiazepine dimers in their antibody-drug conjugates.

LEUKEMIAS AND LYMPHOMAS

The two lead compounds of ADC Therapeutics are ADCT-301 and ADCT-402. The CD25-targeted ADCT-301 has been associated with a 38% overall response rate in a small group of heavily presented, relapsed or refractory patients with Hodgkin's lymphoma, evaluated in in a dose-escalating Phase I study. It was well tolerated, the company added, following scientific presentations at the International Conference on Malignant Lymphoma (ICML) held in Lugano, Switzerland, in June this year.

ADCT-301 is also being evaluated in patients with non-Hodgkin's lymphoma, acute myeloid leukemia and acute lymphoblastic leukemia, and ADC Therapeutics also reported that it will advance ADCT-301 into a combination study for solid tumors. CD25 is expressed on certain lymphomas and leukemia, but its expression in healthy tissue is restricted; the CD25 MAb part of ADCT-301 is licensed from **Genmab AS**.

ADCT-402 targets the CD19 antigen that is highly expressed on certain leukemia and lymphoma cells, and in a Phase I study an overall response rate of 61% was observed in patients with non-Hodgkin's lymphoma and an overall response rate of 57% in patients with relapsing or refractory diffuse large B-cell lymphoma. Side effects included fatigue, neutropenia and thrombocytopenia. ADCT-402 is also being evaluated in a Phase I study in patients with acute lymphoblastic leukemia.

A product partnered with MedImmune, the prostate-specific membrane antigen (PSMA) targeted MEDI3726(a), previously known as ADCT-401, is in Phase I studies in prostate cancer, as is ADCT-502, that is in Phase I in patients with breast and other solid tumors. The funding will also support IND filings for ADCT-602 and ADCT-601, and to progress a pipeline of preclinical ADC programs.

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Shire Will Cut Manufacturing Sites As It Looks For More Baxalta Synergies

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Manufacturing was a primary focus of **Shire PLC**'s third quarter earnings call on Oct. 27, as the company continues to feel pressure to find more synergies out of its $32bn acquisition of **Baxalta Inc.** and has taken aim at operations to do so.

Flemming Ornskov

Shire took a leadership position in the hemophilia space with the 2016 acquisition and increased its global commercial footprint. It originally predicted cost synergies of $500m.

CEO Flemming Ornskov and Shire Head of Technical Operations Matt Walker outlined an ongoing effort to yield savings of $100m annually by 2019, increasing to $300m annually by 2023 by streamlining these operations and increasing their efficiency.

Walker told the Oct. 27 call that after the Baxalta transaction, Shire had 17 manufacturing sites, with a plan to divest five for a net total of 12. It already has sold off two sites, he said, and has selected one in Hayward, Calif., as another to be divested.

Ornskov said that these savings would result on top of the cost synergies already identified from the Baxalta merger.

In an Oct. 27 note, Morningstar analyst Karen Andersen called Shire's cost-control efforts encouraging but suggested even greater synergies might be possible. "We believe synergies between the two businesses on the top line – including Shire's ability to use Baxalta's international footprint for its own products, as well as the hospital overlap between hereditary angioedema and Baxalta's immunology business – have not been fully appreciated," she wrote.

MIXED QUARTER DUE TO CINRYZE, LIALDA DECLINES

Overall, analysts called Shire's latest quarterly performance mixed as its 7% sales growth to more than $3.5bn was offset by cratering sales of its hereditary angioedema preventive drug *Cinryze* and quicker than expected deterioration of *Lialda* sales to generic competition. The firm's dry eye drug *Xiidra* (lifitegrast), now on the market for more than a year, posted sales of $77m during the third quarter, up about 35% from the $57m in sales during the second quarter. *(Also see "Shire Touts Ongoing Xiidra Growth, Targets Increased Medicare Access" Scrip, 27 Oct, 2017.)*

Ornskov pointed to Shire's decision to launch a branded generic version of Lialda (mesalamine) as somewhat mitigating the impact of generic competition for the ulcerative colitis drug.

"We have seen a stabilization of our market share declines, and in the most recent IMS prescription data, branded Lialda commands approximately 20% of the mesalamine class, down from about 40%," Ornskov said. "However, when you look specifically at the share [held by] the Lialda molecule, branded Lialda and our authorized generic command together 47% share and it's still growing."

Lialda and the generic *Mezavant* brought in $87m during the third quarter, down 58% year-over-year for the franchise.

CINRYZE HELD UP BY MANUFACTURING

Cinryze sales plummeted 66% during the quarter to $57m for dual reasons – competition from **CSL Behring**'s recently launched subcutaneous C1 esterase inhibitor product *Haegarda* and manufacturing issues that disrupted supply of Cinryze during the quarter. *(Also see "Shire Sees Another Way To Compete With CSL Behring In HAE With New Version Of Cinryze" Scrip, 12 Sep, 2017.)* Ornskov noted that since Shire acquired Cinryze in 2014, the plasma product – manufactured by a single third-party contractor – has faced issues in supply keeping up with demand, even resulting in a since-lifted FDA warning letter.

"Unfortunately, in the third quarter, we experienced a manufacturing interruption resulting in a subsequent product shortage that began in August," the exec said. "We tackled this immediately, and the good news is that the manufacturer has addressed the issue and resumed production of Cinryze. More importantly, in early October, Shire obtained FDA clearance to release a number of previously manufactured Cinryze lots. As a result, planned third quarter U.S. supply of $100m was shipped in October instead of being shipped in September."

Consistent supply of Cinryze for patients is a top priority for Shire, Ornskov maintained, and because of that it has applied to FDA for authorization to begin manufacturing the drug at one of the sites acquired from Baxalta. Walker told *Scrip* that FDA has agreed to an expedited review process, with an end-of-January action date. "So we're answering questions, we're actively working with the FDA and we look forward to approval in the next few months," he said.

Ornskov conceded that the supply interruption lost Shire some HAE patients to Haegarda, mostly patients new to treatment.

He noted that Shire did see increased sales for its HAE drug *Firazyr* (icatibant), which is indicated for treatment of acute attacks rather than prophylaxis. "As soon as we became aware of this situation [with Cinryze supply], we have another product for hereditary angioedema, which is called Firazyr, and we made that available, so you can see this quarter we had much stronger sales for that," the CEO told *Scrip*.

Firazyr sales rose 34% during the third quarter to $196m.

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Amazon-Express Scripts Partnership? PBM Sees Opportunity In Uninsured Market

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Express Scripts Holding Co. sees opportunity in the possibility that online retailing giant Amazon may be moving into prescription drug sales, President and CEO Tim Wentworth told analysts Oct. 26.

Amazon has not publicly announced plans for entering the prescription drug arena. But recent reports that the company has been pursuing pharmacy distribution licenses in several states have fueled predictions that it is poised to do so, which would cause a major disruption in the pharmacy benefit management and retail pharmacy sectors.

Some speculation has centered on Express Scripts, the only stand-alone business among the largest PBMs, as a potential partner or acquisition target for Amazon. Express Scripts recently endured a business setback when its largest client, **Anthem Inc.,** announced it would not renew the PBM's contract after it expires in 2019. *(Also see "Anthem In-House PBM Will Draw On CVS But Retain Formulary Control" Pink Sheet, 18 Oct, 2017.)*

Analysts also view **CVS Health Corp.**'s reported interest in buying health insurer **Aetna Inc.** as a defensive move anticipating Amazon competition to both its PBM and retain pharmacy units.

Wentworth's comments came in response to a question from JP Morgan analyst Lisa Gill during the company's third quarter earnings call. Gill asked him to elaborate on past statements about how Express Scripts might work with Amazon to reach a relatively untapped market – the uninsured.

"Right now, as I look at the possibility of disruptors such as Amazon in the cash space, I think there absolutely is a population there that deserves good service," Wentworth said. "We certainly see that as something where, if they wanted to move into a space, we could be a very natural collaborator."

He estimated there are "30m people who we view as sort of the cash market that we've not historically participated in very aggressively," representing about 150m prescriptions. "The opportunity, first of all, is to help those folks get access to care that they can afford. …They have not had someone like us in their corner."

Shutterstock: alphaspirit

Express Scripts has already begun to reach out to the uninsured market. The company announced a drug discount program aimed at the uninsured or underinsured in May called InsideRx. The program is offered in partnership with online drug savings resource GoodRx and eligible members can obtain discounts at participating pharmacies by presenting a discount card or mobile app.

Gill asked whether a potential collaboration with Amazon would be like "letting the fox into the hen house by giving them access to your great mail order operations."

COMPARISON TO WALMART $4 GENERICS PROGRAM

Wentworth downplayed the concern, pointing out the PBM survived what he described as a comparable situation 10 years ago when Walmart launched its $4 generics program. The program involved direct product sourcing by the retailer and was viewed as a threat to the traditional supply chain. *(Also see "Wal-Mart Slashes Generic Prices" Pink Sheet, 21 Sep, 2006.)*

"I remember back to the mid-2000s [when] there was a real thought that when Walmart launched a $4 generics list that it was the end of the PBM model as we know it," he said. "And of course what it was instead was another opportunity for PBMs to create competition and drive down costs and drive generic expansion for their client."

"People are always worried about foxes and hen houses; what I'd say is I think our hen house is pretty good," Wentworth quipped. Express Scripts has "been investing for 30 years to create an unparalleled capability to serve our [mail order] members and we continue to improve it both in terms of the cost of delivery and the service that's being provided," he maintained.

"As I think about the role that Amazon could play" as a prescription drug retailer, "to the extent they can do that in a competitive way that meets the clinical and service standards that the market continues to evolve, we'd love to create that competition by introducing them into the mix. So from my perspective, I see that as a net positive."

If they "choose to become a PBM, then we'd have a competitor on our hands and we'd have to deal with it," Wentworth added. "But again, our independent-focused model and the value we have shown clients I feel very confident will stand well against an entry in the PBM space, be it Amazon or anybody."

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

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Selected clinical trial developments for the week 20–26 October 2017

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
Phase III Results Published			
Melinta Therapeutics Inc.	*Baxdela* (delafloxacin)	skin and skin structure infections	PROCEED; *Journal of Antimicrobial Chemotherapy*, Oct. 5, 2017.
Alexion Pharmaceuticals Inc.	*Soliris* (eculizumab)	myasthenia gravis	REGAIN; *The Lancet Neurology*, Oct. 20, 2017.
Updated Phase III Results			
MedDay Pharmaceuticals	*Qizenday* (biotin, high-dose)	multiple sclerosis, progressive	Decreased whole brain and grey matter volumes.
Novartis AG	*Gilenya* (fingolimod)	multiple sclerosis	PARADIGMS; reduced relapses in children.
Novartis AG	siponimod	multiple sclerosis, secondary progressive	EXPAND; reduced MRI activity, slowed brain volume loss.
Trevena Inc.	*Olinvo* (olicerdine)	acute pain	APOLLO-1,2; reduced pain.
Shionogi Inc.	lusutrombopag	thrombocytopenia	L-Plus 2; met primary endpoint.
Boehringer Ingelheim GMBH	nintedanib	idiopathic pulmonary fibrosis	IMPULSIS-ON Ext.; durable long-term efficacy.
Dova Pharmaceuticals Inc.	avatrombopag	thrombocytopenia associated with chronic liver disease	ADAPT 1, 2; well tolerated and effective.
Phase III Interim/Top-line Results			
AbbVie Inc.	risankizumab	psoriasis	ultIMMa-1, -2, IMMvent; met all co-primary endpoints .
DBV Technologies SA	*Viaskin Peanut*	peanut allergy	PEPITES; narrowly missed primary endpoint, showed clinical promise.
Johnson & Johnson	*Symtuza* (darunavir, cobicistat, tenofovir alafenamide and emtricitabine)	HIV/AIDS	AMBER; effective as one tablet once-daily.
Vertex Pharmaceuticals Inc.	*Orkambi* (lumacaftor/ivacaftor)	cystic fibrosis, with 2 copies of F508del mutation	Met primary endpoint, well tolerated.
Vertex Pharmaceuticals Inc.	VX-661	cystic fibrosis	Plus ivacaftor, mixed results.
Amgen Inc.	*Kyprolis* (carfilzomib) once weekly with dexamethasone	multiple myeloma, relapsed and refractory	A.R.R.O.W.; better efficacy than twice weekly.
Evoke Pharma Inc.	*Gimoti* (metoclopramide) nasal	gastroparesis, diabetic	Similar systemic exposure to reference drug.
Phase III Initiated			
Horizon Pharma PLC	teprotumumab	Graves' ophthalmopathy	OPTIC; in patients with active thyroid eye disease.
United Therapeutics Corp.	*Aurora-GT*, cell therapy	pulmonary arterial hypertension	SAPPHIRE; transfected cells to rebuild lung tissue.
BeyondSpring Inc.	plinabulin	chemotherapy induced neutropenia	Taking place in China.
Tricida Inc.	TRC101	metabolic acidosis	In chronic kidney disease.
Phase III Announced			
Alkermes PLC	*Aristada* (aripiprazole lauroxil)	schizophrenia	As a two-monthly injection.

Source: Biomedtracker

BioGeneration Ventures Raises New Seed Fund

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The Naarden, Netherlands-based venture capital company, **BioGeneration Ventures** (BGV), has raised €82m at the final close of its third fund, BGV III, to provide seed investments to European biotech companies involved in developing therapeutics, medical devices and diagnostics, particularly those based in the Benelux countries – Belgium, the Netherlands and Luxembourg – and in Germany.

The fund is four times larger than previous funds raised by BGV (€17m in 2006 and €15m in 2012), and is now one of the largest funds ever raised for making seed investments in European biotech companies.

BGV originally planned to raise €50m, but there was strong demand from investors that included private, institutional and strategic investors, and corporate investors. The European Investment Fund (EIF) was a previously announced investor, and new investors included private equity firm Schroder Adveq and the investment firm MAN Pension Trust as well as **Bristol-Myers Squibb Co.** and **Johnson & Johnson Innovation - JJDC Inc**.

BGV's track record of achieving high returns for investors was instrumental in the size of the new fund. "It helped that we had significant exits from the two previous funds," BGV's managing partner Edward van Wezel told *Scrip*. The corporate investors that BGV III attracted – Bristol-Myers and J&J – have the same rights as other limited partners (LPs), but they like to be close to innovations that have the potential to enhance their R&D pipelines, van Wezel remarked.

The first two BGV funds made investments that turned out to be highly successful. These included the sale of **Dezima Pharma BV** to **Amgen Inc.** for up to $1.5bn.

The funds also benefited from a multibillion-dollar exit from **Acerta Pharma BV** when **AstraZeneca PLC** bought a majority stake in that company, which BGV believes is the largest private exit in Europe in the biotech sector to date.

But as well as previous good performances, van Wezel noted that corporate investors wanted to be aware of, and involved in, early-stage companies in Europe. "We think there is a lot of new, exciting and innovative science taking place in Europe that we can facilitate and build on to develop new innovative drugs for patients," Wezel commented, adding that "there's not a lot of players in this space."

BGV gets involved in setting up companies when it finds projects and innovative scientific breakthroughs that are mature enough to progress further. It also works with founding teams that come forward with an idea or project that needs financing. The firm has a close collaboration with another Dutch VC, **Forbion Capital Partners**, which is more focused on later-stage investments, and can take biotech companies to the next stage of financing.

Capital from BGV III is expected to be invested in about 15 companies during the next two to three years, and already has identified five seed-stage companies in which to invest. They include **Scenic Biotech**, a spinout from the Dutch Cancer Institute that focuses on new target discovery using novel technologies it has developed, van Wezel said. The fund also is investing in **Catalym**, a German academic group active in the immuno-oncology field, **Escalier Biosciences**, **Varmx** and **Mellon Medical**.

"We expect to focus 75% of our funding on therapeutics and 25% on medical devices and diagnostics, van Wezel said.

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APPOINTMENTS

Astellas Pharma Inc. has promoted ***Dr. Gary Thal*** to vice president, specialty, medical affairs, Americas, reporting to ***Dr. Shontelle Dodson***, senior vice president, medical affairs, Americas, effective Oct. 30. Before joining Astellas, Thal served as vice president, medical affairs research, at Vertex Pharmaceuticals, Inc. He also held leadership positions at Bristol-Myers Squibb Co., and DuPont Pharmaceuticals Co. Astellas also recently promoted ***Nate Crisel*** to vice president, real world informatics & analytics (RWI), reporting to Chikashi Takeda, chief financial officer, effective Oct. 1. Crisel joined Astellas in 2008, having previously served as an analytical chemist and pharmaceutical development project manager at Eli Lilly & Co.

MorphoSys AG has appointed ***Dr. Markus Enzelberger*** as chief scientific officer (CSO), as of Nov. 1. Enzelberger has been the company's interim CSO since April 15, and will succeed ***Dr. Marlies Sproll***, who has been on temporary leave from her CSO position for family reasons since then. Sproll will take on a new part-time role at MorphoSys as special adviser to the CEO, ***Dr. Simon Moroney***, as of Nov. 1. Enzelberger joined MorphoSys in 2002 and has served in various leadership positions within its R&D organization, including as senior vice president, discovery, alliances and technologies, since 2012.

AZTherapies Inc. a Boston, MA.-based privately held advanced clinical stage pharmaceutical company developing breakthrough treatments for Alzheimer's disease, ischemic stroke, and other neurological diseases, has appointed ***Dr. Karen Reeves*** as president and chief medical officer. Reeves has held multiple leadership positions at Pfizer Inc., most recently, as vice president, head global clinical submissions quality and innovation, worldwide research and development.

Sigilon Therapeutics, a biopharmaceutical company that discovers and develops immune-privileged living therapeutic implants, has appointed ***Eric Shaff*** to its board of directors. Shaff is executive vice president and chief financial officer of Seres Therapeutics Inc., and previously worked at Momenta Pharmaceuticals Inc. and Genzyme Corp.

Tenaya Therapeutics Inc., a privately held biotech startup focused on the discovery and development of novel therapeutics for the treatment of heart failure, has named ***Tim Hoey*** chief scientific officer. Before joining Tenaya, Hoey was senior vice president of cancer biology and co-chief scientific officer at OncoMed Pharmaceuticals Inc.


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