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Pharma And Intermediaries Split Money Spent On Drugs

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A new analysis, based on a review of public filings with the Securities & Exchange Commission, shows that drug manufacturers roughly split the revenues from the sale of pharmaceuticals with the other players in the drug distribution system, but keep a larger share of the profit.

The study, performed by the University of Southern California Leonard D. Schaeffer Center for Health Policy and Economics, is the latest attempt to try to clarify how US spending on prescription drugs flows through the complex drug distribution system.

"US spending on prescription drugs has been growing rapidly, prompting calls for

government intervention to slow the upward trend," the study authors said. "But any intervention should be predicated on a clear understanding of the economic forces that drive price increases, and the parties responsible for them."

Drug pricing and transparency have become hot button issues in the broader health care debate as politicians look for ways to lower spending. President Trump has turned attention to drug prices time and again, both on the campaign trail and since moving to the White House. But even with Congressional hearings, little progress is being made. (Also see "Biopharma Largely Avoids Partisan Bloodbath At US Pricing Hearing" *Scrip*, 13 Jun, 2017.)

The cost of drug spending also has been increasing, further drawing attention to the area. Prescription drugs sold in retail pharmacies accounted for almost \$325bn, or 10%, of total health care costs in 2015, up 9% from 2014, according to the study.

The industry's pricing tactics historically have been kept secret, with drug makers typically setting a wholesale list price and then negotiating rebates with payers to secure a strong formulary position.

But amidst the recent pricing pushback, industry appears to be reconsidering its approach to transparency as it tries to push some of the blame for high drug prices onto third parties like pharmacy benefit managers, pharmacies and distributors. **Sanofi**, for example, announced a pricing pledge in May and tried to quiet critics by pointing out that while US list prices across the company's portfolio grew 4% in 2016, average aggregate net prices decreased by 2.1%.

Net prices across the industry – including all discounts and rebates – rose 2.8% in 2015, according to the USC study.

The study suggests drug manufacturers generally do share most of the revenues from drug sales with third parties, but they hold onto a bigger share of the profit. More than \$1 in every \$5 in spending on prescription drugs goes towards profits of firms in the pharmaceutical distribution system.

"While the current analysis cannot say definitely whether any sectors make excessive profits, greater scrutiny of pricing policies of each sector and more competition throughout the distribution system is warranted," the authors said. Neeraj Sood, vice dean for research at the USC Sol Price School of Public Policy and director of research at the USC Schaeffer Center, led the study.

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from the editor

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Out of ASCO and into ADA: this week's issue includes special dispatches from San Diego where the American Diabetes Association's 77th Scientific Sessions recently concluded. Mandy Jackson reports on the gathering pace of evidence for the role of newer diabetes medicines in combating or protecting against cardiovascular conditions, kidney disease and obesity on top of their primary purpose of lowering glucose – see p 4. She also brings a closer analysis of the CANVAS data on cardiovascular outcomes for Janssen's SGLT2 inhibitor Invokana in the context of Lilly/Boehringer Ingelheim's prior EMPA-REG CV outcomes data for Jardiance and looking forward to AstraZeneca's ongoing DECLARE CV study for a third SGLT2 inhibitor, Farxiga, as well as eventual results for Merck & Co/Pfizer's investigational rival ertugliflozin. For additional *Scrip* coverage from ADA, check out our [website](#).

The dismantling of traditional siloes of disease and treatment that we are beginning to see in cancer, for example through the [approval of Keytruda](#) for indications based on biomarkers rather than tumor location last month, is clearly evident also in the metabolic/renal/cardiovascular space, as demonstrated by the data highlighted at ADA. Sten Stovall's interview with Ludovic Helfgott, head of AstraZeneca's combined cardiovascular, metabolic disease and renal business sheds light on how one company in the space is approaching the challenge and attempting to turn it into an opportunity. As well as exploring broader uses of its diabetes medicines, AstraZeneca is looking for evidence that its blood thinner Brilinta may have specific cardiovascular benefits for diabetic patients, for example. See p 8.

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Roche Looks To Real World Data And IT To Drive China Partnering

<http://bit.ly/2tk8LJ1>

Mark Noguchi, Global Head, Alliance and Asset Management at Roche, outlines to Scrip's Brian Yang the Swiss group's plans to tap into the emerging IT expertise and partnering opportunities in China.

ASCO 2017 Wrap-Up Podcast

<http://bit.ly/2sP3UCe>

Analysts from Informa Pharma Intelligence's Biomedtracker, Datamonitor Healthcare and Cyteline discuss their impressions following the 2017 annual meeting of the American Society of Clinical Oncology (ASCO), held in Chicago from June 2-6, 2017.

XBiotech Faces Uphill Task With Xilonix

<http://bit.ly/2tjy7GV>

Texas-based biotech XBiotech is going to find it tough to persuade clinicians and regulators about the usefulness of its human antibody Xilonix after it discontinued the second Phase III study of the human antibody, in US colorectal cancer patients.

Pharma Could Do Better With Data, Say IBM, McLaren

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

The great and good of the pharmaceutical industry have again been speaking about the big opportunities that big data provides, but senior executives from IBM Watson Health and Formula 1 giant McLaren believe the sector should be doing more.

pSivida On Cusp Of Uveitis Filings As EU Licensing Deal Nears

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

Phase III data from a second study support the three-year therapy Durasert in posterior uveitis, paving the way for EU and US filings.

Biopharma Largely Avoids Partisan Bloodbath At US Pricing Hearing

<http://bit.ly/2ttBJ9y>

Democrats spent most of their time complaining about Senate Republicans' closed-door process for developing healthcare legislation, leaving little time for the expert witnesses to weigh in on drug pricing.

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Considering The Value Of Cardiovascular Data And Real World Evidence In Diabetes

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Cardiovascular outcomes trial (CVOT) results for newer diabetes medicines from **Janssen Pharmaceutical Cos.** and **Novo Nordisk AS** that were presented during the recent American Diabetes Association (ADA) 77th Scientific Sessions in San Diego highlight the ongoing shift in treatment from lowering blood glucose levels alone to also managing weight, blood pressure and kidney disease.

CVOT trials – Janssen’s CANVAS for the SGLT2 inhibitor *Invokana* (canagliflozin) and Novo’s DEVOTE for the fast-acting basal insulin *Tresiba* (insulin degludec) – showed cardiovascular safety and the potential for CV or other benefits, which are increasingly valuable data for diabetes drug developers. Janssen, Novo and other market players, including **Boehringer Ingelheim GMBH**, **AstraZeneca PLC** and **Merck & Co. Inc.**, believe that they can use CVOT data and real world evidence to get prescribers to switch patients from well-known therapies and to convince payers to cover new medicines.

EMPA-REG PRECEDED CANVAS, DEVOTE

CANVAS and DEVOTE follow on the heels of EMPA-REG, the outcomes trial for **Eli Lilly & Co.’s** SGLT2 inhibitor *Jardiance* (empagliflozin), which was developed and is marketed in partnership with **Boehringer**. The EMPA-REG results were added to the US *Jardiance* label in December, making it the only drug approved with a claim to reduce the risk of cardiovascular death in patients with diabetes and CV disease.

Invokana showed cardiovascular benefits in CANVAS that were largely similar to Lilly and **Boehringer’s** *Jardiance* in EMPA-REG, but the Janssen drug also showed an increased risk of amputation, raising questions about class effects for SGLT2 inhibitors. Novo’s *Tresiba* was non-inferior to *Lantus* (insulin glargine) in terms of cardiovascular outcomes in DEVOTE, but it showed a significant reduction in severe hypoglycemia versus the **Sanofi**-owned standard of care.

DEVOTE was not the first time that *Tresiba* showed superiority to *Lantus* in regard to hypoglycemia. (Also see “*Tresiba Vs. Lantus: Novo Nordisk Scores A Win In Second Head-To-Head*” *Pink Sheet*, 24 Feb, 2016.) Novo has been talking to doctors about the lower rate of low blood sugar events based on the company’s SWITCH clinical trial program for more than a year, but DEVOTE’s hypoglycemia benefit and cardiovascular safety findings relative to *Lantus* should help make the case for *Tresiba*, **Novo Nordisk** US Chief Medical Officer **Todd Hobbs** said in an interview at the ADA meeting.

“Even though *Tresiba* was approved, there still were questions on cardiovascular safety,” **Hobbs** said. The US FDA rejected Novo’s original application for the long-acting insulin in 2013 due to a potential cardiovascular safety issue and required a CVOT versus *Lantus* to support approval. Now, with the DEVOTE data in hand, the company is seeking approvals in the US and EU to add the study’s results to *Tresiba*’s label. However, **Hobbs** said he doesn’t expect a big immediate impact on sales.

“I’d expect to see a reserved uptake,” he noted. “Because of payer issues, reimbursement drives basal insulin sales.”

Biomedtracker noted in a June 12 analysis of the DEVOTE results that patients usually have to fail treatment with the insulin on their health plan’s formulary – often *Lantus* or biosimilar insulin glargine – before physicians are able to prescribe a longer-acting insulin.

“This has frustrated many physicians who feel it is ridiculous to wait to prescribe a superior product until after the patient has had an adverse event,” the **Biomedtracker** report said. “The sentiment is compounded by the difficulty physicians often face in regaining glycemic control in patients who have experienced a hypoglycemic event. However, insurers must be convinced of the benefit *Tresiba* provides, and give it preferential formulary placement, before physicians will be able to significantly increase their use of *Tresiba* as the first line insulin treatment.”

However, some physicians told **Biomedtracker** analysts during the ADA meeting that longer acting insulins only offer a modest benefit relative to their higher prices, even though some patients prefer *Tresiba* for its effect on “the dawn phenomenon (an abnormal early-morning increase in blood glucose).”

US payers have been particularly tough on diabetes drug prices, especially when it comes to insulin, which **Novo** has discussed frankly with its investors for some time. (Also see “*Novo Nordisk Says Global Payer Pressure Limits Price Rises*” *Pink Sheet*, 3 Feb, 2016.) DEVOTE, with its declines in severe hypoglycemia, could be compelling to payers, which can analyze *Tresiba*’s cost versus the expense involved in acute treatment of diabetic patients who experience extremely low blood glucose levels, **Hobbs** acknowledged. However, he said a big increase in insulin product sales may not come until pharma, payers and other stakeholders find solutions to managing the medicines’ high and rising costs.

FRESH MOVES ON INSULIN COSTS

“I think it’s headed for more of a resolution than we have now,” **Hobbs** said, adding that pharma companies, doctors, payers, patients and policy makers may come together soon to work on solutions to the insulin cost problem. Such a meeting would be in pharma’s best interests due to ongoing lawsuits and other efforts by government agencies and payers to address high insulin costs.

“As a CMO and a patient with diabetes, it hurts and bothers me – and us – when patients can’t get their medicines,” **Hobbs** said. He noted that **Novo** has a patient assistance programs to help people with high-deductible health plans afford out-of-pocket insulin expenses and the company has an agreement with **CVS Health Corp.** to help the payer’s customers buy insulin for no more than \$25 per refill.

Hobbs said new competition among insulin makers is not likely to significantly bring costs down, since pharma companies compete by offering payers greater discounts and rebates rather than lowering wholesale prices, but he noted that strong safety data could help doctors and payers determine which insulins to prescribe and reimburse over other products with less health care value.

Lilly’s and **Boehringer’s** experience with *Jardiance* after EMPA-REG and the FDA approval of a cardiovascular claim on the

SGLT2 inhibitor's label seems to confirm Hobbs's suspicion that increased uptake of Tresiba will not be quick or dramatic based on the DEVOTE results. Lilly said sales of Jardiance jumped 94% year-over-year to \$74m in the first quarter of 2017, but the number fell short of analyst consensus of \$102m based on EMPA-REG and the drug's updated label.

"A lot of physicians have adjusted their thinking on including Jardiance" in diabetes treatment plans, Thomas Seck, vice president of clinical development and medical affairs in Boehringer's primary care business, said in an interview. He also noted, however, that doctors, payers and patients still are being educated about the cardiovascular benefits identified in EMPA-REG.

Seck said Boehringer and its partner are having "a good discussion" with payers about incorporating EMPA-REG into their Jardiance reimbursement decisions. Payers are open to looking at the outcomes data, he noted, because cardiovascular complications for diabetic patients cost the US health care system \$20bn annually.

"As an endocrinologist coming to ADA, it's nice to see how much noise there is around data in cardiovascular disease and diabetes," Seck said. "It's important for this landmark data to inform this field."

AstraZeneca will be the third company to report CVOT results for an SGLT2 inhibitor when it releases results from the DECLARE trial for *Farxiga* (dapagliflozin) in the next year or two. However, the UK-based big pharma has tried to get ahead of the game by sponsoring an observational study called CVD-REAL, which examined real world evidence across several countries and found that the three approved SGLT2 inhibitors – Invokana, Jardiance and Farxiga – reduced heart failure and all-cause mortality.

In a new CVD-REAL analysis presented at the ADA meeting, among 30,000 type 2 diabetes patients in two countries who were treated with Farxiga there were significantly lower rates of hospitalizations for kidney disease (-62%), hospitalizations for heart failure (-37%) and death from any cause (-27%) versus patients treated with DPP-4 inhibitors.

Also, among 100,000 type 2 diabetes patients in three countries, rates of cardiovascular deaths and hospitalizations for heart failure were 47% and 30% lower, respectively, for patients who were new to SGLT2 inhibitors versus those who were new to other kinds of drugs.

"CVD-REAL is an interesting piece of observational data, but to prove efficacy you need to look at randomized controlled trial data," Boehringer's Seck said.

'THE GIFT THAT KEEPS ON GIVING'

For AstraZeneca, on the other hand, CVD-REAL is "the gift that keeps on giving," according to Mike Crichton, vice president of cardiovascular and metabolic diseases, and James McDermott, the company's vice president of US medical affairs, metabolism, because ongoing analyses continue to show safety and efficacy for SGLT2 inhibitors.

"We have heard a lot at ADA about 'tight control' and early intervention," Crichton said. "There's been a lot of talk about moving SGLT2 earlier in treatment."

The results of CVD-REAL "gives us reason to believe" that the Farxiga outcomes study DECLARE will be positive, McDermott added.

AstraZeneca reported early results at ADA from a different large study involving Farxiga – the Phase III DURATION-8 trial assessing Farxiga and the company's GLP-1 inhibitor *Bydureon* (exenatide). One-year results from the ongoing three-year study showed signifi-

cant blood glucose reductions for the combination therapy as well as weight loss and reduced blood pressure out to one year of treatment versus Farxiga or Bydureon alone.

"We did the trial, because we were getting a lot of questions from doctors about the combination. We expected an additive effect," McDermott said.

Just before the ADA meeting, AstraZeneca reported results from its large 14,000-patient EXSCEL cardiovascular outcomes trial for Bydureon, which showed the once-weekly injection met the primary endpoint of non-inferiority to placebo, but was not superior to the comparator arm. The company viewed the results as confirming Bydureon's safety when administered on top of other standard-of-care medicines.

"Bydureon continues to evolve the science, which is why we'll compete well in a competitive class," Crichton said.

He noted that doctors are very interested in drugs that lower blood glucose and deliver on weight loss and cardiovascular safety, and said, "This is how we'll differentiate ourselves." For Farxiga, CVD-REAL seems to be working in the SGLT2 inhibitor's favor ahead of the DECLARE results.

"Recent [market] share data in the past few weeks would indicate that doctors are very satisfied with Farxiga," Crichton said.

HELPING DOCTORS, PAYERS FIND DATA

Merck & Co., which reported results for what could be the fourth SGLT2 inhibitor approved in the US during the ADA conference, has increased its focus on real world evidence in recent years. (*Also see "Merck & Co, Pfizer Ertugliflozin Combo Data Beef Up Profile" Scrip, 12 Jun, 2017.*)

Scrip spoke with Swapnil Rajpathak, executive director of the Center for Observational and Real World Evidence at Merck, about results the company presented at the ADA meeting from an observational study assessing rates of hypoglycemia in patients treated between 2007 and 2013 with sulfonylureas or DPP-4 inhibitors, the latter of which includes Merck's blockbuster *Januvia* (sitagliptin). The study relied on data from the MarketScan medical claims database.

"Patients on DPP-4s had half the hypoglycemia burden of those on sulfonylureas," Rajpathak said.

Merck estimated that, based on one year of treatment with either class of drug during the seven-year period studied, DPP-4 inhibitors saved the US health care system \$750m in hypoglycemia-related expenses, including \$200m in 2013 alone – a cost savings data point that could be important to payers.

Rajpathak noted that Merck has been focused on outcomes-based research for at least 25 years, but the company's Center for Observational and Real World Evidence was created three and a half years ago as the availability of real world-data improved and as more people became skilled in analyzing those numbers.

"For our customers, we fill the data gap that they don't get from clinical trials," Rajpathak said, referring to doctors and payers – and the occasional patient group or policy maker.

"Requests are coming in more now than in the previous decades," he said. "People are aware of other products, but they're asking questions specific to our products or we hear at conferences and other venues that they're looking for this other information that's not available."

Rajpathak noted that "clinical trials take a long time, but a well-controlled and run database study takes less time. They can help complement our randomized controlled trials." ▶

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CANVAS Trial Results: Better For Janssen, Lilly Or the SGLT2 Class?

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Johnson & Johnson subsidiary **Janssen Pharmaceutical Cos.** reported a 14% reduction in the risk of major cardiovascular events for *Invokana* (canagliflozin) in the CANVAS outcomes trials, which was the same MACE reduction observed in the EMPA-REG trial for competing SGLT2 inhibitor *Jardiance* (empagliflozin), but it may be too early to declare the drugs' cardiovascular benefits – and *Invokana's* amputation risk – a class effect.

Investigators who talked about the CANVAS results on June 12 at the American Diabetes Association (ADA) 77th Scientific Sessions in San Diego had a generally positive view of the results, but stopped short of calling the MACE risk reductions seen in two sets of cardiovascular outcomes trials (CVOTs) for SGLT2 inhibitors a class effect.

CVOT and other safety results from at least one more SGLT2 inhibitor may be needed to definitively assess class-wide benefits and risks, which are expected within the next year or two from **AstraZeneca PLC's** *Farxiga* (dapagliflozin).

As for the benefit/risk of its own drug, Janssen's Global Therapeutic Head, Cardiovascular and Metabolism, James List said in an interview that based on CANVAS, "We feel like we have a good understanding of canagliflozin through this program."

CANVAS POSITIVE, BUT FOR WHICH DRUG?

"We have a clear outcome in favor of canagliflozin for MACE," said CANVAS Co-Chair David Matthews, professor of diabetes medicine at the University of Oxford, UK, during an ADA symposium dedicated to the *Invokana* CVOT results. Looking at both CANVAS and **Eli Lilly & Co.'s** and **Boehringer Ingelheim GMBH's** EMPA-REG outcomes trial for *Jardiance*, Matthews said, "What we have here is concordant results."

Biomedtracker analyst Peter Chang noted in a June 12 review of the CANVAS results that there still are many unanswered questions related to both *Invokana* and the SGLT2 class.

The CVOT program "was positive in that the trial showed a statistically significant, albeit modest, improvement in the primary MACE (major adverse cardiovascular events) endpoint, along with signs of benefits on heart failure hospitalization and renal outcomes. However, there are questions about the implications of a much smaller benefit on CV death compared to what was seen in *Jardiance's* EMPA-REG, as well as a new safety finding of an increase in amputations," Chang wrote.

Indeed, per the table below, CANVAS and EMPA-REG results were similar across multiple measures, but differed on a few key endpoints, including the reduction in cardiovascular deaths – the EMPA-REG data point that resulted in a new label for *Jardiance*. (Also see "*BI/Lilly's Jardiance Is First Diabetes Drug With CV Benefit Claim*" *Scrip*, 2 Dec, 2016.)

"We see the positive CANVAS study as good news for Lilly, as the study appears to provide support for the SGLT2 class in reducing cardiovascular risk, and Lilly's label at the margin may be better," UBS analyst Marc Goodman wrote in a June 12 report.

Goodman noted that it's unclear how the FDA might view Janssen's request to add a cardiovascular benefit finding to *Invokana's* label without a statistically significant impact on deaths in CANVAS. List didn't shed much light on Janssen's regulatory strategy either, noting only that the J&J subsidiary will work with the FDA to update the label.

Leerink analyst Seamus Fernandez said in a June 12 report from ADA that CANVAS should benefit the SGLT2 class going forward, but the amputation risk associated

with *Invokana* "suggests to us that *Jardiance* likely will continue to be the fastest-growing product in the class due to its differentiated label for reducing risk of CV death and the drug's excellent safety profile to date."

TRIALS HAD SIMILAR RESULTS, DIFFERENT POPULATIONS

CANVAS principal investigator Bruce Neal was less inclined to compare data across the two trials, but told *Scrip* that the different effects that *Invokana* and *Jardiance* had on CV deaths likely had to do with the differences in the trials' populations. Neal is a professor of medicine at the University of New South Wales in Sydney, Australia and senior director of The George Institute for Global Health.

The CANVAS program included two CVOT trials – CANVAS, which enrolled 4,330 patients and was completed in support of US FDA approval for *Invokana*, and CANVAS-R, which enrolled 5,812 patients to meet the agency's post-marketing CVOT requirements for new diabetes medicines. The CANVAS program, which followed patients for up to six years, included diabetic patients with prior cardiovascular events and diabetics at risk for a CV event, enrolling the two types of patients at about a 2:1 ratio across both studies. EMPA-REG only enrolled patients with diabetes with a prior CV event.

Neal considered CANVAS to be "overall very positive" for *Invokana* and "absolutely aligned with what we thought we would get." However, he noted that CANVAS's success will be measured by how prescribers and payers respond.

Hazard Ratios For CANVAS And EMPA-REG In Key Endpoints

	CANVAS	EMPA-REG
MACE (primary endpoint)	0.86	0.86
Cardiovascular death	0.87	0.62
Nonfatal myocardial infarction	0.85	0.67
Nonfatal stroke	0.90	1.24
Hospitalization for heart failure	0.67	0.65
All cause death	0.87	0.68

Sources: UBS, ADA presentation slides

"I suspect we'll see much greater use of SGLT2 inhibitors," Neal said. "We'll see them move up earlier in treatment."

Treatment of diabetes during the past few decades has shifted away from merely lowering blood glucose levels to also trying to prevent deaths caused by cardiovascular events, which is what kills many diabetic patients. "Diabetologists want to lower A1c, but ultimately they want to prevent these events from happening," Neal said.

The primary endpoint for the CANVAS program was a composite of CV mortality, nonfatal myocardial infarction (MI) or nonfatal stroke, which was reduced by 14% versus placebo, a result that was statistically significant in terms of non-inferiority ($p < 0.0001$), but not in terms of superiority ($p = 0.0158$).

The risk of nonfatal MI was cut by 15% versus placebo, while the risk of CV death was reduced by 13%, the risk of nonfatal stroke was lowered by 10% and the risk of hospitalizations for heart failure fell by 33%. There was a slight increase in fractures, but the amputation risk generated the most discussion given the near doubling of risk versus placebo (HR: 1.97).

AMPUTATION RISK PAINTS A MUDDY PICTURE

Put another way, Neal noted during the June 12 press program at the ADA conference that out of 1,000 patients enrolled in CANVAS, 15 more needed an amputation than in the placebo group. About 10 of those amputations involved the toes or forefoot and five had to be done above the ankle.

"The increased rate of amputation is a new finding for which the mechanism is unknown, and care is warranted in the use of canagliflozin in patients at risk for amputation," Neal and other members of the CANVAS Program Collaborative Group wrote in a *New England Journal of Medicine* article published on June 12, concurrently with the data presentation at ADA.

CANVAS presentations at the conference suggested that Invokana's cardiovascular benefits outweighed the amputation risk, since 23 fewer patients per 1,000 who were treated with the Janssen drug experienced MACE than in the placebo group, 17 fewer were hospitalized due to heart failure and 16 fewer experienced renal complications.

The risk of renal composite outcomes – including renal death, renal replace-

ment therapy and a 40% reduced estimated glomerular filtration rate (eGFR) – was cut by 40%. Janssen is conducting a separate 4,200-patient renal outcomes trial known as CREDENCE to assess Invokana's effects on cardiovascular and renal outcomes in diabetic patients with chronic kidney disease.

"To be able to have definitive outcomes data in chronic kidney disease will be very important in understanding the best use of these medicines in patients," List said.

Perhaps following Janssen's lead, Boehringer and Lilly revealed on June 12 that they also plan to run a clinical trial in patients with CKD. However, the trial will be different from CREDENCE, because it will enroll CKD patients with and without diabetes. In EMPA-REG, Jardiance reduced the risk of developing or worsening kidney disease by 39% versus placebo.

As for the risk of amputation, Janssen communicated the increased incidence of amputation in CANVAS to the FDA a year ago and sent out "Dear Doctor" letters to inform prescribers. The FDA also informed doctors about the amputation risk associated with Invokana, but the European Medicines Agency (EMA) went a step further and said it is not yet possible to establish whether it is a risk for all SGLT2 inhibitors, since AstraZeneca's DECLARE outcomes trial for Farxiga is ongoing. (Also see "Invokana Adds Warnings On Amputation Risk, But Will It Give Jardiance An Edge?" *Pink Sheet*, 16 May, 2017.)

"Endocrinologists we talked to at the [ADA] meeting were aware of the warning, but most were only slightly concerned, and not enough to reduce their usage of Invokana other than in patients at high risk due to peripheral vascular disease," Biomedtracker's Chang wrote. "A couple, however, favored other SGLT2 inhibitors that did not have the issue."

Both List and Neal acknowledged the amputation risk, noting that Invokana's mechanism pertaining to that risk is unknown, but they also said the risk remains low for diabetic patients that aren't already at risk of amputation due to a prior amputation or peripheral vascular disease.

"Patients with a low risk of amputation have an increased net risk, but it's still a low risk," List said. Neal indicated that the CANVAS data could represent a class

effect for SGLT2 inhibitors that doctors should consider when prescribing Invokana and other drugs. "This should give them pause for this drug and potentially for this class," he said in an interview.

The balance of preventing a heart attack or stroke with an SGLT2 inhibitor versus the risk of causing an amputation is similar to the consideration cardiologists must make when deciding whether to prescribe blood thinners, which can cause severe bleeding events, to prevent blood clots and strokes, Neal noted.

"Our conversations with experts at ADA suggest many feel this may in fact be a class effect, potentially related to volume depletion in patients who have a history of peripheral artery disease or prior amputation," Credit Suisse analyst Vamil Divan said in a June 13 report. "The ongoing DECLARE study for AstraZeneca's Farxiga will provide additional insights into this issue since amputations are being captured systematically in that trial. While the overall cardiovascular and kidney benefits from CANVAS seem to outweigh the amputation risk, the differences in the product labels on this topic will likely lead to a significant commercial advantage that Lilly should be able to leverage going forward."

Chang noted that a poster presenter on the DECLARE trial design said at the ADA meeting that the study's last MACE event is expected to occur around May or June of 2018 and AstraZeneca has said that it expects to report the CVOT results for Farxiga in 2019. However, the DECLARE trial design presenter "noted that, once 75% of events accrue, which should be soon, the data monitoring committee could also stop the trial early for overwhelming efficacy, which could be on CV death. However, he felt they may not, even if there was a benefit on CV death similar to Jardiance."

CVOT results for a fourth SGLT2 inhibitor – ertugliflozin from **Merck & Co. Inc.** and **Pfizer Inc.** – are expected long after the DECLARE results. The partners, who anticipate an FDA approval decision for their drug later this year, reported additional positive trial results for ertugliflozin as a monotherapy and as part of combination therapy at the ADA meeting. (Also see "Merck & Co, Pfizer Ertugliflozin Combo Data Beef Up Profile" *Scrip*, 12 Jun, 2017.) ▶

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'Synergy Search' Lies Behind AZ's Combined CV, Diabetes and Renal Ops

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AstraZeneca CVMD Head Ludovic Helfgott

The former head of AstraZeneca PLC's Brilinta franchise says his appointment last January as head of the pharma's combined cardiovascular, metabolic diseases and renal franchises reflects its hunt for "synergies" in the three therapeutic areas.

MISSION STATEMENT

Ludovic Helfgott told *Scrip* his mission now "is to bring these three worlds together to talk and discover common underlying mechanisms. I am also putting all the functions that are responsible for these areas in our pipeline together – the early research in big molecules - our biologics, the early research in the small molecules - the chemical entities, along with the product development teams and the commercial teams, so they're all working together."

Helfgott had previously headed solely the franchise behind AstraZeneca's blood thinner *Brilinta* (ticagrelor). His appointment in January as CVMD head has also put him in charge of efforts behind its diabetes drugs *Farxiga* (dapagliflozin), *Bydureon* (exenatide extended-release) and DPP-4 inhibitor *Onglyza* (saxagliptin) as well as therapies for renal impairment - and a pipeline of early-stage compound assets.

TRIOLOGY OF THERAPEUTIC AREAS

He says the amalgamation's logic reflects interconnections between the three therapy areas.

"What we have now is a single body. The CVMD universe leadership team is compiling and combining early science, development and commercial so that one can integrate – from end to end – our strategy and ensure we maximize the assets and the trials and the studies and the mechanisms between the various assets and products. This will ensure people are communicating on a permanent basis, comparing experiences and understanding where something works, and where it doesn't," Helfgott said in an interview.

All these underlying mechanisms between diabetes, cardiovascular and renal are quite new

The three therapeutic areas of cardiovascular, renal impairment and metabolic diseases are key drivers in the UK pharma's quest to return to growth in this year after the loss this year of patent protection for statin *Crestor* (rosuvastatin) in the US – a challenge that follows the patent expiry in 2015 of proton-pump inhibitor *Nexium* (esomeprazole).

His appointment to oversee the aggregated group coincides with the demonstration of reduced heart failure and death and other cardiovascular benefits with major classes of diabetes drugs.

It also reflects increased urgency to grow Brilinta's commercial prospects, after the sales of the therapy fell below the company's previous expectations.

"What I'm trying to do with my team across the US, the UK and in Sweden is to align them on the strategy of trying to meet this huge unmet need represented here. But every additional step is more dif-

ficult," Helfgott added. "All these underlying mechanisms between diabetes, cardiovascular and renal are quite new. I'm trying to take the great assets that AstraZeneca has in our pipeline and align them to the objective of reducing cardiovascular risk through these three areas. Making sure all my team are talking together, making sure the compounds that exist in the pipeline are tested in other settings and ensure that we are really going deep into science to understand what's happening in each of the areas and the connections between them."

Towards that end his researchers are now testing compounds, or combinations of compounds, across these interconnected diseases.

For example, dapagliflozin is being explored for efficacy and safety in both heart failure and chronic kidney disease in patients with, and patients without type 2 diabetes. Brilinta (ticagrelor) - already licensed for acute coronary syndrome and post-myocardial infarction – is also being explored additionally in patients with type 2 diabetes who also at high risk of cardiovascular disease. And research is also being conducted around the potential regeneration of cardiac cells.

BUT OBESITY MUST WAIT

While acknowledging the interrelations between type 2 diabetes and obesity, he said AstraZeneca would not commit just yet to that therapy area on a commercial scale.

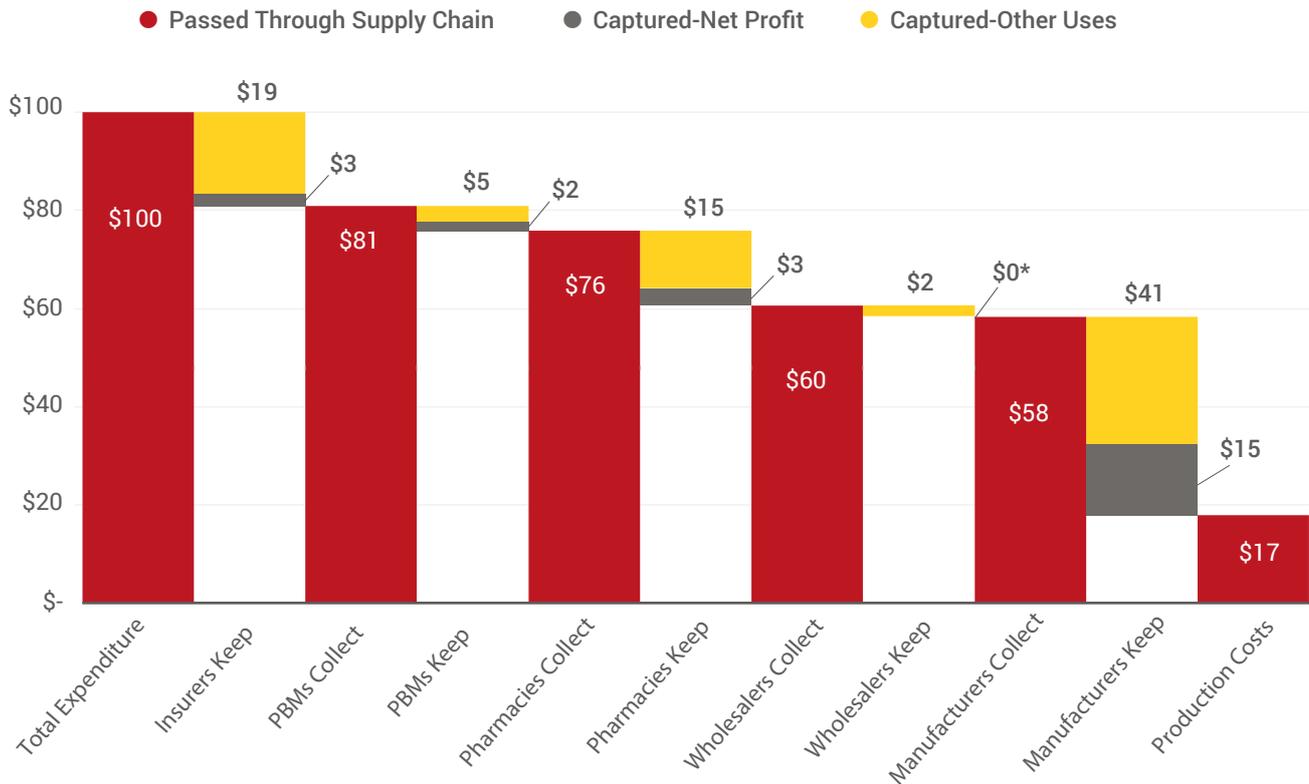
That contrasts with the recent commitment by Danish rival **Novo Nordisk AS** to view obesity as a disease and to commercially develop therapies for the condition.

"From a scientific perspective, of course it's very interesting. We are extremely interested in the science behind obesity and we are looking at what would be the impact of several of our compounds – either in-licensed or in our pipeline – in obesity; these diseases are connected. We are trying to see whether it's worth pursuing. But we're at a very early stage. The hurdles are extremely high for the obesity population." ▶

Published online 14 June 2017

CONTINUED FROM COVER

Flow of \$100 Across Various Channels - Overall



Source: USC Schaeffer

*Wholesaler net profit is \$0.32.

The study evaluated the flow of funds through the distribution system by developing a conceptual framework of the participants and their role in the system and then using data from financial statements and regulatory filings to estimate the average gross and net profit margins of companies along the distribution system. The study looked at financials from publicly traded companies across the different players in the system, including 21 drug companies.

The team applied the estimates to calculate the proportion of funds retained at each step in the process and then used the proportions to illustrate a scenario to show how \$100 in retail spending would be allocated across the system.

In that process, gross/net margins averaged 71%/26% for manufacturers, 22%/3% for insurers, 20%/4% for pharmacies, 6%/2% for pharmacy benefit man-

Drug manufacturers generally do share most of the revenues from drug sales with third parties, but they hold onto a bigger share of the profit.

agers and 4%/0.5% for wholesalers. These margins imply that for every \$100 spent at retail pharmacies, about \$17 compensates for direct production costs, while \$41 accrues to the manufacturer and \$41 accrues to the other third parties. Manufacturers keep \$15 in net profit, while the wholesalers, pharmacies, PBMs and insur-

ers retain \$8 split among them. The hypothetical expenditure applies to spending under private insurance.

Allocations differ depending on whether the drug is generic or branded, with branded drug manufacturers and intermediaries having higher gross profit margins and generic manufacturers and intermediaries having lower gross margins.

The Pharmaceutical Research and Manufacturers of America recently commissioned a report from Berkeley Research Group to similarly evaluate how drug spending is distributed across the supply chain. The study concluded that brand manufacturers realized \$219bn of the \$349bn in total initial gross expenditures for brand medicines, or 63% of the gross amount. (Also see "Drug Pricing: PhRMA Report Aims To Shift Focus To Supply Chain" Scrip, 19 Jan, 2017.)

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LET'S GET SOCIAL

@PharmaScrip

Google Joins Novartis Backing Medicxi's New \$300m Late-Stage Fund

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Spotting what it sees as a clear gap in European life sciences, **Medicxi** has raised \$300m to establish Medicxi Growth 1 (MG1), which primarily will focus on growth stage companies, with **Novartis AG**, Alphabet's **Verily Life Sciences LLC** and the European Investment Fund as cornerstone investors.

Medicxi, the European venture capital firm created by the former **Index Ventures** life sciences team, will take advantage of the dearth of sophisticated specialist investors willing to back European companies that have achieved proof of concept for their assets. (Also see "INTERVIEW: Why Medicxi Ventures Spun Itself Out Of Index" *Scrip*, 2 Feb, 2016.) That lack of financing in Europe is forcing life science firms to either be acquired by pharma companies or move to the US to tap into its deep pools of capital.

"When you count the number of Phase II companies in Europe and calculate how much will be needed to take them to the next stage, it will come to billions of dollars. This \$300m fund is just a first step for the most promising companies where it does not make sense to sell to pharma too early," Francesco de Rubertis, Medicxi co-founder and partner, told *Scrip*.

While still strongly believing that pharma companies are the best place to develop Phase II compounds, de Rubertis does believe there are exceptions. "These depend on the company's strategy and willingness of the management team. In such cases, we will tell the biotech that it does not have to do an early compromised deal with pharma nor move to the US," he added.

This is a message that has clearly resonated with MG1's cornerstone investors. The European Investment Fund wants to nurture high growth, high tech European businesses. Novartis is keen to keep close tabs on any promising new assets emerging from biotechs. Verily Life Sciences (formerly Google Life Sciences) sees its participation as a route to increasing its exposure in the European life sciences market.

Novartis expressed its interest in the growth fund during 2016. "In conversations

with Novartis executives it became clear that, while they acknowledged that there are more companies with Phase II assets, they were concerned that they were sometimes too immature and decisions to invest were probably being made too early. They said they would rather wait a couple more years before buying them and we started thinking that we could have a business model here," de Rubertis noted.

For Novartis, participating in the fund gets it close to interesting molecules and their evolution through development. "They will get proximity, better knowledge, dynamic diligence while establishing connections with entrepreneurs ahead of them becoming super-hot companies," he added.

Investing in the fund does not give Novartis any preferential rights over any of the assets in the MG1 portfolio. The company will have two of its top research executives – Vas Narasimhan, global head of drug development and chief medical officer, and Evan Beckman, global head of translational medicine – on the fund's scientific advisory board.

CONNECTING WITH GOOGLE

Google's interest in the life sciences space is not a new one. Through various routes, the company has been building a presence, including in the past three years through 17 transactions completed by the GV (formerly Google Ventures) investment arm.

Significantly, Verily, the life sciences arm of Google's parent Alphabet, has already established partnerships with **GlaxoSmithKline PLC** on miniaturized electronic devices for peripheral nerve stimulation, with **Johnson & Johnson** on surgical robotics, Novartis for glucose-checking contact lenses and **Sanofi** on devices for type 2 diabetes management.

Recalling how the company reached out to him at the end of 2016, de Rubertis does not think it coincidental that three of the pharma companies that Verily has deals with are also investment partners of Medicxi. GSK and J&J are limited partners of Medicxi's \$200m early-stage, asset-centric fund Medicxi Ventures 1 (MV1). Neither company is or will be an

investor in MG1, but there is the possibility that Medicxi might welcome an additional pharma investor as a limited partner.

Verily is looking to get more exposure to European biotech. "They want to penetrate the European biotech network, support entrepreneurs, and believe that the most efficient way to do that is through a fund like ours," de Rubertis noted.

Verily will also be nominating two of its executives to the scientific advisory board. The remaining five places on the SAB will be filled by Medicxi nominees.

To qualify for investment, companies will need to have at least one Phase IIb asset. "We will invest in companies not because we think the management team is great, or that it has a nice vision for the business, or that the pipeline looks promising and there is an attractive platform. We will invest in a company if we believe it has an asset that has a good chance of being a differentiated medicine," de Rubertis said.

EUROPEAN FOCUS

While acknowledging that such companies will more than likely have additional molecules or maybe a platform, he noted that the key driver for investment will be a specific asset although the fund will be investing in the whole company. The fund anticipates splitting its spending 80:20 between Europe and the US, and 80:20 between private and public opportunities.

The ideal investment would be a private European company with a late-stage Phase IIb asset, but MG1 will not be allowed to invest in pre-existing Medicxi portfolio companies. "This fund has been created because there is a market need, not a Medicxi need," de Rubertis acknowledged.

"We would envisage leading rounds of \$100m, putting in \$30m ourselves and raising the other \$70m from a syndicate. We will have agreed the use of proceeds with the management team up front, fully powering the key assets past the milestones," he explained. ▶

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Will Epoetin Biosimilar Serve As Non-Medical Switching Case Study?

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The US launch of **Hospira Inc.**'s epoetin biosimilar, assuming FDA approval, could become an early example of how so-called non-medical switching may manifest on a large scale in the marketplace.

Biosimilars have never been thought to have the same power over price as small molecule generics. But given the wide use of epoetin products and demand for a cheaper alternative, more patients and providers may be interested in moving from the brand to the biosimilar than in the past.

The fact that most dialysis patients are treated at centers run by a few providers may allow for rapid adoption.

Hospira, which is part of **Pfizer Inc.**, is seeking approval of its proposed biosimilar to **Amgen Inc.**'s *Epogen/Procrit* (epoetin alfa) and has a June user fee goal date. It would be the first Epogen biosimilar approved in the US.

The FDA's Oncologic Drugs Advisory Committee recently recommended approval for all four approved indications. But committee member Julia Lewis, a nephrologist and professor at the Vanderbilt University School of Medicine, suggested that the product could be launched in dialysis patients "massively, all at once, in these large dialysis organizations."

Lewis' comment was out of concern for adverse event detection. However, it also raises questions about how uptake of this product could be different from other biosimilars because of the distribution model.

It will be an interesting case study to see how the care setting may affect uptake of a biosimilar over the brand product.

Gillian Woollett, Avalere Health senior VP, said in an interview with *Scrip* that attention also will fall on "the decision maker for the product chosen as well as the incentives surrounding that decision."

Hospitals may have a contract in place to purchase an entire portfolio of products from the brand biologic maker and receive a more lucrative discount than what the biosimilar could offer.

Johnson & Johnson has previously stated its broad portfolio offered an opportunity to leverage contracts and defend against biosimilar competition.

A dialysis center also may be interested in the savings that could come with buying the biosimilar at a discount over Epogen and may be more willing to move patients off the brand product.

That change may not occur should Hospira try to launch the product immediately after approval. Amgen is reportedly in the midst of a multi-year deal to supply Epogen and its *Aranesp* (darbepoetin alfa), a similar ESA that requires less frequent dosing, to **DaVita HealthCare Partners Inc.**, one of the largest dialysis clinic networks in the US.

Amgen said in an April SEC filing that it extended the contract with DaVita by four years. It will now run until January 2023.

Opponents have coined the term "non-medical switching" to describe moving a patient from the brand biologic to the biosimilar for a non-therapeutic reason. Several complained about the practice during the ODAC meeting on the epoetin biosimilar, say-

ing that the change could occur even though the products are not deemed interchangeable.

Larry LaMotte, VP of public policy for the Immune Deficiency Foundation, who spoke on behalf of the group Patients for Biologics Safety and Access, said FDA should discourage the practice.

"Payers are moving through use of formularies and taking reference products off their formularies and instead putting biosimilars, forcing non-medical switching of patients who are stable," he told the advisory committee. "This is unconscionable and it goes against the law. We need to protect stabilized patients from non-medical switching and we call on the FDA in its guidance to develop policies related to that to discourage that kind of effort."

The National Kidney Foundation also told *Scrip* that "the discretion of clinicians and patients to approve the substitution of medications should be preserved."

In addition, payers are getting the question, particularly as it relates to the oncology setting.

CVS Health Corp. decided to place **Sandoz Inc.**'s *Zarxio* (filgrastim-sndz) on its formulary at the expense of the reference product, Amgen's *Neupogen* (filgrastim). **UnitedHealthCare** also cut **Sanofi's** *Lantus* (insulin glargine) product from its formulary and gave **Eli Lilly & Co.**'s unofficial biosimilar *Basaglar* preferred status.

CHEAP ALTERNATIVES NEEDED

Epogen accounts for 74% of all erythropoiesis-stimulating agent (ESA) US sales in the anemia in chronic kidney disease market.

Biosimilar epoetin alfa is expected to reduce Epogen sales by \$1.5bn in 2024. Revenue was expected to decrease from \$2.2bn in 2015 to \$769m in 2024, with about \$1.4bn of the loss coming in the US market, according to a report from Datamonitor Healthcare.

Datamonitor analyst Hristina Ivanova suggested that there may be some hesitation by providers, at least early on, to use the biosimilar, in part because of a lack of experience.

However, Woollett said moving patients from Epogen to the epoetin biosimilar would be less of a change than moving patients from Epogen to *Aranesp*. That would suggest prescribers may be more easily convinced to make the change.

Stephen Fadem, clinical professor of medicine at Baylor College of Medicine and chairman of the American Association of Kidney Patients medical advisory board, said in an interview that one would hope that new medicines or biologics would drive down prices and reduce cost burdens.

"We do live in a market-driven environment and the natural history of health care is that newer and hopefully better medications are going to be released and ultimately replace the original drugs if they show better effectiveness, safety or lower cost," Fadem said.

Uptake is expected to be driven by prescribers' desire for a lower-cost alternative to Epogen. More than half of Epogen patients eventually are expected to be switched to the biosimilar, according to the report. ▶

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Amgen Faces New ICER Roadblock To Repatha Reimbursement After CVOT

MARY JO LAFFLER & CATHY KELLY



The Institute for Clinical and Economic Review's decision to lower its "value-based" pricing benchmark for **Amgen Inc.'s Repatha** (evolocumab) based on the results of the FOURIER cardiovascular outcomes trial is a surprising blow for the company's plans for the PCSK9 inhibitor.

The level of benefit seen in FOURIER, which was released at the American College of Cardiology annual meeting in March, was viewed as a disappointment. The final results showed a 15% reduction in risk for a composite of major adverse cardiovascular events (MACE), including cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina or coronary revascularization, and a 20% reduction on the harder secondary endpoint of CV death, MI or stroke. But, no reduction was seen in cardiovascular mortality.

It is the lack of effect on cardiovascular mortality that has prompted ICER to lower its value-based pricing benchmark for Repatha, "With data now available on these patient-centered outcomes from an important study of one of the two available drugs, and with insurers and others in the process of revising earlier coverage and pricing decisions, we felt it would be helpful to provide an update that summarizes our view of the implications of the new evidence for judgments of comparative clinical effectiveness," ICER President Steven Pearson explained in a June 13 release.

ICER now believes that, for the subpopulation treated in FOURIER of patients with ASCVD whose LDL-C levels had not met the target of 70mg/dL or lower with statin therapy alone, the comparative clinical effectiveness of Repatha in combination with statins is "comparable or better" than treatment with statins alone. The previous assessment found the data on the clinical benefit from the PCSK9 inhibitors to be "promising but inconclusive."

NO STRANGER TO DISCORD

The initial ICER assessment from 2015 called for a 67% price reduction, which was revised after receiving comments to a 47% discount to the list price. (Also see "PCSK9 Revised Analysis Indicates Less Price Discounting May Be Needed" *Pink Sheet*, 9 Oct, 2015.)

ICER has not yet revealed what the new benchmark will be, except that it will be lower than the previous benchmark for Repatha and **Sanofi/Regeneron Pharmaceuticals Inc.'s** PCSK9 inhibitor *Praluent* of \$5,404 to \$7,735 annually. ICER's price benchmarks are used by payers as one reference point in negotiating contracts with manufacturers.

Repatha's annual wholesale acquisition cost is \$14,523, but according to Amgen, after rebates and discounts the net price tends to come in between \$7,700 and \$11,200 per year. *Praluent* (alirocumab) carries a similar

WAC of \$14,600 per year. In a statement on the ICER update, an Amgen spokesperson said that the company "disagrees with ICER's assessment that Repatha on top of statins conveys a small net benefit compared to statins alone. Their assessment was based on an incorrect statement that statin studies have consistently shown a mortality benefit. Amgen remains concerned that inappropriate interpretations of the data continue to create access barriers for patients at high risk of heart attack or stroke."

The company also said that "consistent with recent trials of more intensive LDL lowering, this study was not designed to, and did not show, an impact on cardiovascular death. In its report ICER failed to acknowledge the important point that none of the lipid-lowering studies comparing more versus less intensive LDL-C lowering, conducted over the last decade, have shown significant cardiovascular mortality benefit."

The FOURIER study "clearly demonstrated a significant reduction in heart attack and stroke in a relatively short duration (2.2 years) and in a well-treated population, which clinically, given the natural history of atherosclerotic CV disease, should lead to a long-term reduction in mortality. Many of the patients who take lipid lowering therapies have already suffered from a heart attack or stroke and preventing additional events is not an insignificant benefit," the firm added.

EFFECT ON CV DEATH AT ISSUE

This time around, debate is sure to focus on the issue of long-term benefit and the difficulty in hitting a CV mortality endpoint with the current state of treatment.

When FOURIER was presented at ACC, lead investigator Marc Sabatine, Harvard Medical School, reported that there were directional trends toward benefit for death due to acute MI and death due to acute stroke, but the analysis is limited by the infrequency of events. "Over the past decade, none of the trials of intensive LDL lowering versus moderate statins showed a reduction in CV mortality," Sabatine said. He noted that

with contemporary medicine, CV death “is less common than it was in the past.” The *New England Journal of Medicine* write-up of the study pointed out that the rate of CV mortality in FOURIER was one-third the rates in the landmark Scandinavian Simvastatin Survival Study (4S).

In its “New Evidence Update,” ICER acknowledges that other trials of intensification therapy have not reduced CV mortality: “For instance, in the IMPROVE-IT trial, the addition of ezetimibe reduced cardiovascular disease event rates, but did not reduce CVD mortality (HR 1.00, 95% CI 0.89-1.13).”

It also cites the FOURIER investigators’ assessment that the results underestimate the long-term benefits of therapy with Repatha and includes their landmark analyses showing improvement for the MACE components in year two and beyond, but not for CVD death. That seems to be the sticking point in the end.

“The major limitation of FOURIER, as the authors point out, was the relatively short duration of follow-up (26 of 48 months planned) because the event rate was substantially higher than expected,” ICER concluded. “It is also concerning that there was no trend toward a reduction in death from cardiovascular disease and the increase in mortality was greater in years 2+ than it was in the first year of the trial. Studies of statin therapy for secondary prevention have consistently demonstrated a reduction in CVD and total mortality.”

As to the lack of benefit on CV death, which had been assumed in ICER’s earlier assessments, Biomedtracker analyst Peter Chang told *Scrip* that “while different sides could take issue with the price range they came up with, questions about the degree of a potential benefit on CV death is a valid point, since even the investigators acknowledged that in this age of better treatment, trials of intensification of statins have failed to show a statistically significant benefit on CV death.”

Part of the problem is that as deaths from heart attacks come down – as shown by the drop between FOURIER and 4S – “there may be questions about how modifiable other events captured under CV death are with LDL-C lowering,” the analyst commented. “FOURIER did show a numerical reduction in death due to myocardial infarction, and one could argue whether these should be included in the modeling, particularly for

patients starting at higher LDL-C values, though in FOURIER overall these were only a minority of CV deaths.”

Some of the issues raised by ICER come from trial design, Chang noted. “The shorter trial appears to have led to a more modest risk reduction, which could well be larger with longer follow up, as in most statin CVOTs, because the risk reduction can take time,” he said. “Hence they felt moderate certainty of a small benefit, and gave a rating that acknowledged the benefit could be larger. However, it is not yet clear which they will use in their revised economic evaluation. If they take a more conservative approach and use the smaller value, it could well be a point of contention, since a number of experts have viewed the benefits per LDL lowering as consistent with the statins.”

Chang pointed out that **The Medicines Co.’s** trial for its investigational PCSK9 inhibitor inclisiran will use coronary heart disease death in its composite endpoint and enroll patients with higher LDL levels to show a greater difference in MACE. FOURIER and Sanofi/Regeneron’s ODYSSEY Outcomes trial, expected next year, enrolled patients with LDL levels closer to physician treatment targets.

IN DEFENSE OF THE PRICE

Analysts and clinicians were hoping for a greater level of effect in FOURIER, but Amgen went to great lengths to defend both the level of benefit and explain how its price point was justified based on the evidence seen.

Amgen defended its pricing and laid out the model used during an analyst briefing at ACC, which assumes a 25% relative risk reduction at the end of the first year of treatment and 33% relative risk reduction on fatal and nonfatal MI and stroke at the end of the first year. The model assumes a benefit on cardiovascular mortality, which Ofman said was “typical” for health economic assessments of lipid-lowering therapies “even when the benefit was not demonstrated in the clinical trials themselves.”

With the data from FOURIER, “we have a lot of conviction that the net prices that exist in the market today, the prices that payers are paying, are value-based and in fact may even be below the value-based range of the types of patients that are actually getting access to Repatha now,” Ofman said during the March 17 briefing. “Should the drug not

perform the way we anticipate, then yes, indeed the net prices will go down. But if the drug performs as we expect, they shouldn’t.”

He also predicted during the March event that FOURIER would be enough to ensure better reimbursement for Repatha. “The payers have said that the lack of outcomes data has been a driving force for the access restrictions, and I think now, after the data you’ve seen today, we can take that objection off the table,” Ofman said.

Following the FOURIER presentation at ACC, Express Scripts Steve Miller told *Scrip* that although the results “maybe [were] not the benefit some were hoping for,” but should spur demand and make physicians “a bit more enthusiastic” – and that payers “will be appropriately more willing to pay.” He reported Express Scripts was working on ideas with both Amgen and Sanofi.

Both sets of sponsors have been counting on the CVOT data to give a boost to their flagging franchises, which have had poor uptake in part because of the lack of outcomes evidence and in part because of the resulting reimbursement hurdles. In the first quarter, Amgen reported worldwide sales of just \$49m for Repatha – down from \$58m the quarter before and far short of the \$72m analysts had forecast. Praluent came in 26% below expectations for the first quarter, with Sanofi reporting worldwide sales of €34m (\$36m), down from €37m (\$40m) in the fourth quarter of 2016. (Also see “PCSK9 Sponsors Still Face Challenges In Turning Around Dismal Launches” *Scrip*, 11 May, 2017.)

With the FOURIER evidence in hand, Amgen has been negotiating new contracts, offering full refunds on the drug costs in exchange for reducing access restrictions. (Also see “Amgen’s Repatha Contract With Harvard Pilgrim Includes A Full Refund” *Pink Sheet*, 3 May, 2017.)

Amgen has said it would submit the FOURIER data to FDA for inclusion in labeling mid-2017.

ICER’s evidence and pricing update does not apply to Praluent. ICER noted that longer-term studies of Praluent are underway, “which may provide important new evidence to assess the relative clinical effectiveness of each PCSK9 inhibitor and of the class as a whole.” Results of the ODYSSEY outcomes study for Praluent are expected to be announced in the first quarter of 2018. ▶

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Boehringer Ingelheim Limbering Up With Humira Biosimilar

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Boehringer Ingelheim GMBH has presented pivotal Phase III results for BI 695501, its biosimilar version of **AbbVie Inc.**'s top-selling anti-TNF drug *Humira* (adalimumab), at the Annual European Congress of Rheumatology (EULAR) in Madrid, Spain. The results of VOLTAIRE-RA demonstrate clinical equivalence of 501 and Humira, completing the body of evidence needed to prove biosimilarity and earn approval from regulators. The candidate has already been accepted for filing in both the EU and US, but the company is not commenting on its expectations for the timing of approval decisions. In any case, commercial launch is likely to be delayed by AbbVie's patent defenses.

Humira is the world's top-selling drug, generating revenues of \$16.5bn for AbbVie in 2016, and there are multiple biosimilar contenders hoping to capture a slice of its pie. Most advanced is **Amgen Inc.**, which has already won regulatory approval for *Amjevita/Amgevita* in the US and EU (in September 2017 and March 2017, respectively). Amgen has not yet launched its product commercially in the US or the EU, and doesn't expect to do so before 2018 because of ongoing patent litigation. (Also see "Biosimilar Launches Depend Mostly On Patents After Supreme Court Ruling" *Scrip*, 13 Jun, 2017.) (Also see "Amgen's Biosimilar Adalimumab First To EU Nod But No Launch" *Scrip*, 27 Jan, 2017.)

Karsten Kissel, head of global medical affairs biosimilars at Boehringer Ingelheim, told *Scrip* that his company was well positioned to compete in the space eventually, and said that "even with the number of competitors that may be in the [anti-TNF biosimilar] market and the impact on price that the competitors in the market may have, it will still be a very attractive space to be in, which is why many companies have gone for it, including us." Although, as a biosimilar, it will not be possible to differentiate BI 695501 on its efficacy, safety or immunogenicity, Kissel said it was part of Boehringer's biosimilars strategy to "deliver value beyond the product" in various ways, which may in-



Karsten Kissel, MD - head of global medical affairs biosimilars, Boehringer Ingelheim

clude patient on-boarding tools, packaging and other solutions to help enhance the patient's experience.

As the biosimilars space is still in its infancy, particularly in the US, companies are keeping their cards close to their chest when it comes to competitive strategies. However, Kissel confirmed that Boehringer would provide data on BI 695501 beyond the single pivotal trial required for approval, "to help make patients, physicians, payers and other stakeholders comfortable" with the product. For example, while the main trial demonstrating equivalence was in rheumatoid arthritis, Boehringer is gathering additional data on BI 695501's use in Crohn's disease and psoriasis "to support extrapolation" of the biosimilarity data to other indications for which Humira is approved, and to "increase the confidence in biosimilars." He said that Boehringer was "listening to all the stakeholders" and was "confident our strategy will pay off". Kissel confirmed also that Boehringer is collecting data on switching patients from Humira to BI 695501 in its pivotal phase III study in rheumatoid arthritis.

Boehringer is not disclosing whether it has already filed for approval of BI 695501 in all of the indications currently on Humira's label; nor will it discuss its commer-

cial strategies for different markets beyond saying that "there will clearly be different challenges in different geographies and we will develop appropriate strategies for the different geographies". Nevertheless, Kissel said the company was "ultimately interested in obtaining labels for all the indications that the reference product [Humira] has."

Acknowledging the long line-up of companies of different types, from generics players to big pharma to newcomers, limbering up to enter the biosimilar space, not least with anti-TNFs, Boehringer Ingelheim's director of product communications, Matthias Kagerbauer, said he expected the field to "continue to be highly dynamic" with some attrition of products in development likely and that Boehringer Ingelheim would need to be flexible to adapt to emerging challenges. However, he affirmed the company's commitment to biosimilars; its other late-stage candidate (BI 695502) is a biosimilar version of **Roche's** *Avastin* (bevacizumab) that is in a pivotal Phase III comparing its safety and efficacy in comparison with *Avastin* for patients with advanced, non-small cell lung cancer.

PARTNERSHIPS A POSSIBILITY

Kagerbauer said that Boehringer was looking into "partnerships, innovative ways of collaborating with others" both in product development and commercialization in the biosimilars space, although it did not have anything specific to disclose at this point.

Kissel highlighted the company's "exceptionally good history and experience in biologics manufacturing" both in terms of developing its own products and in biopharmaceutical contract manufacturing (the company is investing more than €700m in a new large-scale biologics production facility in Vienna, Austria). However, the firm does not currently sell drugs for inflammatory disorders, and its presence in oncology is relatively limited. Kissel highlighted Boehringer's past and ongoing commercial partnerships – including with **Pfizer Inc.** for the respiratory product *Spiriva* and with

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Basilea's Business Strategy Emboldened By \$500m Pfizer Deal

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Upfront, milestones and royalty payments from **Pfizer Inc.**, the newly recruited European licensee for **Basilea Pharmaceutica Ltd.**'s antifungal, *Cresemba* (isavuconazole), should give a welcome boost to the Swiss company's strategy of developing early clinical-stage products to overcome resistance to anti-infective and oncology medicines, and finding additional partners around the world for its marketed products that include *Cresemba* and the anti-biomatic, *Zevtera/Mabelio* (ceftobiprole).

Basilea has spent the past year or so making *Cresemba* available in key European markets, including Germany, Italy, the UK, France and Austria, and finding licensees in other markets. In addition to the Pfizer deal announced on June 14, Basilea on the same day revealed an agreement with **Avir Pharma Inc.** involving the distribution of *Cresemba* and *Zevtera* in Canada.

The drug has put in a solid performance in countries where it has been launched

These agreements add to the ones that Basel-based Basilea, spun-out from Roche in 2000, have signed for other markets: an agreement to distribute *Cresemba* in the Middle East and North Africa was signed with **Hikma Pharmaceuticals PLC** in August 2016, and Basilea has since entered into *Cresemba* licensing agreements with **Grupo Biotoscana SL** covering Latin America, with **Asahi Kasei Pharma Corp.** covering Japan, and with **Uni-medic Pharma AB** covering the Nordic countries (Sweden, Denmark, Norway, Iceland and Finland).

Basilea received EU approval for oral and intravenously administered *Cresemba* in Oct. 2015 for the treatment of adult patients with invasive aspergillosis and mucormycosis for whom amphotericin B is inappropriate, and currently markets the product in key countries including Germany, Italy, the UK, France and Austria. In the US, *Cresemba* is marketed by the licensee **Astellas Pharma Inc.**, having been approved in March 2015 for invasive aspergillosis and invasive mucormycosis.

The drug has put in a "solid performance" in countries where it has been launched, according to Basilea. In the US, *Cresemba* garnered \$46m in sales in 2016, and **Astellas** believes sales could reach \$56m in 2017, a 20% increase.

That initial experience has proven attractive to big pharma. Pfizer said on June 14 it was paying to Basilea an upfront of CHF70m (\$71.7m) and up to \$427m in milestones based on pre-specified regulatory and sales achievements, and mid-teen royalties on sales, for the rights to manufacture isavuconazole and to exclusively commercialize the antifungal in Europe (excluding the Nordic countries), Russia, Turkey and Israel.

Invasive aspergillosis accounts for around 70,000 deaths in Europe every year among immunocompromised patients, while mucormycosis is associated with around 3,000 deaths annually in Europe. *Cresemba* has a broad-spectrum antifungal activity, produces consistent plasma levels, and can be given to patients with renal impairment, Basilea reports. It can also be administered once daily in patients requiring maintenance therapy.

Basilea claims *Cresemba* has marketing exclusivity through to 2027, because of its orphan drug status, potential EU pediatric extension and US qualified infectious disease product (QIDP) designation.

Pfizer will assume responsibility for marketing *Cresemba* in Europe over the next few months, and will conduct additional *Cresemba* launches in Europe in 2017 and 2018. In Europe, *Cresemba* will join Pfizer's arsenal of antifungal agents that includes *Vfend* (voriconazole), *Fasigyn* (tinidazole) and *Diflucan* (fluconazole), and its range of other anti-infectives. The US-headquartered big pharma also completed the acquisition of **AstraZeneca PLC**'s small-molecule anti-infectives business in Dec. 2016, primarily outside the US.

The transaction is expected to reduce Basilea's total operating expenses by CHF9-10m per month, with *Cresemba* sales booked by Pfizer. Basilea said it expects to receive \$6m in revenues from the agreement with Pfizer in 2017.

STRENGTHENING R&D PIPELINE

The funds available from the deal will be used to support Basilea's own research into compounds that fight drug-resistant disease in oncology and infective diseases, noted CEO Ronald Scott in a June 15 briefing. Basilea is also looking at product opportunities outside the company, and wants to bring new compounds into its research and clinical development portfolio, Scott added. The company is also in discussions with potential partners for *Zevtera*, and for partners in additional markets, including China.

The *Cresemba* deal comes at a crucial time for Basilea, which expects to start Phase III US studies with *Zevtera* in the US in the next few months, with financial support from a \$54.8m grant from the US Biomedical Advanced Research and Development Authority (BARDA) program. The drug is approved for marketing in Europe but has a troubled development history in the US.

A Phase III US study in *Staphylococcus aureus* bacteremia and a second Phase III study in acute bacterial skin and skin-structure infections are currently being planned.

Basilea also has a tumor checkpoint controller, BAL101553, and a pan-RAF/SRC kinase inhibitor, BAL3833, in Phase I/II studies. BAL101553 is thought to cause checkpoint activation that leads to tumor cell death and has shown initial clinical benefit in Phase I/IIa studies, while BAL3833 targets the RAF and SR kinase families, and is being evaluated in collaboration with the Wellcome Trust for the treatment of solid tumors. ▶

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BMS's Fouad Namouni On The Future Of Immuno-Oncology

LUCIE ELLIS lucie.ellis@informa.com

Bristol-Myers Squibb Co.'s Head of Oncology Fouad Namouni told *Scrip* on the sidelines of the 2017 American Society of Clinical Oncology (ASCO) annual meeting, held June 2-6 in Chicago, that BMS is ready to build on its foundations of using the immune system to fight cancer – with resistance to immunotherapy as its next big target.

Almost a year into his new role at BMS, having been promoted to head the US big pharma's oncology unit in July 2016, Namouni told *Scrip* about his expectations for the company's marketed cancer portfolio in 2017 and discussed impending disruptions in cancer R&D.

Namouni – who joined BMS in France in 1999 and previously led development for the company's programmed cell death protein 1 (PD-1) inhibitor *Opdivo* (nivolumab) and its anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA4) drug *Yervoy* (ipilimumab) – also revealed how BMS will tackle the issue of resistance in patients treated with immuno-oncology therapies and gave his opinion on the future of tissue agnostic drug approvals in cancer.

BMS's biggest cancer rival **Merck & Co. Inc.** won the first US FDA tissue agnostic approval based on biomarkers last month for its PD-1 inhibitor *Keytruda* (pembrolizumab) in solid tumors.

LUCIE ELLIS: *What is BMS doing differently to its peers in the immuno-oncology space?*

FOUAD NAMOUNI: Back in the early 2000s people did not believe that a checkpoint inhibitor could improve overall survival in such a devastating disease like melanoma – but see where we are today and all the knowledge accumulated at BMS over the years. There are more than 230,000 patients in clinical studies for our IO agents alone and in combination with other drugs. All of this is helping us to better understand how we can develop medicines faster and is giving us a better understanding of the biology of oncological diseases. It's help-



Fouad Namouni, Oncology Development Head at BMS

ing us understand the biology of tumors and highlighting novel endpoints, new biomarkers and new ways to accelerate development.

LE: *BMS has signed a few oncology deals recently – such as the June 5 agreement with Novartis AG for the development of Opdivo and Opdivo plus Yervoy regimen in combination with Mekinist (trametinib) as a potential treatment for metastatic colorectal cancer – but what do you look for in drug development partnerships in oncology?*

FN: We have most of the [current] IO mechanisms in-house and we continue to develop new mechanisms in-house, but in the fight against cancer it's never a done deal and you need to see every interesting piece of data. We source our pipeline in many ways, [including looking] at partners if they have mechanisms that are interesting or that are ahead of what we could develop in-house, and we need to get patients very quickly with combinations. We also look at business development opportunities as we have been doing recently. We hope that with all this, sometime, we will be able to cure more patients with cancer.

LE: *What is next for Opdivo considering Merck's Keytruda, the closest PD-1 competitor to BMS's own IO therapy, has recently secured the very first tissue agnostic FDA label for use in solid tumors?*

FN: Overall, I think Opdivo will continue – either as a single agent or in combination with Yervoy or other new agents – to be expanded as a foundational medicine for a variety of tumor types.

Let me talk about lung cancer: we brought Opdivo to second-line lung cancer at a time when people didn't really believe it would work and they did not know much about checkpoint inhibitors. With Opdivo we put to rest decades of chemotherapy use in second-line lung cancer. In the first-line setting it is really just the beginning; we have packed the development of immunotherapy into very few years. I see first-line lung cancer as a complex disease and BMS has the most comprehensive program in this space, looking at combination immunotherapy, combinations with chemotherapy and looking at biomarkers. The treatment of first-line lung cancer is going to be set by many combinations in different populations driven by biomarkers, and we will see what are the right combinations for the right patients. That is the only way we will see incremental benefit in lung cancer.

LE: Do you have concerns around having too broad a development program for products like Opdivo? It can seem as though companies are testing combinations of everything with anything to see what sticks.

FN: Our pipeline is deliberately rational in the way we think about using mechanisms to fight cancer. The major guidelines for the way we should be looking at cancer are: combination therapies - two drugs, three drugs or maybe more; precision medicine and more biomarkers - maybe more than one or two biomarkers, we will need better profiling of patients' immune systems to see what is the right drug to go to the right patient; and we will also need to deal with the growing issue of resistance to immunotherapy.

Our pipeline was built to look at the effector T-cell and stimulate it with checkpoint inhibitors or agonists. But that is not enough because around that T-cell we have the tumor microenvironment trying to block those therapies. So, we are looking also at most of the tumor mechanisms in the tumor microenvironment. Colony stimulating factor 1 receptor (CSF1R) is one example in the clinic; CTLA4 also plays a role not just as a checkpoint inhibitor; and most recently Indoleamine-pyrrole 2,3-dioxygenase (IDO) has come forth as an important mechanism in the tumor metabolism.

Lastly, I would say the way we have designed our pipeline is to tap into the innate immunity. Not a lot of people are looking at the innate immunity but we believe at BMS that it could be a strong ally to the adaptive immune system. When you step back, you see that we are attacking cancer and the immune system from most, if not all, the angles. BMS owns a lot of these mechanisms internally, this gives us a lot of leverage in the way we develop our medicines.

LE: How are you preparing to market multiple combination variations at once?

FN: I joined BMS many years ago and at that time we would be putting on the market, in general not just in oncology, a product every couple of years or so. Over the last two years though progress has been unprecedented; we have had 11 approvals in the US, as well as approvals in many other places around the world, for products across six different cancers. The BMS commercial and medical teams have reached

a level of excellence in terms of launching new products. All these learnings, from working on multiple launches across several cancers all at the same time, provide a good set up for us to do even more.

We have to continue to learn though and follow the signs. We must continue to understand biology and challenge ourselves and aim for the greatest benefit for patients that shifts the paradigms of treatment, as we did with Yervoy and Opdivo.

LE: What do you anticipate to be the next big disruptor in oncology R&D?

FN: I think this mindset we are seeing, of not just combining one drug or two but combining several medicines in the right way for each patient, will be very disruptive. We are also seeking better incremental benefits because the bar has been set high, PD-1s and CTLA4s have pushed the bar high when it comes to overall survival in some cancers. The most important thing is to find the right patients and the right combinations.

However, I think resistance to IO therapies is going to be a big problem and we have not improved survival in every patient. There are still patients that relapse after immunotherapy. If we can get that population of relapsed patients to a much better outcome that would be a major shift.

LE: To conclude, what should we look out for from BMS in the coming months?

FN: Post-ASCO you should look forward to more on how we are going to treat the right patients with the right combinations of immuno-therapy. We reported data [this month] for our lymphocyte-activation gene 3 (LAG3) combination in refractory melanoma patients, and one patient out of five is responding when they are LAG3 positive, so it's very precise. Also, in Hodgkin's lymphoma we have seen a complete response in a patient treated with LAG3 that was previously refractory to immunotherapy and I think that really summarizes what's ahead.

[Bristol presented Phase I/IIa data that demonstrated "encouraging activity" of anti-LAG-3 (BMS-986016) and Opdivo combination in heavily pretreated advanced melanoma patients who were relapsed or refractory on anti-PD-1/PD-L1 therapy. The company plans to explore this therapy in a number of other cancer types.] ▶

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Eli Lilly & Co. in diabetes – as examples of how the group embraces collaboration where it makes sense.

Boehringer Ingelheim's in-house biosimilar program is both bolstered and constrained by its established role as a contract manufacturer. Contracts with clients include specific conditions which limit the ability of BI to develop or make biosimilars to specific products that it makes for clients.

BOX-TICKING VOLTAIRE-RA DATA

On the data presented at EULAR, Kissel said it was "nothing unexpected" and that while it was "an important milestone on the way to registration, for biosimilars the clinical data isn't the most exciting part from a scientific perspective because ultimately you want to show similarity, and that's what we achieved." It is "an important tick the box" exercise that confirms the quality of the product and the ability of the company to deliver this type of biosimilar development program, he said.

In the VOLTAIRE-RA study presented at EULAR, 645 patients aged 18-80 with moderate to severe active rheumatoid arthritis on stable treatment with methotrexate were randomized to receive Humira or BI 695501 at 40mg every two weeks for 48 weeks. The co-primary endpoints, measuring the proportion of patients achieving an ACR20 improvement at weeks 12 and 24, were met. 67.0% of patients on BI695501 achieved ACR20 response at 12 weeks and 69% did so at 24 weeks; among patients on Humira, 61.1% achieved ACR20 at 12 weeks and 64.5% did so at 24 weeks.

Equivalence was demonstrated as the relevant confidence intervals for differences in the ACR20 response rates at weeks 12 and 24 were within the predefined margins. At week 12 the 90% confidence interval was -0.9%, 12.7%, versus the predefined margin of -12%, 15%. At week 24 the 95% confidence interval was -3.4%, 12.5% versus the predefined margin of -15%, 15%. One-year results will be presented at a future medical meeting.

Boehringer also announced data from its VOLTAIRE-AI study in 71 healthy male subjects, demonstrating the pharmacokinetic, safety, tolerability and immunogenicity similarity of 501's prefilled syringe and auto-injector presentations. ▶

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Merck & Co. Strengthening Its Strong Position In Immuno-Oncology

EMILY HAYES & MARY JO LAFFLER

This year’s American Society of Clinical Oncology meeting left **Merck & Co. Inc.** in an even more attractive immuno-oncology position than before – with additional data helping to secure the lead for its PD-1 inhibitor *Keytruda* in key indications like lung and bladder cancer, where competitors have fallen back, as well as promising debuts in new tumor types like breast and gastric tumors.

Merck stressed during a June 5 investor briefing at ASCO that it is working to establish *Keytruda* as a foundation in cancer treatment. It presented 50 abstracts for *Keytruda* across 16 different types of tumors at the conference, which was held from June 2 to 6 in Chicago.

More than 500 trials of *Keytruda* in 30 tumor types and 300 combination studies are ongoing. About 40 registrational studies are under way in numerous lines of therapy and tumor types – including liver cancer and triple-negative breast cancer (TNBC).

Credit Suisse analyst Vamil Divan deemed Merck’s ASCO briefing “a tidy summary of the progress [Merck] has made in oncology over the past several years and ... the significant opportunity ahead of the company over the next several years.”

In a June 5 note, Divan expressed confidence that *Keytruda* and the IO opportunity is enough to carry the company. “*Keytruda* has now shown activity in more than 20 tumor types, has regulatory approvals in 10 different indications and has ~40 registration-enabling studies ongoing, driving our view that *Keytruda* can continue to drive the story in a company where we acknowledge the base business is facing pressure and where the non-oncology pipeline is not as robust as we would prefer.”

Divan wasn’t alone in his positive assessment. Leerink analyst Seamus Fernandez concluded after the event – in a note titled “How Broad Are *Keytruda*’s Shoulders?” – that “if there is one theme that continues to resonate at [Merck], it is that science-driven clinical execution has been the foundation of *Keytruda*’s success and this is likely to continue for the foreseeable future.”

Merck notes that *Keytruda* (pembrolizumab) is emerging in three waves across tumor types, starting with melanoma and NSCLC (see table). It is currently approved across different lines of therapy for lung cancer, melanoma, classical Hodgkin lymphoma, head and neck squamous cell cancer, bladder cancer and microsatellite instability-high cancers.

LOOKING AHEAD TO NEW CANCERS

The company announced in late May that FDA has accepted yet another supplemental filing in gastric cancer after two or more prior lines of therapy. The filing is under priority review. At ASCO, Merck presented data from the heavily pretreated single arm “Cohort 1” of the KEYNOTE-059 study supporting the filing. The objective response rate (ORR) was 11.6% overall, with a 15.5% ORR in those positive for expression of the PD-L1 biomarker and 6.4% ORR in PD-L1-negative patients.

Phase II data from the I-SPY study at ASCO suggest that *Keytruda* with chemotherapy in the neoadjuvant setting would have a very high probability of succeeding in Phase III studies in certain types of high-risk breast cancer, including triple-negative breast cancer. Among other promising findings, I-SPY researchers noted that there was a tripling of the rate of pathological complete response, a surrogate marker for overall survival, for *Keytruda* and chemo versus chemo

alone. Merck is running five studies that it views as registration-enabling of *Keytruda* in breast cancer.

In addition to moving into new tumor types, Merck is benefiting from early leads in certain markets where others are failing – chiefly **Bristol-Myers Squibb Co.**’s PD-1 inhibitor *Opdivo* (nivolumab) failing in first-line non-small cell lung cancer in last year’s CheckMate 026 study and more recently, **Roche**’s PD-L1 inhibitor *Tecentriq* (atezolizumab) failing in its confirmatory bladder cancer trial.

BUILDING EVIDENCE IN LUNG CANCER

Lung cancer is the most valuable indications for PD-1/L1 immunotherapies and *Keytruda* has gained the first and only approval as a monotherapy in first-line NSCLC in October 2016 and the first and only approval of a combination in the first-line setting this May.

Even with competition looming from PD-1/CTLA-4 combination studies – “soon” for AstraZeneca’s MYSTIC trial of durvalumab/tremelimumab and next year for Bristol’s *Opdivo*/*Yervoy* pairing in first-line lung – the early lead Merck has with its cheaper *Keytruda*/chemo combo could be a significant advantage.

“The strong foundation [Merck] is building in the space now will benefit them over time,” Credit Suisse’s Divan said, which the analyst thinks is underappreciated.

Keytruda Advancing In Three Waves

FIRST WAVE	SECOND WAVE	THIRD WAVE
Melanoma [X] NSCLC [X]	Head and neck [X] Bladder [X] Gastric TNBC Colorectal [X] Hodgkin lymphoma [X] MSI-high [X]	Esophageal Renal Ovarian Prostate Multiple myeloma Non-Hodgkin lymphoma Hepatocellular Other thoracic malignancies Gynecological malignancies Rare tumors

Source: Merck ASCO 2017 investor briefing

The combination of Keytruda with **Eli Lilly & Co.**'s chemotherapy *Alimta* (pemetrexed) and carboplatin chemotherapy received accelerated approval for first-line, non-squamous, metastatic NSCLC, about one quarter of the first-line market, based on ORR data. The confirmatory study for the filing is the Phase III KEYNOTE-089 study of Keytruda in first-line NSCLC, which is due to report later this year.

At ASCO, Merck released some positive updates that bolster Keytruda's position in lung cancer. In KEYNOTE-024, the pivotal trial for the monotherapy approval in first-line NSCLC with at least 50% PD-L1 expression, the company reported an overall survival benefit continued through the two-year point.

Merck also presented an update on the "G1" cohort of the KEYNOTE-021 study that supported the Keytruda/chemo combo approval. The ORR in the trial was 56.7% for the combination with Keytruda versus 30.2% for the comparator. An overall survival benefit is starting to emerge – the survival rates at nine months and 12 months, respectively, were 84.6% and 76% for the Keytruda arm vs. 82.3% and 69.3% for the chemo combo alone, a non-significant improvement, Merck reported.

During the investor briefing, Merck Research Labs President Roger Perlmutter noted that there had been substantial crossover of 75% in the study and that despite this, the company is beginning to see a trend toward improvement in overall survival.

"Importantly, these responses seem to be durable, as they typically are with Keytruda treatment," Perlmutter said.

Though the combination is approved, many lung cancer specialists are "disinclined to embrace it without an overall survival benefit," Howard (Jack) West, director of the thoracic oncology program at the Swedish Cancer Institute in Seattle, tweeted after the meeting. "Will a non-significant trend move us from 'can' to 'should' pursue this?" he asked.

In an interview, Merck's Roy Baynes, senior vice president of global clinical development at Merck, noted that the study is the first randomized trial to improve progression-free survival in 35 years and showed "quite striking efficacy." Furthermore, a big confirmatory study is coming, he added.

Credit Suisse's Divan sees the commercial opportunity for Keytruda expanding in lung cancer.

"In NSCLC, Keytruda is already capturing the bulk of patients with tumors that have high levels of PD-L1 expression. With the recent FDA approval for Keytruda + Alimta across all of 1L non-squamous NSCLC and, following data at ASCO that showed a trend in overall survival in the KN-021G study, we expect that combination to gain further traction as we move into 2H 2017," Divan said.

Frank Clyburn, president of Merck's global oncology unit, said during the company's ASCO briefing that overall, early feedback in the marketplace about the combination has been "very positive" and that physicians are comfortable using it. Merck also has received some positive feedback on the updated OS curves for the 21G cohort, the exec said.

Another notable release in lung cancer at the meeting was data for Keytruda in combination with partner **Incyte Corp.**'s

epacadostat, an inhibitor of the up-and-coming immuno-oncology target indoleamine 2,3-dioxygenase (IDO1), an enzyme that plays an important part in immune response, in the Phase I/II ECHO-202 study. (Also see "Scrip's Rough Guide To IDO" Scrip, 18 May, 2017.)

A cohort of 40 patients with NSCLC showed an objective response rate of 35%, including complete responses in two patients (5%). Responses were demonstrated regardless of the level of PD-L1 expression, the company said. Results for other tumor types were in line with expectations, though data for the tough-to-treat triple-negative breast cancer and ovarian cancer were disappointing (see table).

BLADDER DATA HOLD UP OVER TIME

Survival data presented for Keytruda in bladder cancer is also encouraging. Keytruda became the first PD-1/L1 inhibitor to secure full approval in second-line metastatic urothelial cancer after platinum-based chemotherapy, having proven a survival benefit over chemotherapy in this setting.

All of the other leading PD-1/L1 drugs approved for second-line bladder cancer hold accelerated approvals based on response rate data – Roche's Tecentriq (atezolizumab), Bristol's Opdivo (nivolumab), **AstraZeneca PLC's Imfinzi** (durvalumab), and **Merck KGAA/Pfizer Inc.'s Bavencio** (avelumab). And Roche's Tecentriq recently failed to show an overall survival benefit in a confirmatory trial in second-line bladder cancer.

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Phase I/II ECHO-202 Results: Keytruda/Epacadostat Data, IO Naïve Population

Tumor type & number of patients	Squamous cell cancer of the head and neck (n=38)	Non-small cell lung cancer (n=40)	Renal cell carcinoma (n=30)	Bladder cancer (n=40)	Triple negative breast cancer (n=39); ovarian cancer (n=37)
Abstract number	#6010	#9014	#4515	#4503	#1103
Objective response rate	34% overall ORR; 39% after 1-2 prior lines of therapy, 14% ≥3 prior lines.	35% overall ORR; 39% after 0-2 prior lines therapy	33% ORR overall; 47% after 0-1 prior lines, 9% ≥2 prior lines	35% ORR overall; 38% after 0-1 prior lines, 25% after ≥2 prior lines	TNBC: 10% ORR overall, 12% after ≤2 prior lines, 9% ≥3 prior lines Ovarian: 8% ORR overall; 13% after ≤2 prior lines therapy, 7% ≥3 prior treatments
Treatment-related adverse events (Abstract #3012): In an updated pooled analysis, TRAEs in 67% of 294 patients. Most common: fatigue (29%), rash (17%), nausea (11%) and pruritus (10%). Grade ≥3 TRAEs in 18%. Most common: increased lipase (asymptomatic) (4%) and rash (3%). TRAE-related discontinuation rate: 4%.					

Sources: Adapted from presentation by Siwen Hu-Lieskovan (UCLA) at ASCO 2017, company releases

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Keytruda also holds the only approval in the first-line setting for cisplatin-ineligible metastatic bladder cancer. At ASCO, Merck presented updated data from the Phase III KEYNOTE-045 study that supported the second-line approval. In the study, median overall survival was 10.3 months for Keytruda monotherapy vs. 7.5 months for physician's choice of chemo, a significant 27% reduction in risk. Investigators reported in a poster study at the meeting that Keytruda's survival advantage held with longer follow up – at 12 months, 44% were alive in the Keytruda arm versus 30.2%, and at 18 months, 36.1% were alive versus 20.5%.

Memorial Sloan Kettering oncologist Jonathan Rosenberg noted in a discussion of the poster that the longer follow-up of survival data confirmed the initial analysis from the trial and that objective responses occurred rapidly and were durable. Safety and tolerability also clearly favor pembrolizumab over second-line and third-line chemotherapy, he said.

Keytruda is the only PD-1/L1 agent to have a "Category 1" recommendation, meaning the highest level of evidence, from the National Comprehensive Cancer Network in this indication. Rosenberg said that Keytruda is now the standard of care in second-line metastatic bladder cancer, though the field is moving rapidly and is subject to change (*see table*).

"Many of the newer agents have been approved in bladder, but we feel very good about our data. And in fact ... one of our key customers just announced that they are going to add Keytruda for bladder into their regimens based on the strength of KEYNOTE-045," Merck's Clyburn said during the analyst briefing.

The combination of Incyte's epacadostat with Keytruda represents a new approach to the tumor type. In the ECHO-202 study, the ORR was 35% in 40 patients. Rosenberg noted that the population was rather lightly pretreated – 80% had one or fewer prior regimens in the metastatic setting – but that was also the case in Keytruda's KEYNOTE-045 and Opdivo's CheckMate 275 monotherapy studies. In those trials, the ORR was 19.6% and 21%, respectively.

"We can be at least somewhat comfortable that the objective response rate [for the combination] is a real thing. Certainly, this is worthy of further evaluation," Rosenberg said.

WHAT ELSE FOR MERCK

Leerink's Fernandez noted that the two biggest questions from investors are:

1. "How broad and early can Keytruda go?"
2. "When will a fully owned [Merck] combination emerge?"

More than half of the 500 trials ongoing with Keytruda involve combinations, Perlmutter told the call. There are "lots of opportunities to combine it with other therapies using a very scientific approach to try and identify those things that will improve lymphocyte activation, improve priming, improve durability and increase the representation of recognizable epitopes on the tumor cells the immune system must attack, the exec explained.

Merck does have a stable of internal partners in the clinic, including direct immune agonists like GITR and STING, and approaches to affect the tumor microenvironment.

But the nearest term combinations are likely to come from partnerships like the IDO alliance with Incyte or vaccine combinations, such as an RNA-based vaccine program partnered with **Moderna Therapeutics LLC**.

Merck announced a setback for one of its combination programs June 12, when it halted enrollment in two Phase III trials of Keytruda plus an immunomodulator from **Celgene Corp.** (*Pomalyst* and *Revlimid*) in multiple myeloma due to reports of higher deaths in patients on combination therapy.

Pushed as to why Merck hasn't emphasized advancing combinations in the same way Bristol and Roche have, Perlmutter responded that Merck's strategy is based on better understanding why patients aren't responding to find the best way to broaden that response base – different approaches for different situations should yield the best responses. "As we begin to evaluate patients and to assign them systematically to these mechanistically quite different reasons for nonresponsiveness, we'll understand how best to apply new mechanisms," he said. "And we're exploring new mechanisms that address all of those different areas."

Immediately following ASCO, Merck advanced its own CTLA-4 combination trial into Phase I, in lung and other tumor types. The trial is pairing Keytruda with Merck's own internal candidate, MK-1308, rather

than Bristol's marketed Yervoy or AstraZeneca's Phase III tremelimumab – which both firms are testing with their own PD-x inhibitors.

"We have felt that if [Merck] is going to pursue CTLA-4 combo – either as a hedge, or because it genuinely believes in the opportunity – it either needs to 'go big or go home,'" Bernstein Research analyst Tim Anderson said in a June 8 note. "Unless [Merck] believes it has a differentiated product, it is difficult to justify development of this new molecule given the substantial lead-time advantage that its two competitors have in this area."

He noted that Merck execs have previously indicated that there might be some differentiation – but as that would be based on preclinical/mechanistic studies "the supporting evidence behind this claim is weak at the moment." Instead, Anderson suggested Merck should simultaneously pursue a Keytruda/Yervoy trial, not necessarily a full registrational trial but something that would be "practice enabling" and build physician comfort "mixing and matching" products. He indicated Merck management has been receptive in the past but may have paused due to lackluster combination data emerging – like Bristol's CheckMate-067 data in melanoma at the American Association of Cancer Research meeting or the CheckMate-012 data at ASCO.

During the ASCO briefing, Perlmutter weighed in on the CTLA-4/PD-1 pairings: "There's reason to believe that you can see some improvement as a result of combining the two," but "the question is sort of is the juice worth the squeeze?" – i.e., does the added benefit justify the increased toxicity. There are "slightly different properties" with Merck's CTLA-4 agent, he added. "We're systematically trying to understand how best to use the combination together because we're concerned about the toxicity."

The landscape will become clearer as the AstraZeneca and Bristol trials report out, but in the meantime Merck is concentrating on making the most of the chemo combo opportunity and steadily building its own mechanistically based combinations.

As Bernstein's Anderson concluded, "the long-term IO landscape may always feel like it could shift again as newer approaches (e.g. IDO combination, CEA-CD3 bispecific) advance into Phase III!" ▶

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Death Excess Gives Pause To Merck & Co's Keytruda MM Phase III Studies

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Merck & Co. Inc. has halted enrolment into two Phase III studies of its leading checkpoint inhibitor *Keytruda* (pembrolizumab) after receiving higher reports of death in the arms receiving the drug.



Putting On The Brakes

Shutterstock: Maksym Dvornik

'To date, Keytruda has had a clean safety profile'

The two studies – KEYNOTE-183 and KEYNOTE-185 – are looking at the anti-PD1 monoclonal in combination with other therapies for the treatment of multiple myeloma. The company says the pause allows it to better understand the increased death rate in the Keytruda arms.

Patients currently enrolled in these two studies will continue to receive treatment, Merck said, and its other Keytruda studies are unaffected.

No further data has been disclosed on the number of deaths or whether the imbalance was seen in both studies, or just one and the other trial halted as a precaution, and analysts said that without more information it was difficult to draw any meaningful conclusions about the development.

Analysts at Credit Suisse said in a research note that they did not think there was any undue cause for concern as yet. "To date, Keytruda has had a clean safety profile, and with the number of studies ongoing in very sick patient populations, it is reasonable to assume that a certain combination or indication could yield a negative safety result, if that is in fact the cause of the imbalance. We do not view this pause as having any material impact on Merck's near-term prospects in immuno-oncology."

However, Datamonitor Healthcare's Dominique Fontanilla said it was still a disappointment "coming off the high of its approval for MSI-H expressing tumors" and pointed out that while Keytruda is an established immunotherapy in solid tumors, it is still in the develop-

ment phase for hematological and lymphatic malignancies. Both Phase III trials are looking at Keytruda in combination with dexamethasone and an immunomodulatory thalidomide analog:

- KEYNOTE-183 is comparing pomalidomide (Celgene's *Pomalyst*) and low-dose dexamethasone with Keytruda to pomalidomide and low-dose dexamethasone alone in patients with refractory or relapsed and refractory multiple myeloma who have undergone at least two lines of prior treatment. According to Clinicaltrials.gov, this study had been expected to enrol 300 patients and complete in August 2018.
- KEYNOTE-185 is comparing lenalidomide (Celgene's *Revlimid*) and low-dose dexamethasone with Keytruda to lenalidomide and low-dose dexamethasone alone in patients with newly diagnosed and treatment-naïve multiple myeloma who are ineligible for autologous stem cell transplant. This study had been due to enrol 640 patients and complete in August 2019.

The Credit Suisse analysts also noted that there was no sign of "obvious toxicity" in a Phase I study on the Pomalyst combo in a Phase I trial reported at the American Society of Hematology meeting in 2015.

But Fontanilla noted that triplet combinations are the initial preferred treatments for multiple myeloma and while novel combinations could potentially result in improvements in survival and efficacy, they also carry a significant risk of more adverse or fatal side effects.

"Looking at the trial designs from Keynote 183 and 185, the doses of drugs used in the combinations (pembro + pomalidomide + dex; pembro + lenalidomide + dex) were used at their standard doses which could have potentially contributed to the unacceptable risk-benefit. The data from trials studying combinations with IO agents suggest that dosing adjustments may be required in order to produce manageable safety profiles. Having said that, these IO agents and combinations sometimes behave differently in specific tumor types and this recent development with Keytruda in multiple myeloma illustrates the increasing complexity with regards to clinical trial design in oncology," she said.

Multiple myeloma is just one of a raft of indications in which Keytruda is being tested and is not expected to be a huge market for the product especially compared with segments like lung cancer.

Recent years have seen a mushrooming of approved products for multiple myeloma (recent additions include **Bristol-Myers Squibb Co's** *Empliciti* and **Janssen Pharmaceuticals Inc's** *Darzalex* (daratumumab)), making Keytruda a latecomer to the market and an expensive one at that.

The only other anti-PD1/L1 product that appears to be in industry-sponsored Phase III studies for multiple myeloma is Bristol-Myers Squibb's *Opdivo* (nivolumab) together with its SLAMF7 inhibitor *Empliciti* (elotuzumab) in combination with pomalidomide and dexamethasone in relapsed and refractory patients (CheckMate 602). ▶

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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 9–15 June 2017

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
Phase III Suspended			
XBiotech Inc.	<i>Xilonix</i> (anti-IL-1 antibody)	colorectal cancer	XCITE; lack of efficacy in an a US trial, but EU filing continues .
Phase III Results Published			
Novo Nordisk AS	<i>Tresiba</i> (insulin degludec) vs. insulin glargine U100	type 2 diabetes, CV outcomes	DEVOTE; NEJM, June 12, 2017 .
Vertex Pharmaceuticals Inc.	<i>Orkambi</i> (lumacaftor/ivacaftor) and <i>Kalydeco</i> (ivacaftor)	cystic fibrosis, in children with two copies of F508del mutation	<i>The Lancet Respiratory Medicine</i> online, June 9, 2017.
Adamas Pharmaceuticals Inc.	ADS-5102 (amantadine)	levodopa-induced dyskinesia	EASE LID; in <i>JAMA Neurology</i> online, June 12, 2017.
Johnson & Johnson	<i>Invokana</i> (canagliflozin)	type 2 diabetes	CANVAS; NEJM online, June 12, 2017 .
Novartis AG	<i>Zykadia</i> (ceritinib)	non-small cell lung cancer	ASCEND-5; <i>The Lancet Oncology</i> online June 8, 2017.
Updated Phase III Results			
AstraZeneca PLC	<i>Farxiga</i> (dapagliflozin)	type 2 diabetes	CVD-REAL; ongoing positive CV outcome and safety analysis.
Johnson & Johnson	<i>Simponi Aria</i> (iv golimumab)	ankylosing spondylitis	GO-ALIVE; improved symptoms.
Amgen Inc./Novartis AG	erenumab (AMG 334)	migraine prevention	STRIVE, ARISE; reduced frequency of attacks, well tolerated.
AstraZeneca PLC	<i>Bydureon</i> (exenatide) once weekly	type 2 diabetes	DURATION-7, -8; well tolerated and effective.
Eli Lilly & Co./Arteaus Therapeutics LLC	galcanezumab	episodic migraine, chronic migraine	EVOLVE-1, -2; REGAIN; reduced migraine days.
Eli Lilly & Co.	<i>Taltz</i> (ixekizumab)	psoriatic psoriasis	SPIRIT-P2; disease symptoms improved.
Phase III Completed			
UCB SA	<i>Cimzia</i> (certolizumab pegol)	ankylosing spondylitis, axial spondyloarthritis	RAPID-axSpA; benefits shown in four-year imaging study.
Sanofi/Lexicon Pharmaceuticals Inc.	sotagliflozin	type 1 diabetes	inTandem1, 2; pivotal studies showed efficacy, safety .
Novartis AG	<i>Cosentyx</i> (secukinumab)	psoriatic arthritis and axial spondylarthritis	MEASURE 1; effect sustained for two and three years.
Phase III Interim/Top-line Results			
GlaxoSmithKline PLC	tafenoquine, single dose	prevention of <i>P vivax</i> malaria	GATHER, DETECTIVE; reduced relapse risk.
Merck & Co. Inc./Pfizer Inc.	ertugliflozin, as add-on therapy	type 2 diabetes	VERTIS-MET, -SITA; met primary endpoints .
Sanofi/Regeneron Pharmaceuticals Inc.	<i>Praluent</i> (alirocumab)	dyslipidemia in diabetes	ODYSSEY DM; positive results, lowered LDL-C.
Mylan NV/Biocon Ltd.	insulin glargine, biosimilar	type 1 diabetes	INSTRIDE 1, -2; shown bioequivalent to Sanofi's Lantus.
Sanofi/Lexicon Pharmaceuticals Inc.	sotagliflozin	type 1 diabetes	inTandem3; well tolerated, positive results.
RedHill Biopharma Ltd.	<i>Bekinda</i> (ondansetron) controlled-release tabs	acute gastritis, gastroenteritis	GUARD; met primary endpoint, effective and well tolerated.
Pharmaxis Ltd.	<i>Bronchitol</i> (mannitol)	cystic fibrosis	Met primary endpoint, could underpin NDA resubmission.

Source: Biomedtracker

Pfizer/Astellas Amend Trial To Position Xtandi In Early Prostate Cancer

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Astellas Pharma Inc. and **Pfizer Inc.** have amended the protocol for the registrational PROSPER trial of *Xtandi* (enzalutamide) in patients with non-metastatic castration-resistant prostate cancer (CRPC). The companies now anticipate PROSPER's top-line results will be available later this year. Previously the expected primary completion date for PROSPER was June 2019.

If the data readout from the PROSPER trial does eventually lead to approval, this would be significant for androgen receptor signaling inhibitor Xtandi's positioning in the market in regards to its main competitor, androgen biosynthesis inhibitor *Zytiga* (**Johnson & Johnson**). Datamonitor Healthcare analyst Zachary McLellan told *Scrip*. "Potential approval up to two years earlier than anticipated is important for revenues and would give Xtandi first-to-market advantage over *Zytiga* in this patient segmentation. Both Xtandi and *Zytiga* compete for metastatic

castration-resistant prostate cancer (mCRPC) patients and a label expansion into non-metastatic patients would increase Xtandi's target patient population and better differentiate it from fellow blockbuster *Zytiga*."

The companies emphasize that the primary endpoint remains the same: metastasis-free survival (MFS). The main purpose of the amendment is to revise the plan for the analyses of the primary and several secondary endpoints, which allows for a reduction in the target sample size to around 1,440, from 1,560 patients. This should accelerate the evaluation of the data, say the companies.

With regards to the timing of the amendment, a spokesperson for Astellas told *Scrip* that the company continuously evaluates its study plans in the context of patient medical need and evolving published literature, which provides "important contextual data and progress" of the study. "In this case, we have reduced the target hazard ratio based

on recent clinical data for enzalutamide in non-metastatic and chemotherapy-naïve metastatic CRPC and believe we need fewer metastasis-free survival events (MFS) to sufficiently power the study. This amendment will not negatively impact the strength of the data, and we look forward to potentially bringing forward a new treatment option for patients with earlier-stage disease based on this trial," said the Astellas spokesperson.

"We know more now than we did when the original study was designed and initiated in 2013," Pfizer told *Scrip*. "As the understanding of prostate cancer has evolved and other trials have demonstrated the overall survival benefit of Xtandi, we have better confidence to appropriately size the trial and evolve the protocol. As a result, on the acquisition of Medivation, the Pfizer team worked with the Astellas team to identify the potential to amend the protocol and accelerate the timeline." ▶

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APPOINTMENTS

Tiziana Life Sciences PLC., a company focused on cancer and autoimmune diseases, has appointed **Kunwar Shailubhai** CEO and chief scientific officer – effective immediately. Shailubhai was previously non-executive director at the company and has 30 years of experience in R&D in gastrointestinal disorders, inflammatory diseases and cancers. He joins the company from Synergy Pharmaceuticals Inc., a company he founded and was chief scientific officer for since 2008.

Ashfield, part of UDG Healthcare Plc., has appointed **Greg Flynn** regional president of Ashfield commercial and clinical in the US and **Mick O'Leary** regional president of Ashfield commercial and clinical in Japan. Flynn was previously regional president in Japan and representative director of CMIC Ashfield and O'Leary will be taking over the role as regional president in Japan.

Ergomed PLC. has appointed **Dan Weng** CEO and a board director of the company – effective July 1, 2017. Weng will join the

Ergomed from EPS Holdings Inc., a CRO company, where he was chair, president and CEO. Weng has experience in managing CRO businesses like EPS Holdings and before this, he worked at companies including Medpace Inc., Icon Clinical Research, PharmaNet and Quintiles.

Crescendo Biologics Ltd. has appointed **Edward J. Stewart** chief business officer and joins the company from Merrimack Pharmaceuticals Inc., where he held various executive roles. Stewart led Merrimack's commercial business unit and was one of the company's first employees.

Markus L.E. Ewert joins **Ablynx NV** as chief business officer – effective June 20, 2017. Most recently, Ewert led the business development team of the healthcare division of General Electric and before this, he worked at Novartis in its cardiovascular and metabolism franchise and later transferred to the molecular diagnostics unit as head of strategy, global BD&L, and M&A.

Alexion Pharmaceuticals Inc. has named **Paul Clancy** chief financial officer – effective July 31, 2017. Clancy has spent the past 16 years at Biogen, where he was chief financial officer for the last 10 years. Before this, he spent 13 years at PepsiCo in various executive positions.

Biotech Axcella Health Inc. has appointed **Tony Tramontin** chief scientific officer and senior vice president of research & development. Tramontin brings 13 years of executive advisory experience in biopharma to the company; previously, he was a partner McKinsey & Company's Global Healthcare Practice.

John McHutchison, Gilead Sciences Inc.'s executive vice president, clinical, has joined **Oxford BioTherapeutics Ltd.**'s board of directors. With almost 20 years' experience in clinical and drug development, McHutchison previously was senior vice president, liver disease therapeutics at Gilead.

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