Scrip
Informa Pharma Intelligence
No. 3980
November 8, 2019


Paul Hudson

New Sanofi CEO's Big Priority Is Bolstering R&D

JESSICA MERRILL jessica.merrill@informa.com

Sanofi's new CEO Paul Hudson said a fundamental component of his plan to drive long-term growth at the big pharma will be bolstering the R&D engine.

"We will have to execute on the new priorities of our refocused R&D organization under John Reed with the ambition to bring first and best-in-class treatments to patients," Hudson told investors during the company's third quarter earnings call on 31 October.

Reed, the global head of R&D at Sanofi, joined the company in mid-July 2018 from Roche, succeeding longtime head of R&D Elias Zerhouni. *(Also see "Zerhouni Retires, Sanofi's New R&D Chief John Reed Brings Early Research Experience From Roche" - Scrip, 24 Apr, 2018.)*

The R&D initiative will be counterbalanced by improving cost efficiencies, Hudson added. "Even at this formative stage of thinking, I believe we can be more efficient by continuing and amplifying the cultural change in mindset on cost and cashflow management," he added.

"So where does this end up? Ultimately, my goal is for Sanofi to be an innovation leader, commercial leader, cultural leader, and one of the most important investment opportunities in the biopharma industry," Hudson said.

The third quarter financial update was the first presided over by Hudson, who took over from Olivier Brandicourt on 1 September. Given that Hudson is only about two months into the job, he didn't provide investors with any details about his strategy. More specifics will be presented on 10 December, when the company will host a Capital Markets Day in Cambridge, Mass.

Details are certainly something investors will be eager to hear more about, given the French pharma's lackluster near-term growth outlook. The third quarter financial results only underscored the need for Sanofi to develop a strategy to reinforce its growth potential.

DUPIXENT SHINES

The atopic dermatitis and asthma drug Dupixent (dupilumab) is blossoming into a mega-blockbuster, becoming critically valuable to Sanofi for offsetting declines in other parts of the business, including diabetes, vaccines and rare blood disorders. Dupixent, which Sanofi commercializes with Regeneron Pharmaceuticals Inc., generated €570m ($635.4m) in the third quarter, growth of 142% over the prior-year period. The company said it just launched a TV ad campaign to further support the launch of Dupixent in various indications.

Sanofi's diabetes sales declined 9.9%, however, to €1.26bn ($1.4bn), due to lower sales of the insulin glargine products Lantus and Toujeo in the US. Sales of diabetes drugs in the US declined 25% in the quarter. Sales of the company's PCSK9 inhibitor, Praluent (alirocumab), for high cholesterol – once expected to be a big blockbuster – declined 11.8% to €61m ($68m). Sales of Amgen Inc.'s rival drug Repatha (evolocumab) increased 40%, on the other hand, to $168m in the third quarter.

The decline in vaccines was attributed to a delay in selecting the flu strain by the World Health Organization, which is

CONTINUED ON PAGE 4

Off To A Good Start
Brisk drug launches for Vyndaqel and Skyrizi (p4 & 15)

KRAS Competition
Mirati throws its hat into this oncology ring (p20)

Q3 Reporting Season
Results from Pfizer, Amgen, GSK, Merck & Co, BMS, Chugai, Bayer and AbbVie (p4-15)

from the editor

eleanor.malone@informa.com

We have plenty of updates from the last major batch of third-quarter big pharma results in *Scrip* this week.

On a high were Merck & Co, driven by galloping sales of Keytruda and Gardasil (p8); Pfizer, with a surprisingly strong launch for the rare disease drug Vyndaqel/Vyndamax (p4); GlaxoSmithKline, upping its profit forecast after its shingles vaccine Shingrix performed well (p5); AbbVie, with healthy sales of new products in its mainstay immunology disease space helping to defend it against declining revenues of the biggest drug in the category, Humira (p15); and Roche-controlled Chugai, which has seen sales of the hemophilia A antibody Hemlibra far exceed expectations (p12).

Feeling under the weather were Bayer, whose pharma business's decent performance was overshadowed by the ongoing challenges the wider business faces as lawsuits over its Roundup weedkiller gather pace (14); Sanofi, which continues to struggle with its diabetes franchise while also failing to reap the expected returns on its acquired rare blood disease drugs (cover story); Amgen, which reported disappointing sales for two products that were once touted as likely blockbusters (Aimovig and Repatha; p6); and Bristol-Myers Squibb (p9), which is on the back foot trying to grow Opdivo and still waiting to close its acquisition of Celgene.

With new CEOs at Sanofi and Pfizer and major pending acquisitions at BMS and AbbVie we anticipate further significant strategic updates from these companies in the coming months.

Scrip
Informa Pharma Intelligence

LEADERSHIP
Phil Jarvis, Mike Ward, Karen Coleman

SUBSCRIPTIONS
Dan Simmons, Shinbo Hidenaga

ADVERTISING
Christopher Keeling

HEAD OF PUBLICATION DESIGN
Gayle Rembold Furbert

DESIGN
Paul Wilkinson

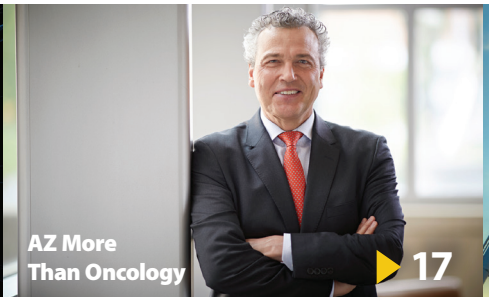
EDITORIAL OFFICE
Blue Fin Building
3rd Floor, 110 Southwark St
London, SE1 0TA

CUSTOMER SERVICES
US Toll-Free: +1 888 670 8900
US Toll: +1 908 547 2200
UK & Europe: +44 (20) 337 73737
Australia: +61 2 8705 6907
Japan: +81 3 6273 4260
Email: clientservices@pharma.informa.com

TO SUBSCRIBE, VISIT
scrip.pharmaintelligence.informa.com

TO ADVERTISE, CONTACT
christopher.keeling@informa.com

All stock images in this publication courtesy of www.shutterstock.com unless otherwise stated



exclusive online content

Sickle Cell Disease Market Snapshot: "The Time Has Come"

JESSICA MERRILL jessica.merrill@informa.com

With one new drug on the market in the US and two more pending at the US Food and Drug Administration, 2020 is positioned to be a turning point for the treatment of sickle cell disease. Patients with the devastating blood disorder, which results in acute pain crises, long-term organ damage and a shortened lifespan, have had few treatment options, but the outlook for sickle cell R&D is brighter than it has been.

"The time has come. We are at the cusp of improving the quality of life for people with sickle cell disease," said hematologist Charles Abrams, director of the blood center for patient care and discovery at the University of Pennsylvania and Children's Hospital of Philadelphia. "I'm confident that the landscape of options for treating these patients is going to change dramatically over the next couple of years."

"It's a hard question to answer, which is more important, taking care of [patient's] day-to-day pain or preventing them from dying in the long term, and the answer is they are both important," Abrams said.

It's positive news for patients – and for the drug makers that have finally developed the first of what is expected to be a wave of new treatments for SCD – after decades of failures, disappointments and a lack of investment.

Published online 31 October 2019

To read the rest of this story go to: https://bit.ly/34nBfTY

inside:

CONTINUED FROM PAGE 1

expected to result in more sales in the fourth quarter.

Meanwhile, sales in one of the company's new therapy areas, rare blood disorders, have been disappointing. Sanofi bought the hemophilia specialist Bioverativ Inc. in 2018 for $11.6bn, gaining two hemophilia drugs viewed as young and growing franchises: Eloctate (recombinant Factor VIII) for hemophilia A and Alprolix (recombinant Factor IX) for hemophilia B. *(Also see "Sanofi Builds Blood Disorder Specialty With Bioverativ Buy" - Scrip, 22 Jan, 2018.)* But the hemophilia A category has come under intense competitive pressure from Roche's Hemlibra (emicizumab). Sales of Eloctate declined 20.2% in the quarter to $162m.

Another new drug, Cablivi (caplacizumab), for the rare blood disorder acquired thrombotic thrombocytopenic purpura (aTTP), is off to a slow start, generating €20m ($22.3m) in third quarter sales in its first full quarter on the market. Sanofi gained the product with the €3.9bn acquisition of Ablynx NV in 2018, and as the first approved therapy for aTTP, Sanofi has expected it will need to build the market. *(Also see "Sanofi Genzyme's Sibold On Investing In Blood Disorders And Fending Off Rivals " - Scrip, 23 May, 2019.)*

"Our rare blood disorder franchise was the only real disappointment," Hudson said of the quarterly performance.

Altogether, the company's sales increased 1.1% to €9.5bn ($10.59 bn). The company reported net income of €2.4bn ($2.68bn), up 4.3%.

Published online 31 October 2019

Pfizer Vyndaqel Launch Surprises With An Early Burst Out Of The Gate

JESSICA MERRILL jessica.merrill@informa.com

Pfizer Inc.'s new rare disease franchise Vyndaqel/Vyndamax (tafamidis) got off to a strong start, surprising investors by generating notable revenues in its first full quarter on the market. Management had set low expectations for initial uptake of the first-in-class transthyretin stabilizer, indicated for treatment of cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis (ATTR-CM), because of low diagnosis rates.

Vyndaqel generated $79m in the US and $156m worldwide, the company reported in its third quarter financial report on 29 October, helping to fuel a stronger than expected quarter for the big pharma.

The company expects tafamidis to be an eventual blockbuster but will need to educate physicians about the disease and improve diagnosis rates to get there. There are only about 100,000 patients in the US with ATTR-CM and the diagnosis rate has been only about 1-2%.

Pfizer said it has improved on that rate since launch, with diagnosis now at 4-5%. "It is still a severely undiagnosed disease, and we have a long way to go in terms of achieving what we believe our patients deserve," biopharmaceuticals group president Angela Hwang said during the company's quarterly earnings call.

The company's focus has been two-fold: building disease awareness among physicians and building awareness of non-invasive nuclear imaging scintigraphy for diagnosis.

"We're pleased to see that to date about 90% of our diagnoses is now being driven through scintigraphy," Hwang said.

As of the end of August, approximately 4,100 new patients were diagnosed, approximately 2,600 patients received a prescription of Vyndaqel, and 1,300 patients received the drug, CEO Albert Bourla reported.

Vyndaqel and Vyndamax were approved by the US Food and Drug Administration in May, two months ahead of the FDA action date. *(Also see "Pfizer Wins Tafamidis Approval; Now It Will Need To Build The Market" - Scrip, 6 May, 2019.)* Vyndaqel 20mg capsules launched first, while Vyndamax 61mg capsules were delayed slightly to build supply. Pfizer expects to eventually transition patients to Vyndamax once sufficient supply is available since it is a single capsule dosed daily, while Vyndaqel is dosed as four capsules.

The launch of Vyndaqel started with a bang.

The early launch numbers substantially outpaced analyst consensus estimates of $21m for US revenues. Evercore ISI analyst Umer Raffat said in a same-day note that investors should expect 2020 tafamidis revenue numbers to be revised as a result of the strong start.

"For reference, Pfizer consensus has $316m and $540m in 2020 and 2021 for tafamidis in [the] US. With the current disclosure on diagnosis alone, Pfizer should track close to $1bn in US revenues," Raffat said.

Vyndaqel was just one of several drugs that turned in a strong third quarter performance for the firm. The breast cancer drug Ibrance (palbociclib) grew 25% year-over-year to $1.28bn, the rheumatoid arthritis pill Xeljanz (tofacitinib) increased 38% to $599m and the blood thinner Eliquis gained 18% to $1.03bn.

PFIZER FOCUS SHIFTING TO BIOPHARMACEUTICALS GOING FORWARD

The biopharmaceutical business grew 9% operationally; that's the business that will be the remaining company now that the consumer health care business was spun out into a joint venture with GlaxoSmithKline PLC on 31 July, and after the Upjohn off-patent business is merged into a new company with Mylan NV. *(Also see "GSK And Pfizer Assemble Consumer Healthcare Leadership Team As JV Closes" - HBW Insight, 7 Aug, 2019.)*

In the meantime, however, the loss of the blockbuster Lyrica (pregabalin) franchise to generics in July weighed on the Upjohn business (-26%), which along with the missing consumer healthcare sales resulted in a 5% decline in third-quarter revenues for Pfizer to $12.68bn.

Investors have been bracing for a challenging year for Pfizer because of the loss of Lyrica, with management forecasting roughly flat revenues in 2019 versus 2018 before cycling through the loss in 2020 and moving ahead into a period of organic growth. *(Also see "Pfizer: Time To Face The Lyrica Pain" - Scrip, 29 Jan, 2019.)*

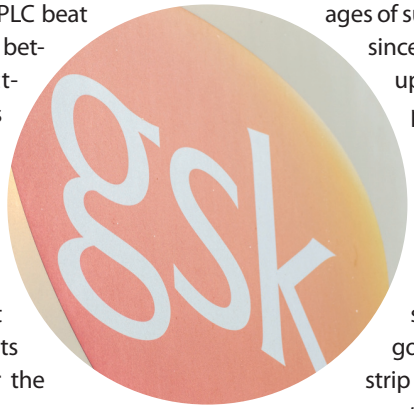
But Pfizer is in the midst of an even bigger reshaping, following the announcement in July that the company will split off its Upjohn business and merge it with Mylan to establish a top generic drug company. *(Also see "Upjohn/Mylan: Will "Potential Moderate Growth" Lure Investors?" - Scrip, 29 Jul, 2019.)* The combination is expected to be completed in mid-2020. The remaining Pfizer will be a substantially smaller, innovation-focused pharma, shaving off about $10bn in revenues from the 2019 guidance of $51.2bn -$52.2bn. *(Also see "At Pfizer, A Split A Decade In The Making" - Scrip, 29 Jul, 2019.)*

Bourla said the new Pfizer will be focused on achieving organic growth at a five-year compound annual growth rate of 6%, and will not be building through M&A. The business development strategy will be focused on enhancing the pipeline, namely Phase II or Phase III-ready assets that could drive mid- to long-term growth.

Published online 30 October 2019

GSK Says Shingrix Shortage, Oncology Push Continues

STEN STOVALL sten.stovall@informa.com



GlaxoSmithKline PLC beat forecasts with better-than-expected third-quarter results 30 October, as robust sales of its shingles vaccine Shingrix, its HIV franchise, and some older drugs allowed the UK's biggest drug maker to increase its 2019 profit forecast for the second time this year.

GSK now expects 2019 Adjusted EPS (earnings per share) to be roughly flat when measured in constant exchange rates (CER). The new guidance improves on that previously given in July of an expected decline in adjusted EPS of 3 -5% at CER.

"The new guidance reflects operating performance in the nine months, increased investment in R&D and priority assets and a lower expected effective tax rate of around 17% for the year," Emma Walmsley, who has been CEO of GSK since April 2017, told an analyst call.

Leading that performance were sales of Shingrix, a recombinant subunit adjuvanted vaccine given intramuscularly in two doses, which rose 76% in the third quarter measured in CER terms compared with the same year-ago period, reaching £535m. Shingrix sales have already hit £1.24bn in the year's first three quarters and look set to beat consensus sales forecasts of £1.52 bn for 2019 as a whole.

"Shingrix is going extremely well. This is very much a supply driven business for us, but it is a fantastic product. And we do expect it to be a material contributor to growth for the company for quite some years yet," Walmsley said.

SHINGRIX SHORTAGE

The vaccine was FDA approved in October 2017 with accelerated adoption that was backed by an efficacy rate of up to 90% in clinical trials. But the resulting heavy demand for the vaccine has caused shortages of supply. The company has since been able to speed up the manufacturing process to four months from a more typical six to nine months.

"Once we got the preferential recommendation and could see that demand was going to very swiftly outstrip supply, we did mobilize very materially … to try and increase our supply. It's very complicated to produce a vaccine," the CEO explained.

She said that efforts to bump up manufacturing capacity for Shingrix meant the company "is now expected to deliver high-teens millions of [Shingrix] doses this year, with continued improvements in supply." That represents almost a doubling of the supply created in 2018.

"All across that value chain, we've been quite successful in making that progress, which is why we were allowed to bring forward that delivery [forecast for 2019] to high teens," Walmsley said.

She added that GSK "would expect slightly more doses in 2020, but we don't expect a step change until we have that new [planned] facility in place, which we've said externally would look to be operating by around 2024."

Added pressure on global Shingrix supply will come from China, where the shingles vaccine has been approved by the National Medical Products Administration (NMPA) for the prevention of shingles (herpes zoster) in adults aged 50 years or older.

Introduction of the vaccine into China will be phased, starting in 2020, to ensure consistent and reliable supply to all countries in which it has been launched, the company said. Shingrix is licensed for use in the US, EU, Canada, Japan and Australia.

ONCOLOGY PUSH

The company also used the third-quarter update to emphasize its push into oncol-

ogy, which the group underscored in late 2018 by spending over $5bn to buy Tesaro Inc. and its PARP inhibitor Zejula. *(Also see "GSK Embraces PARP Promise With Tesaro Buy" - Scrip, 3 Dec, 2018.)*

Walmsley has committed GSK to a returned emphasis on oncology – reversing course from predecessor Andrew Witty, who divested oncology assets. *(Also see "From Witty To Walmsley – The Priorities For GSK's New CEO" - Scrip, 4 Apr, 2017.)*

Luke Miels, head of the global pharma division, told analysts: "We're making rapid and material progress on building out our oncology promotional capabilities and the acquisition of Tesaro has catalyzed to this process."

"We've also rebalanced our sales force in the US and have been actively recruiting people with a great track record in oncology into key markets, and we're already seeing some of this benefit come through and expect to see this reflected in our sales performance starting from the end of this year as our refocused approach flows through." *(Also see "Walmsley: GSK Will Take Incremental Deal-Making Approach In Building Up Oncology" - Scrip, 25 Sep, 2019.)*

Miels added that "GSK's PARP inhibitor Zejula presents an important treatment option for ovarian cancer patients in the second-line maintenance setting. We're maintaining our leading position in this indication and are now focused on the opportunity to expand the reach of Zejula for women in the first-line maintenance setting through our PRIMA data which we presented at ESMO last month." *(Also see "New Front Opens in First-Line Ovarian Cancer Market: GSK's Zejula Vs. AZ's Lynparza " - Scrip, 29 Sep, 2019.)*

He said the PRIMA data "showed clear benefit" in using Zejula across all biomarker subgroups.

"We think the PARP inhibitors are an underutilized class. In the US, only 31% of patients currently receive one in the second line maintenance setting, falling to 12% first line setting. With the data presented at ESMO, I'm confident that this will change."

Published online 31 October 2019

Amgen's Q3 Sales Beat Consensus, But Two Key New Drugs Fell Short

MANDY JACKSON mandy.jackson@informausa.com

Even though Amgen Inc. continues to see sales of multiple blockbuster products decline due to biosimilar and generic competition, the company reported better than expected third quarter 2019 revenue of $5.74bn, down 3% year-over-year, but above analyst consensus of $5.62bn. However, sales of newer drugs needed to make up for declining sales of older products fell short of expectations.

Amgen's sales of Aimovig (erenumab) for migraine prevention totaled $66m, down from $83m in the second quarter, the company revealed in its third quarter earnings report on 29 October. Availability of a lower list price version of the cholesterol therapy Repatha (evolocumab) in the US resulted in a 40% year-over-year increase to $168m globally, but that was below consensus expectations of $176m. Both are still far from anticipated blockbuster sales more than a year and four years, respectively, after their US Food and Drug Administration approvals.

However, the company reported that sales of its top-selling product Enbrel (etanercept) grew 6% in the third quarter to $1.37bn globally, including $1.32bn in the US, versus consensus of $1.23bn in worldwide sales despite biosimilar competition in Europe. Increased net pricing and a favorable $60m accounting change boosted sales despite overall lower demand.

Also providing an unexpected boost to third quarter earnings, Amgen reported that the osteoporosis drug Evenity (romosozumab) – approved by the US FDA in April – exceeded forecasts with $59m in sales in its first full quarter on the market, versus consensus of $37m. *(Also see "Amgen Launches Evenity For High-Risk Osteoporosis At $21,900 List Price" - Scrip, 15 Apr, 2019.)*

The company's portfolio of biosimilar products, which generated just $19m in the year-ago quarter and jumped to $173m in the third quarter of 2019, also beat expectations with more than double the second quarter total of $82m.

AIMOVIG DECLINES AS LILLY'S EMGALITY GAINS GROUND

Aimovig's sales decline from the second quarter comes as the first-to-market CGRP inhibitor's closest competitor Emgality (galcanezumab) is gaining ground.

Eli Lilly & Co. – which markets Emgality on its own, whereas Amgen has a global partnership for Aimovig with Novartis AG – reported $48m in third quarter sales, up from $34m in the second quarter. Lilly said Emgality now has a 46% share of new-to-brand prescriptions in the CGRP market. *(Also see "Lilly's Diabetes Franchise Poised For A Shakeup As Conterno Steps Down" - Scrip, 23 Oct, 2019.)*

Without the $20m in unfavorable accounting changes that resulted in $66m in sales for Aimovig in the third quarter, Amgen's drug would have posted $86m in third quarter sales – just a $3m increase from the second quarter and still far below consensus of $102m.

"These adjustments result from a higher proportion of our paid business coming from the lower priced Medicaid population than initially anticipated," Amgen executive vice president of global commercial operations Murdo Gordon explained during the company's 29 October earnings call. "As a reminder, we reported $20m of favorable changes in accounting estimates in Q4 of 2018 demonstrating the impact on net price of early variability and source of business."

"Considering there are 4m migraine patients in the US who are eligible for CGRP treatment, Aimovig has significant potential remaining to penetrate this market," Gordon continued. "Each week approxi-

mately 7,000 patients start a CGRP therapy and to date more than 260,000 patients have been prescribed Aimovig. Additionally, the number of prescribers is consistently increasing as more than 30,000 physicians have now prescribed Aimovig since launch, including 10,000 primary care prescribers."

As of the end of the third quarter, Aimovig is the market leader with 50% of total prescriptions, he reported. Also, the percentage of prescriptions that are for paid drug versus free product given to patients whose health plans haven't yet decided to cover Aimovig has grown from 74% in the second quarter to 81% in the third quarter.

"Aimovig continues to struggle, given the multiple headwinds in the CGRP market," Credit Suisse analyst Evan Seigerman said in a 29 October note.

REPATHA MAKES SLOW GAINS, CLINCHES PCSK9 MARKET MAJORITY

Repatha also continues to struggle with reimbursement even after Amgen introduced a lower list price version of the biologic in the US in October 2018, which will be the only version available starting in 2020. The lower-cost version launched with a 60% reduced list price in an effort to make out-of-pocket costs for the drug more affordable for hypercholesterolemia patients covered by Medicare Part D plans and reduce the rate of patients abandoning the product at the pharmacy counter.

Gordon said 72% of commercial plans now require only physician attestation that patients should be treated with a PCSK9 inhibitor, which is up from 23% last year. "Additionally, more plans are removing specialty pharmacy mandates, moving Repatha to more accessible retail pharmacies, which now fill a majority of Repatha prescriptions," he said. "Overall in the US, commercial approval rates increased from 39% to 59% and the abandonment rate for Medicare patients has improved meaningfully."

About half of patients covered by Medicare Part D plans can get Repatha for a copay of less than $50, but Amgen still is negotiating to improve that number. Even so, the company's efforts to date around getting more plans to cover the product at more favorable terms for patients has given Repatha a 70% share of the PCSK9 inhibitor market.

Sanofi/Regeneron Pharmaceuticals Inc.'s Praluent (alirocumab) continues to play catch-up with Repatha, including through their own price-lowering efforts for the partners' PCSK9 inhibitor.

EVENITY, BIOSIMILARS AND ENBREL SURGE AS OTHER LEGACY PRODUCTS SAG

Regarding Amgen's third-quarter boosters, Gordon noted that most Evenity sales were posted in Japan; US sales totaled $12m in the third quarter versus $47m ex-US. Evenity – approved only in the US and Japan – recently was recommended for approval in the EU.

The strong launches of Kanjinti and Mvasi, biosimilars for the Roche oncology blockbusters Herceptin (trastuzumab) and Avastin (bevacizumab), respectively, helped Amgen's $173m in biosimilars sales significantly beat consensus of $99m in the third quarter.

Payers and prescribers in the US have been especially receptive to the idea of lower-cost versions of commonly used cancer drugs, with important reimbursement decisions in Amgen's favor from major payers, such as UnitedHealthcare.

> "Aimovig continues to struggle." – Credit Suisse

"Our global sales are already annualizing at approximately $700m with the adoption of Kanjinti and Mvasi in the US and continued growth of Kanjinti and [Humira (adalimumab) biosimilar] Amgevita outside the US," Gordon said.

Among Amgen's legacy products facing their own biosimilar competitors, Enbrel only has such competition in Europe, since Amgen has been able to successfully block less expensive copycats in the US. *(Also see "Amgen's Future Looks Brighter After Ruling Lifts Threat Of Enbrel Copycat " - Scrip, 12 Aug, 2019.)*

The Institute for Clinical and Economic Review (ICER) recently criticized Amgen for its Enbrel and Neulasta (pegfilgrastim) pricing alongside price increases for other big pharma blockbusters, but the company disputed the drug-pricing watchdog's net price calculations for its two products. *(Also see "Drugs With 'Unsupported Price Increases' Add $5bn To US Spending – ICER" - Scrip, 8 Oct, 2019.)*

Neulasta sales continue to decline with launches of two biosimilars for the long-acting neutropenia therapy in the US, falling 32% year-over-year to $711m globally in the third quarter versus consensus of $778m. Gordon said Neulasta has a just under 80% share of the pegfilgrastim market, helped by the on-body injector Neulasta OnPro. However, he noted, "we anticipate that additional competitors could launch in the US at some time in the future, but the timing is uncertain."

Sales of the secondary hyperparathyroidism drug Sensipar (cinacalcet) have been hit by at-risk launches of generics in the US this year, falling 73% year-over-year in the third quarter to $109m versus consensus of $122m. *(Also see "Amgen Fails To Block Cipla's Generic Cinacalcet In US, And It May Change How Patent Settlements Are Drafted " - Pink Sheet, 6 May, 2019.)*

OTEZLA, KRAS AND OTHER POTENTIAL GROWTH DRIVERS

Amgen has been in cost-cutting mode over the last several years to operate more efficiently in anticipation of biosimilars for its blockbusters while at the same time trying to make its R&D pipeline more productive and attempting to grow through acquisitions.

The company's $13.4bn purchase of the multibillion-dollar psoriasis and psoriatic arthritis pill Otezla (apremilast) from Celgene Corp. – helping reduce anti-competition regulators' scrutiny of Bristol-Myers Squibb Co.'s $74bn acquisition of Celgene – is expected to close in the fourth quarter of this year. *(Also see "Amgen's $13.4bn Otezla Buy Helps Bristol/Celgene Merger Close By Year-End" - Scrip, 26 Aug, 2019.)*

Gordon noted that total product sales for Amgen's existing product portfolio will be stable in 2020, but will grow next year with the addition of Otezla.

"We will continue to invest in the growth of our business internally and through business development aligned with our stated strategy while also providing attractive returns to our sharehold-

ers through our growing dividend and continued share repurchases," Amgen CEO Bob Bradway said during the company's earnings call.

Amgen revealed that it increased R&D spending by 8% to $1bn in the third quarter and retiring chief financial officer David Meline noted that the full-year R&D spending increase will be in the high single digits as well. The company anticipates that it will have $500m in R&D spending related to new Otezla indications in 2020.

One of the closest watched assets in Amgen's pipeline is its KRAS inhibitor AMG 510, and Mirati Therapeutics Inc. reported results on 28 October for its MRTX849 that look similar to early data to date for Amgen's drug. Amgen executive vice president of R&D David Reese was asked for his opinion on MRTX849 and for news on AMG 510, but didn't provide any meaningful insights beyond the company's last updates in September. More advanced Phase I results, PD-1 combination data and an initial Phase II monotherapy readout are expected in 2020. *(Also see "Amgen KRAS Inhibitor Less Effective In Colorectal Cancer Than Lung" - Scrip, 28 Sep, 2019.)*

Elsewhere in the pipeline, Reese revealed that a Phase III study for tezepelumab in severe uncontrolled asthma has completed enrollment and data are expected in late 2020. A Phase II study in chronic obstructive pulmonary disease also is enrolling patients. The drug is being developed in partnership with AstraZeneca PLC. *(Also see "Interview: AstraZeneca 'Is More Than Oncology' " - Scrip, 28 Oct, 2019.)*

Published online 30 October 2019

Amgen's Playing To Its R&D Strengths, Which No Longer Include Neuroscience:
https://bit.ly/2Cevbkw

Amgen Joins China Oncology Market Race With $2.7bn BeiGene Stake:
https://bit.ly/2WG8grN

Merck Confident In Keytruda's Dominance In Lung Cancer, Despite Competitors' Data

JOSEPH HAAS joseph.haas@informa.com

Merck & Co. Inc.'s third- quarter revenue growth of 15% was driven largely by its cancer and vaccine portfolios, as Keytruda (pembrolizumab) notched worldwide sales of nearly $3.1bn, good for 62% growth year-over-year. The pharma told its quarterly earnings call on 29 October that it expects Keytruda to maintain its strong market-share hold in lung cancer despite positive readouts in the past week for competing immuno-oncology regimens from Bristol-Myers Squibb Co. and AstraZeneca PLC.

Overall, Merck reported sales of $12.4bn for the third quarter as its vaccines business, headed up by the HPV preventative Gardasil, grew 17% to more than $2.4bn. Gardasil posted sales of $1.32bn, up 26% from one year earlier. But the main focus by both Merck executives and analysts on the call was Keytruda, its growth prospects and the potential of competing regimens that include a CTLA-4 inhibitor in lung cancer.

Chief financial officer Robert Davis noted that Keytruda's US growth was driven by demand across all its labeled indications. "In squamous and non-squamous first-line lung, Keytruda continues to penetrate all eligible patient populations," he said. "The survival benefits demonstrated across our four first-line lung cancer trials have firmly established Keytruda as the standard of care in these settings."

Keytruda's launches in new indications are encouraging as well, the exec said. "In advanced first-line renal cell carcinoma, we are seeing strong uptake across all three patient risk groups for which we are indicated," Davis said. "And in adjuvant melanoma, the positive momentum continues since our approval earlier this year." *(Also see "Keeping Track: US FDA Approves Esperoct, Tightens Chantix Label, Starts Review Of Alder's CGRP Candidate " - Pink Sheet, 24 Feb, 2019.)*

For the first nine months of 2019, Keytruda sales totaled $7.97bn globally, up 59% from the $5.02bn posted during the first three quarters of 2018. Outside the US, Keytruda sales rose 75% during the third quarter, with lung cancer again the driver, Davis said.

BMS caught attention on 22 October with its announcement that its Checkmate-9LA study had demonstrated that combination therapy with its anti-PD-1 agent Opdivo (nivolumab) and its CTLA-4 inhibitor Yervoy (ipilimumab) plus two cycles of chemotherapy offers a better overall survival benefit than chemotherapy alone in first-line non-small cell lung cancer. *(Also see "An Early Surprise Win For BMS's Opdivo/Yervoy In Lung Cancer" - Scrip, 22 Oct, 2019.)* Like the earlier Checkmate-227 data, which showed the combo's potential in the first-line setting as a chemo-free option, BMS is hoping these data may help boost sales of Opdivo, which was the top-selling IO drug before Keytruda passed it (*see chart*).

Another potential shot across Keytruda's bow came on 28 October, just one day before Merck's earnings call, AstraZeneca reported that the POSEIDON study, testing its PD-L1 inhibitor Imfinzi (durvalumab) with its experimental CTLA-4 inhibitor tremelimumab, met its primary endpoint of progression-free survival in first-line NSCLC. *(Also see "POSEIDON Delivers For AstraZeneca's Imfinzi, But More Clarity Is Needed" - Scrip, 28 Oct, 2019.)*

MERCK CONFIDENT IN ITS DATA, REAL-WORLD EXPERIENCE

Merck Research Laboratories president Roger Perlmutter told the earnings call that while Merck has long anticipated that other companies will try to demonstrate utility in first-line NSCLC, "the set of studies that we have already performed provide an enor-

mously strong foundation for the treatment of non-small cell lung cancer."

He also addressed speculation of whether Merck's ongoing study combining Keytruda with BMS' Yervoy could offer a new avenue for both companies.

"All of us are eager to understand whether anything else could be added to Keytruda," Perlmutter said. "But thus far, we don't really have any data that supports that. Our own study, our [KEYNOTE-598] study with Keytruda and ipilimumab will provide, we hope, definitive information on whether [that combination] actually improves results as compared to what it seen with Keytruda alone. Thus far, it's kind of a mixed bag from what we can see."

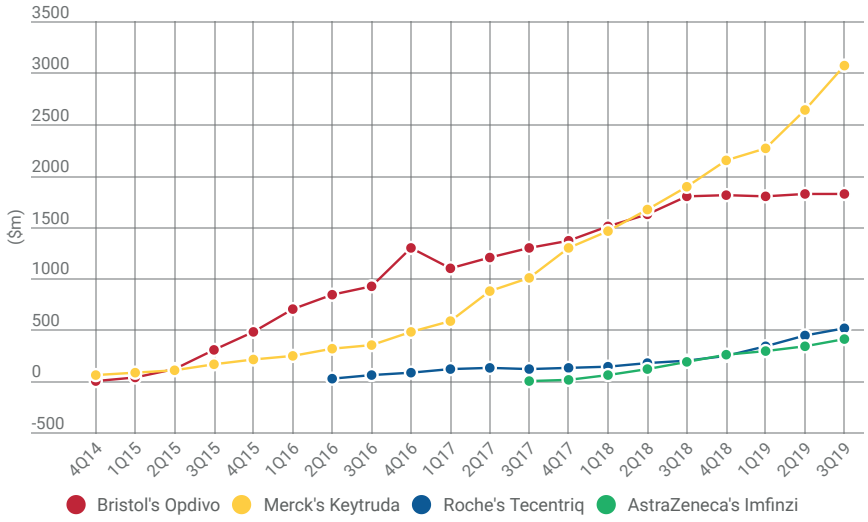
He added that without numerical data from the Checkmate-9LA and POSEIDON studies – which have only reported topline results so far – Merck can't really compare those regimens to Keytruda. Both trials are expected to be presented at upcoming medical meetings.

The KEYNOTE-598 study isn't slated to read out until 2023, although Merck also has its own CTLA-4 antibody, MRK-1308, in Phase I.

Merck's chief commercial officer Franklin Clyburn emphasized Keytruda's standing in the US as the standard of care in first-line NSCLC. "Approximately eight out of every 10 eligible patients are receiving a Keytruda regimen, either a monotherapy or in combination," he said. "And what we're hearing from both the academic community … and the community physicians is that they really believe Keytruda has now established itself as a standard of care in lung.

"I think also, importantly, we have to note that there's significant real-world experience based on our first-mover advantage with Keytruda in lung," Clyburn continued. "So, while we know it'll be eventually competitive in this space, we feel very confident in our position."

Sales Of PD-1/L1 Inhibitors



ANALYSTS TAKE "WAIT AND SEE" STANCE ON COMPETITOR STUDIES

SVB Leerink analyst Daina Graybosch questioned in a 29 October note how much of a threat the competitor trials pose for Merck right now. "Feedback from our August survey of medical oncologists treating NSCLC suggests an all immuno-oncology regimen (such as Opdivo + Yervoy) could have utility in patients that cannot tolerate chemotherapy, which could be a niche for the combination," she wrote. She added however, "Keytruda currently has a roughly 80% share of the first-line NSCLC market in the US, and we agree with Merck that this lead will be difficult to dislodge given the high barriers [that] physician familiarity and real-world experience provide."

Morningstar analyst Damien Conover concurred in a same-day note: "We are skeptical that the forthcoming detailed data behind the [BMS and AstraZeneca] studies will provide strong enough data to displace Merck's entrenchment."

Published online 30 October 2019

BMS Projects Opdivo Sales Will Grow Again In 2021

MANDY JACKSON mandy.jackson@informausa.com

Bristol-Myers Squibb Co. is optimistic that one-time PD-1 inhibitor market leader Opdivo (nivolumab) can return to growth in 2021 now that its Opdivo/Yervoy (ipilimumab) combination has delivered positive overall survival results in two first-line lung cancer studies, the company said during its 31 October third quarter earnings call.

But even with Opdivo sales flattening out due to competition from Merck & Co. Inc.'s anti-PD-1 drug Keytruda (pembrolizumab) in first-line non-small cell lung cancer (NSCLC), BMS's third quarter sales of $6bn exceeded analyst consensus of $5.9bn, driven by growth in the rest of its portfolio. The company said its $74bn acquisition of Celgene Corp., whose same-day third quarters earnings report also beat consensus, is on track to close before the end of 2019, which will help BMS diversify beyond Opdivo and its top-selling drug, the blood thinner Eliquis (apixaban).

"We now have a second trial demonstrating an overall survival benefit for the combination of Opdivo plus low-dose Yervoy in a first-line lung cancer population regardless of PD-L1 status or histology," CEO Giovanni Caforio said at the start of BMS's call. "With the results of both CheckMate-9LA and -227, coupled with the strength of our commercial capability, I feel good about our ability to maximize the opportunity we see in the first-line lung cancer market."

Caforio said the CheckMate-227 study showed that a dual immuno-oncology (IO) agent approach to first-line NSCLC "offers a unique potential for long-term survival in first-line lung cancer,"

providing the depth and durability of response that physicians have said is important – and a chemo-free option. *(Also see "BMS Ready To Pounce On Non-Chemo Opportunity In Lung Cancer With Checkmate-227 Data" - Scrip, 25 Jul, 2019.)*

"We also know that due to rapidly progressing disease, some first-line lung cancer patients need chemotherapy," the CEO said. "A key question for the CheckMate-9LA study was to determine whether a limited amount of chemo – two cycles – would be enough to stabilize the disease for those patients and manage the early part of the curve, allowing for the potential durability of effect of dual IO."

While BMS did not provide any new details about the top-line results from its interim analysis of CheckMate-9LA, first disclosed on 22 October, Caforio said Opdivo and low-dose Yervoy plus two cycles of chemotherapy "demonstrated a meaningful overall survival benefit."

The company will present the study at an upcoming medical meeting, but not until next year. There was no update during the earnings call about when BMS will submit the CheckMate-227 and -9LA data to regulators, but Caforio said the company will share the findings with health authorities soon.

Without approval to treat first-line NSCLC, Opdivo's sales growth has fallen flat over the last five quarters at around $1.8bn, while Keytruda has surged, surpassing BMS's drug since the second quarter of 2018. Merck recently reported $3.1bn in third quarter 2019 sales, up 62% year-over year. *(Also see "Merck Confident In Keytruda's Dominance In Lung Cancer, Despite Competitors' Data" - Scrip, 29 Oct, 2019.)*

Keytruda and Roche's PD-L1 inhibitor Tecentriq (atezolizumab) are facing competition in the first-line NSCLC setting not only from Opdivo, but from AstraZeneca PLC's Imfinzi (durvalumab) after the anti-PD-L1 therapy recently showed positive progression-free survival results in combination with the company's CTLA-4 inhibitor tremelimumab in the POSEIDON study. *(Also see "POSEIDON Delivers For AstraZeneca's Imfinzi, But More Clarity Is Needed" - Scrip, 28 Oct, 2019.)*

DEFENDING OPDIVO IN CURRENT INDICATIONS

Chief financial officer and head of global business operations Charles Bancroft told BMS's earnings call that "our US commercial team continues to execute very well, maintaining strong [Opdivo] share in key indications. As expected, we continue to see the size of the eligible pool of second-line lung patients declined during the quarter. This trend has been in line with our projections, and we continue to expect it to level off towards the end of this year."

In first-line renal cell carcinoma (RCC), Bancroft said, "we continue to perform well where Opdivo/Yervoy remains a standard of care in intermediate and poor risk patients. As we've described in the past, [tyrosine kinase inhibitor (TKI)]/IO combinations are expanding the use of IO, mainly at the expense of TKI monotherapy. However, as we mentioned in Q2, there has been some attrition of new patient share for Opdivo/Yervoy."

Executive vice president and chief commercialization officer Christopher Boerner added that Opdivo's RCC market share is holding steady at about 30%-35% in the first line and 36% in the second line.

Q3 Global Product Sales

Opdivo $1.82bn, up 1% year-over-year

Eliquis $1.93bn, up 22%

Orencia (abatacept) $767m, up 14%

Sprycel (dasatinib) $558m, up 14%

Yervoy $353m, down 8%

Empliciti (elotuzumab) $89m, up 51%

Baraclude (entecavir) $145m, down 17%

Other established brands $539m, down 35%

"We do see that decline in the eligible pool [of patients] in second-line as a result of first-line dynamics," Boerner noted. "But I think there's one thing to keep in mind in renal that's different from, for example, lung cancer at least as of to date, and that is in the renal cell market while you see a decline in eligibility in second line, you also see Opdivo-plus-Yervoy playing a role in the first-line setting. And obviously, at least right now, that's not the case in non-small cell lung cancer."

LOOKING TO THE FUTURE IN FIRST-LINE LUNG

Given the competitive dynamics in the US and the timing of BMS's regulatory submissions in first-line NSCLC based on CheckMate-227 and -9LA, Boerner said, "we do still see Opdivo under pressure in 2020."

"However, as we've said consistently, the trajectory of growth beyond 2020 is going to be dependent upon new indications," he continued. "And based on the data readouts we've seen thus far and the continued very strong execution of our commercial teams, we feel pretty good about returning to growth in 2021."

Morningstar analyst Damien Conover said in a same-day note that Opdivo sales are likely to fall in 2020 as the second-line NSCLC market continues to shrink due to the efficacy of Keytruda in the first line.

"We expect BMS's combination of Opdivo plus Yervoy to gain approval in first-line NSCLC in 2020 based on positive data in CheckMate-227 and -9LA, but unless detailed data from 9LA shows significantly better data than Keytruda, we continue to believe BMS will only penetrate about 10% of the metastatic NSCLC market. Outside NSCLC, we expect BMS's immuno-oncology platform to perform well in melanoma and renal cancer."

Boerner noted that there still is a lot of significant unmet need in the first-line lung cancer setting, based on conversations with doctors who say there's considerable need for additional treatment options, such as a dual IO regimen like Opdivo/Yervoy, including for patients that don't want chemotherapy and in combination with a short course of chemo.

The executive noted that Opdivo's growth trajectory "will continue to be a function of additional data readouts in the metastatic setting. Those include [CheckMate-9ER] in first-line renal, CheckMate-648 in first-line esophageal and first-line gastric

TURN TO PAGE 12

Scrip Awards
Finalists 2019

Scrip Awards
Informa Pharma Intelligence

Business Development Team of the Year

This Award will honor the achievements of business development teams whether they are from a pharma or biotech company or a cross-company team responsible for a specific deal.

ASTRAZENECA'S BUSINESS DEVELOPMENT OPERATIONS TEAM

This relatively small and specialised team exceeded its performance targets and completed multiple strategically important deals in a short period of time. The BDO team led on transactions which were important milestones towards AstraZeneca's long-term aspirations. The collaborations with Innate Pharma and Daiichi Sankyo were key elements towards consolidating AstraZeneca's position as a science-focused leader in oncology.

BEIGENE BUSINESS DEVELOPMENT TEAM

In the 12 months, BeiGene's BD team secured five unique partnerships, among which the multifaceted partnership with Zymeworks was the most distinctive achievement for the company. The "three-in-one" structure of the deal gave BeiGene access to two programs and technology platforms to develop and commercialize up to three bispecific antibody therapeutics. Additionally, BeiGene partnered with BioAtla, MEI Pharma, and SpringWorks.

BRISTOL-MYERS SQUIBB'S BUSINESS DEVELOPMENT TEAM

This team broadly impacted the organization through a number of transactions, but most notably through the acquisition of Celgene in one of the largest pharmaceutical transactions ever. This deal required a comprehensive search across 20 potential transformational opportunities, continuous Board and executive leadership involvement throughout the process, and an extensive six-month deep-dive analysis and confidential cross-functional due-diligence.

CLINIGEN'S CORPORATE DEVELOPMENT TEAM

Clinigen's corporate development team achieved five significant deals during the 12 months, each contributing to the expansion of Clinigen's geographical and patient reach, infrastructure and the acquisition of important oncology drugs which will be revitalized and made more accessible to those who need them. While delivering these deals, Clinigen continued to meet its earnings expectations and its share price grew by 20%.

PROCTER & GAMBLE'S BUSINESS DEVELOPMENT TEAM

This team successfully negotiated the P&G acquisition of Merck Consumer Health providing P&G with all the capabilities it lost with the dissolution of the PGT Healthcare Partnership between P&G and Teva. It also gained a fast-growing portfolio of brands that offered P&G accelerated OTC growth, a stronger geographic footprint and a more balanced portfolio. The PGT agreement also enabled the transfer of several Teva OTC regulatory experts to P&G.

SERVIER'S GLOBAL BUSINESS DEVELOPMENT AND LICENSING TEAM

At the end of 2017, Servier's president Olivier Laureau committed the company to entering the US market as part of its ambition to become a key player in oncology. With the BD team in the vanguard, Servier acquired Shire's oncology portfolio for $2.4bn, after a rapid transaction codenamed "Project Hurricane." Today, thanks to the team, Servier is embedded in Boston's Seaport, serving patients in the US and worldwide.

Financing Deal of the Year

This Scrip Award seeks to reward successful and creative fundraising by pharma and biotech companies.

ALLOGENE THERAPEUTICS' $372.6M IPO

After completing a series A financing and subsequent financing totaling $420m, in October 2018, Allogene went public in the second largest initial public offering in biotechnology that year, raising $372.6m in gross proceeds, just six months after the company was launched. Allogene is using the proceeds to advance the clinical and preclinical development of its portfolio of allogeneic chimeric antigen receptor T-cell (AlloCAR T) therapies.

ARTIOS'S $84M SERIES B FINANCING

Cambridge-based Artios Pharma's significantly oversubscribed series B round in August 2018 raised $84m from both financial and corporate venture investors, and followed a $36m series A in September 2016. Artios is now a leader in next-generation DNA damage response therapies, developing a pipeline of three promising new products in a field that has been clinically validated by the success of PARP inhibitors.

CAMBRIDGE INNOVATION CAPITAL'S £150M FUNDING ROUND

The venture capital investor Cambridge Innovation Capital completed a funding round of £150m in April 2019, bringing the total amount of capital raised since its foundation in 2013 to £275m. The financing was one of the largest private financing rounds in Europe this year and more than doubles the resources available to CIC. The funds will be used to support CIC's portfolio of 25 companies.

GALAPAGOS'S $345M SECONDARY FOLLOW-ON FINANCING

Galapagos raised $345m in gross proceeds from a secondary follow-on financing transaction on 12 September 2018, in line with its financing goal of raising an additional year of R&D spend, following announcement of first and very positive Phase III results with its lead program filgotinib. The transaction was completed in seven hours, at a price 29% higher than the previous fundraising.

ITEOS THERAPEUTICS' $75M SERIES B FINANCING

In June 2018 Belgium-based iTeos Therapeutics completed an oversubscribed $75m million (€64m) series B financing led by US venture capital firm MPM Capital, with participation from new and existing investors. The funding enabled iTeos to advance several promising programs, including taking its adenosine A2A antagonist EOS100850 into the clinic and its expansion into its new US offices in Cambridge, MA.

SENSYNE HEALTH'S £60M IPO

In August 2018, the UK-based clinical AI company Sensyne Health completed its IPO, raising £60m with an initial market cap of £225m. It has since signed collaboration agreements with partners including Bayer and the University of Oxford's Big Data Institute. The funds are also helping to progress the commercial roll-out of its digital health software products into the NHS and beyond.

To find out more about attending the Scrip Awards, visit www.scripawards.com

CONTINUED FROM PAGE 10

cancer from CheckMate-649. All of those will read out in 2020. And then we also expect to see adjuvant programs to begin to read out in 2021," including bladder, melanoma, gastric and neoadjuvant lung cancer.

CELGENE DEAL SOON WILL DIVERSIFY BMS PORTFOLIO

While growth for Opdivo is key to increasing BMS's revenue over the long term, so is diversification of the company's overall commercial portfolio, which will grow significantly next year after the acquisition of Celgene closes at the end of this year. Right now, BMS depends heavily on Opdivo and Eliquis, which accounted for 63% of the company's Q3 sales.

Celgene is in a similar situation as the multiple myeloma therapy Revlimid (lenalidomide), which may face generic competition in 2022, was 62% of the company's $4.52bn in third quarter revenue; the total exceeded analyst consensus of $4.41bn. However, sales of Revlimid as well as other key Celgene products grew significantly in the quarter, giving BMS multiple new sources of revenue in 2020 and beyond.

Revlimid sales rose 13.1% year-over-year to $2.77bn in the third quarter, while Otezla (apremilast) surged 26.6% to $547m. BMS will sell Otezla to Amgen Inc. to satisfy anti-competition regulators' concerns about BMS's psoriasis portfolio and the company will use its proceeds from the $13.4bn transaction to pay down debt related to the Celgene acquisition. *(Also see "Amgen's $13.4bn Otezla Buy Helps Bristol/Celgene Merger Close By Year-End" - Scrip, 26 Aug, 2019.)*

Celgene also reported that sales of its other multiple myeloma therapy, Pomalyst (pomalidomide), jumped 29.4% to $664m in the third quarter and its branded chemotherapy drug Abraxane (nab-paclitaxel) posted a 10.4% increase to $318m globally.

Both BMS and Celgene said their merger is on track to close this year, with the Otezla disposition closing soon thereafter, now that the European Commission has signed off on the deal. US Federal Trade Commission clearance is the last major action needed before completing the transaction.

Celgene investors will receive a contingent value right (CVR) when the deal closes that will give them an additional $9 per share upon US Food and Drug Administration approval of the company's ozanimod for multiple sclerosis and lisocabtagene maraleucel (liso-cel; JCAR017) for lymphoma by 31 December 2020, and bb2121 for multiple myeloma by 31 March 2021.

In its third quarter report, Celgene noted that the US FDA accepted the new drug application (NDA) for the S1P receptor modulator ozanimod and set a 25 March 2020 action date. Meanwhile, a biologic license application (BLA) submission for the CD19-targeting chimeric antigen receptor T-cell (CAR-T) therapy liso-cel in third-line relapsed or refractory large B-cell lymphoma is on track for the fourth quarter of 2019.

A BLA submission for the CAR-T therapy bb2121 targeting B-cell maturation antigen (BCMA), developed in partnership with bluebird bio inc., is expected in the first half of 2020. New and updated results for an additional BCMA-targeting CAR-T, bb21217, and for liso-cel will be presented at the American Society of Hematology annual meeting 7-10 December in Orlando, FL.

"Key investor questions these days are related to the CVR and whether CELG/BMY can meet the deadlines with sufficient time and/or if there are any risks around each of the approvals," Jefferies analyst Michael Yee said in a note to Celgene investors. He noted that each of the approvals needed for the CVR payout are likely to come through well ahead of each candidate's deadline under the deal.

Published online 31 October 2019

Chugai Ups Forecast On Star Performer Hemlibra

IAN HAYDOCK ian.haydock@informa.com

After reaching record levels in the first nine months, Chugai Pharmaceutical Co. Ltd. says it now expects consolidated revenues to reach JPY680.0bn ($6.25bn) in calendar 2019, JPY87.5bn ahead of its original forecast and 15% up on the previous year.

It would be the first time for Roche's majority-owned Japanese affiliate to exceed the JPY600bn mark, and "this is our first revision to the forecast in eight years," chief financial officer Toshiaki Itagaki told a results briefing in Tokyo on 24 October.

The stronger sales performance is also seen flowing through to profit, where the company is now giving guidance for core operating profit of JPY218.0bn, JPY75.0bn higher than the January expectation and a whopping 52% ahead of the actual 2018 figure.

Group revenues in the nine months ended 30 September surged by 19% to JPY508.9bn, while operating and net profit rocketed by 64% to JPY160.9bn and by 66% to JPY117.4bn. As well as the higher sales, a big 81% increase in royalties and other operating income, mainly from Roche, to JPY68.4bn pushed up operating profit.

MOSTLY ABOUT HEMLIBRA

The growth story was mostly about Hemlibra (emicizumab), and Roche's global sales of the bispecific anti-Factor IXa/X antibody

TURN TO PAGE 14

Scrip Awards
Informa Pharma Intelligence

Book a Table

The 15th Annual Scrip Awards

4 December 2019 | London Hilton on Park Lane, London

www.scripawards.com

General Enquiries:
Lisa Anderberg | Tel: +44 (0) 20 7551 9560 | Email: lisa.anderberg@informa.com

Sponsorship and Table Booking Enquiries:
Christopher Keeling | Tel: +44 (0) 20 3377 3183 | Email: christopher.keeling@informa.com

CONTINUED FROM PAGE 12

for hemophilia A "are dramatically exceeding our expectations," Itagaki said. While the rheumatoid arthritis antibody Actemra (tocilizumab) still accounts for most of Chugai's sales to Roche, on the same basis Hemlibra should rise by 44% in the year to JPY3.3bn, versus JPY3.1bn in the nine months.

The drug is now approved in major markets for use in patients either with or without Factor VIII inhibitors and was one reason why Roche recently raised its own outlook for the year.

In Japan, Itagaki noted that prescription switching in both type of patients had exceeded the original types forecast, driving Hemlibra sales in this market (where it was launched in May 2018) to JPY16.8bn in the nine months. JPY25.1bn is now expected for the year, almost twice Chugai's internal forecast in January.

The overall nine- and 12-month figures were also helped by lower than expected costs during the year for the firm's planned $1bn-plus investment in a new Life Science Park in Yokohama and a bump in sales before the introduction of a higher (10%) general consumption tax in Japan from 1 October.

Itagaki told the briefing that the strong performance this year is also prompting Chugai to look at whether "we need to revisit the target of high single-digit CAGR [compound annual growth rate] for core EPS [earnings per share]" under the current IBI21 mid-term business plan.

Any change would be announced in the early part of next year after the annual figures come in. Reflecting the global success of Hemlibra, royalty and profit-sharing income for the year is forecast to surge by 207% to JPY74.0bn.

There was much analyst interest at the briefing over Chugai's supply price for Hemlibra, the Japanese firm disclosing that, starting next year, it would move from its "initial" (lower) supply price to an "ordinary" one.

In the meantime, the risk of a supply injunction from a patent infringement lawsuit in Japan related to emicizumab (now settled in favor of Chugai) had also caused shipments to Roche to be brought forward, Itagaki said.

BIOSIMILAR, PRICING CLOUDS ON HORIZON

In the nine months, Japanese sales were still led by multi-indication cancer drug Avastin (bevacizumab), which logged JPY73.0bn (+5%) in the period but is expected to be flat for the year. "We benefited from the delay in the launch [in Japan] of a biosimilar from our assumption," the CFO said.

Also on the domestic market, the threat of an anticipated reimbursement repricing – triggered by stronger than government-forecast sales – is hanging over Actemra. But this now looks to come later than first expected, towards the end of the year at the earliest.

In the meantime, the oral ALK inhibitor cancer drug Alecensa (alectinib) is strong globally through Roche and may be listed for reimbursement in China, which should improve uptake there.

Looking further ahead to next year, Itagaki conceded the Japanese business expects to see more "headwinds", coming from more general pricing reforms and the possible price recalculations.

Biosimilars are already approved in Japan for Rituxan, Herceptin and Avastin, and may begin to bite more next year, when the first generic version of osteoporosis drug Edirol (eldecalcitol) may also be launched.

For the business outside Japan (mainly comprising exports to Roche) "we assume the current positive trend will continue for some time," the executive said. "We think Actemra has not peaked yet globally."

Published online 28 October 2019

Roundup Lawsuits Overshadow Pharma Growth At Bayer

KEVIN GROGAN kevin.grogan@informa.com

The promising performance of Bayer AG's pharmaceuticals business in the third quarter has once again been put in the shade by a steep rise in the lawsuits the German group is facing over its glyphosate-based weedkillers such as Roundup.

Pharma sales rose 5.9% to €4.35bn, with the anticoagulant Xarelto (rivaroxaban) contributing €1.03bn of that, representing a jump of 10.8% from the third quarter of 2018. The drug is selling particularly well in China, where it is on the country's National Drug Reimbursement List, and Russia, while revenues in the US, where Xarelto is marketed by Johnson & Johnson, exceeded the level of the third quarter last year.

The firm's other big earner is the eye drug Eylea (aflibercept), sales of which increased 18.3% to €541m. Bayer chairman Werner Baumann said the drug was doing particularly well in the UK and Germany, with Japan also contributing to the rise.

Bayer under pressure as Roundup lawsuits soar.

A strong performance in China also drove growth for the colorectal cancer, gastrointestinal stromal tumors and hepatocellular carcinoma drug Stivarga (regorafenib), which shot up 36.4% to €105m. On the negative side, strong competition in the US meant that the old multiple sclerosis treatment Betaferon/Betaseron (interferon beta-1b) showed another marked decline, down 16.5% to €111m.

Addressing the question of how sustainable growth in China will prove, Bayer's pharmaceuticals chief Stefan Oelrich said he expected continued strong sales of most of the firm's major brands there. Much will depend on how Bayer fares in the next round of volume-based procurement contracts in China, he added, saying "we have a few products that could be eligible for the list…if we get on, we'll have to see how our bidding strategy is going to be."

CONFIDENCE IN EYLEA

Eylea is facing competition from Novartis AG's Beovu (brolucizumab), which won approval from the US Food and Drug Administration for wet age-related macular degeneration earlier this month. Oelrich said that "this is an interesting one because they have to go up against the standard that we've established with Eylea which is really hard to beat."

He cited the "slightly different type of label" of Beovu compared with Eylea on side effects, saying that "when you consider that an ophthalmologist probably sees about 60 to 100 Eylea patients per month and you have a side effect profile that gives you 5% or so in unpleasant side effects, then I would say this is significant…and we feel quite confident that we can handle this."

Bayer did not say anything about the recent US launches of the prostate cancer drug Nubeqa (darolutamide) and the tissue-agnostic therapy Vitrakvi (larotrectinib). However, Oelrich said the company was pleased with the launch of Jivi, its longer-acting Factor VIII therapy for hemophilia A.

The hemophilia A space is a busy one which has been transformed by the arrival of Roche's Hemlibra (emicizumab). Oelrich noted that "we were predicted to come into really heavy weather but what we're seeing…is that Jivi is hitting a nerve in the market and that we are serving the needs of our customers." Bayer noted that studies on an investigational hemophilia drug, an anti-tissue factor pathway inhibitor (TFPI) therapy codenamed BAY 1093884, have been terminated over safety concerns.

NO ROUNDUP RELIEF

The company's media call was dominated by the controversy surrounding the glyphosate-based weedkillers that Bayer got hold of through its $63bn acquisition of Monsanto Co. last year.

Baumann confirmed that the number of plaintiffs alleging a link between the weedkillers and cancer had leapt to 42,700 by 11 October, up from 18,400 plaintiffs as of 11 July 2019. He claimed that the increase "is clearly driven by a substantial surge in anti-Roundup advertising spend from the plaintiffs' side….they are estimated to have spent over $50m on TV advertising alone in the third quarter. That's roughly twice as much as in the entire first half of this year."

Baumann argued that "the number of lawsuits tells us nothing about their merits" and reiterated Bayer's stance that "we will vigorously defend ourselves in any future cases. We remain convinced of the safety of glyphosate-based products, as do all the leading regulatory bodies worldwide."

He concluded by saying that the Leverkusen-headquartered group was "constructively engaging in the mediation process" ordered by a judge in California "with a view to finding a solution." Noting that the negotiations are confidential, Baumann added "it is clear that Bayer will only accept a mediation outcome that is financially reasonable and is structured in a way that will bring the matter to a reasonable conclusion."

Bernstein analyst Wimal Kapadia said in a note on 30 October he thought that "a settlement is the most likely and beneficial outcome for investors." Its survey in August suggested that investors are expecting a $12bn settlement figure or $650,000 per plaintiff, although he said "the figure will unlikely be this high for the new number of cases."

Published online 30 October 2019

Skyrizi Launch Skyrockets, Boosting AbbVie Hopes For Humira Successors

JOSEPH HAAS joseph.haas@informa.com

Third quarter 2019 was one of balance for AbbVie Inc. as a continued strong launch for Skyrizi, good early uptake of Rinvoq, ongoing US sales growth for Humira and steadily rising sales for its hematological cancer franchise offset Humira's revenue decline in Europe due to biosimilar competition.

The Chicago-area firm reported quarterly net revenues of $8.5bn on 1 November, up 3% year-over-year, as its two new immunology drugs and its hematology products more than made up for a 33.5% decrease in ex-US sales of Humira (adalimumab) – bringing in a combined $1.6bn against a loss of $529m in adalimumab sales.

AbbVie also said its planned merger with Allergan PLC remains on track for closing during the first quarter of 2020. *(Also see "Deal Watch: Another Delay For Roche/Spark, While FTC Ups AbbVie/Allergan Merger Scrutiny" - Scrip, 3 Oct, 2019.)* The pharma recently informed the US Federal Trade Commission that it will divest Allergan's Phase III Crohn's disease candidate brazikumab and cystic fibrosis drug Zenpep (pancrelizumab) to facilitate the transaction.

AbbVie chairman and CEO Rick Gonzalez described the Skyrizi (risankizumab) performance as "well above recent launch analogs in the psoriasis category," as the IL-23 inhibitor posted sales of $91m during the third quarter. The drug brought in $48m during the second quarter, its first full quarter on the market. *(Also see "AbbVie's Five Biggest Priorities, Apart From Allergan" - Scrip, 26 Jul, 2019.)* SVB Leerink analyst Geoffrey Porges, hailing AbbVie's "solid, no-fuss quarter" in a 1 November note, said Skyrizi Q3 sales beat consensus by 25% and Leerink's projections by 47%.

Gonzalez told a same-day investor call that Skyrizi now has US commercial access above 80%, signifying a best-in-class profile, and called the product a significant, long-term growth-driver for AbbVie.

"Through the first six months on the market, we already have approximately 3,500 prescribing physicians and more than 9,000 patients treated with Skyrizi, including those in our bridge access program," the exec said. "And in this short timeframe, Skyrizi has already established its position as the leader for in-play psoriasis patient share. This includes both new patients and switching patients."

AbbVie president Michael Severino attributed the drug's fast start out of the gate partly to its duration of response, pointing to recently reported data showing that 61% of patients remain at PASI 100 (Psoriasis Severity and Area Index 100% clearance) scores after two-and-a-half years on treatment.

RINVOQ'S NICE BREAK FROM THE STARTING GATE

AbbVie's JAK1 inhibitor Rinvoq (upadacitinib) has also enjoyed quick market uptake in the US, following its 16 August approval for moderate to severely active rheumatoid arthritis. *(Also see "AbbVie's Post-Humira Strategy Continues Taking*

Shape With Rinvoq Approval" - Scrip, 16 Aug, 2019.) The therapy yielded $14m in sales during the third quarter, despite launching midway through the three-month period.

More than 1,400 Rinvoq prescriptions have been filled so far, Gonzalez said, and the therapy is capturing an estimated 6% of available market share in RA.

"After less than 90 days on the market, Rinvoq's in-play patient share has surpassed [Johnson & Johnson's] Remicade (infliximab) and several other established products and is rapidly approaching the in-play share for [Amgen Inc.'s] Enbrel (etanercept). We're also seeing very little cannibalization of Humira market share thus far," he noted.

"Commercial access is ramping strongly and in line with our expectations," Gonzalez continued. "By early January, we expect Rinvoq to have commercial access above 75%, and we expect paid prescription volume to increase significantly as this access expands over the next several months. So, while we're still early in the launch, we're certainly pleased by the feedback we received from the field, from physicians and the robust demand trends that we are seeing."

Rinvoq's market potential picture grew a bit brighter on 31 October, when AbbVie announced that the drug at both 15mg and 30mg doses met all primary and secondary endpoints in the first of two pivotal Phase III studies in psoriatic arthritis. In patients who had inadequate response to other disease-modifying therapies, the drug showed statistical significance on the primary endpoint of ACR20 response, with 57% who got the 15mg dose and 64% on the 30 mg dose achieving the endpoint at 12 weeks, compared to 24% of the placebo arm.

Severino said the pharma expects data from the second pivotal trial in PsA during the first half of 2020, with a US filing anticipating during mid-year and a launch in 2021. Rinvoq would be the second JAK1 inhibitor approved in the competitive PsA market, after Pfizer Inc.'s Xeljanz (tofacitinib). Severino pointed to PsA, axial spondylarthritis and atopic dermatitis as important potential label-expansion opportunities for Rinvoq and AbbVie's overall immunology portfolio.

POST-HUMIRA STRATEGY SEES SOLID START

Both Skyrizi and Rinvoq have both entered crowded fields and strong launches are a reassuring accomplishment for AbbVie, which has counted on the two immunology drugs to help it through the anticipated long and steady biosimilar-driven revenue erosion of Humira, already under way in Europe and expected to intensify by 2023-2024 in the US. *(Also see "AbbVie's Humira Succession Plan Begins Taking Shape With Skyrizi US Approval" - Scrip, 24 Apr, 2019.)*

Morningstar analyst Damien Conover deemed AbbVie's post-Humira strategy as off to a promising start. The ability of Skyrizi and Rinvoq, along with hematological cancer drugs Imbruvica (ibrutinib) and Venclexta (venetoclax), to offset Humira sales decreases should continue over the next two years, he wrote in a 1 November note.

"Based on strong efficacy, we expect AbbVie's next generation of immunology drugs will offset some of these Humira headwinds," he opined. "While these drugs are launching slightly behind other drugs with similar mechanisms of action, the markets are large, and AbbVie will likely leverage its strong formulary entrenchment with Humira to gain favorable positioning for its new drugs."

Humira posted global sales of $4.94bn during the third quarter, down 4% year-over-year but up 1% sequentially. US sales of nearly $3.89bn rose by 9.6% over a year earlier, but international sales of $1.05bn declined 33.5%. "International biosimilar trends and dynamics remain consistent with our expectations," Gonzalez said.

IMBRUVICA MAINTAINS STRONG POSITION IN CLL

Hematologic oncology posted unit sales of $1.48bn during the quarter, up 38% from third quarter 2018. Imbruvica sales of $1.26bn increased 29%, while Venclexta brought in $221m. During the call, Gonzalez downplayed any potential threat to Imbruvica in the chronic lymphocytic leukemia space from AstraZeneca PLC's Calquence (acalabrutinib), which posted successful Phase III data in CLL in June. *(Also see "AZ's Calquence Hits Endpoint In Second CLL Phase III Study" - Scrip, 6 Jun, 2019.)*

"Imbruvica has a strong position across multiple indications and remains the clear market-share leader across all lines of therapy in CLL," Gonzalez said. "We're especially pleased with the recent inflection in the front-line setting driven by Imbruvica's growing body of clinical evidence, label augmentation and update to treatment guidelines."

While AbbVie's post-Humira strategy is showing initial signs of success, Leerink's Porges cautioned that the pending acquisition of Allergan still is needed to grow both AbbVie's commercial portfolio and its R&D pipeline and suggested that more will be needed after that.

"Despite all these label-expansion opportunities, AbbVie's pipeline update was conspicuously lacking in important new molecular entities reaching proof-of-concept or other validating endpoints, and this situation reinforces our view that after the Allergan acquisition is bedded down, AbbVie will still need to be a net-acquirer of innovation and product opportunities," Porges said.

Morningstar's Conover, however, offered a more glowing take. "We continue to view [AbbVie] as undervalued, with the market not likely fully appreciating its next-generation immunology and cancer drugs," he concluded.

Published online 1 November 2019

Interview: AstraZeneca 'Is More Than Oncology'

STEN STOVALL sten.stovall@informa.com

While clearly enjoying the rewards of its strengthening oncology portfolio, AstraZeneca PLC also used its third-quarter results update 24 October to stress that its two other therapeutic pillars – respiratory and CVRM – are performing well and hold great promise.

Ruud Dobber

"Yes, we are very proud of our oncology performance at AstraZeneca, but equally we're trying to signal that AstraZeneca is much more than oncology and that we have an incredible pipeline, both in respiratory and CVRM (cardiovascular, renal and metabolism)," said Ruud Dobber, who heads the UK group's biopharmaceuticals operations. "And that's by purpose, because we don't want to be too dependent on one therapeutic area. That strategy is working out nicely," he said in an interview.

This year's third quarter "was one of the busiest periods in our pipeline, with four regulatory approvals in biopharmaceuticals, and the release of eight major Phase III studies," Dobber noted.

The double-barreled biopharmaceuticals business now generates 41% of AstraZeneca's total revenues. In the year's first nine months, CVRM sales grew 14% year-on-year while respiratory sales advanced 13%.

"This business is growing at double digits, which is not always a given for products like these," he said.

"Moving forward, our pipeline is very strong in both therapeutic areas … I cannot overemphasis the importance of these two therapeutic areas for this company," Dobber said.

RESPIRATORY TRIO HIGHLIGHTED

He highlighted to *Scrip* prospects for the biologic tezepelumab, which AstraZeneca is developing in partnership with Amgen Inc., and two other respiratory pipeline assets which he believes have huge potential. *(Also see "Tezepelumab Deemed Breakthrough But Can Phase III Reproduce Data? " - Scrip, 7 Sep, 2018.)*

"Next year we expect the Phase III outcome of tezepelumab which is potentially a best-in class biologic for severe, uncontrolled asthma. And we are in the process hopefully next year of getting PT010, which is called Breztri Aerosphere in Japan, registered in both Europe and the US next year, and we are also developing a very unique product for the United States called PT027 as a treatment for early-stage asthma," he said. PT027 is investigational fixed-dose combination of budesonide, which is an inhaled corticosteroid, and albuterol, a short-acting beta-2 agonist.

THERAPEUTIC SYNERGIES

Dobber said the company's drug development efforts were revealing synergies between cardiovascular, renal and metabolism as a co-related therapeutic focus for organ protection.

"What we have learned is that, if you take the heart, if you take the pancreas, and you take the kidney, there is more and more scientific evidence that those three organs are working almost in concert with each other and if you intervene at the level of the kidney, that gives a positive effect on the heart. We call it 'Cardiovascular, Renal and Metabolism' for that reason, in that there's an interlink between the three organs."

He noted that AstraZeneca's Farxiga, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, is now being marketed in the US to reduce the risk of hospitalization for heart failure (hHF) in patients with type 2 diabetes, making it the first drug in its class to win a heart failure indication outside of diabetics with renal co-morbidities. *(Also see "AstraZeneca's Farxiga Approval In Heart Failure A First For SGLT2 Inhibitors" - Scrip, 22 Oct, 2019.)*

While the Johnson & Johnson and Eli Lilly & Co./Boehringer Ingelheim International GmbH drugs have a lead over Farxiga with their CV risk reduction indications, Farxiga may be the first SGLT2 inhibitor to market as a heart failure treatment for patients regardless of whether they have diabetes. AstraZeneca has said it will seek a broad heart failure indication in the first half of 2020 based on the DECLARE-TIMI 58 and DAPA-HF studies.

Janssen Pharmaceutical Cos.'s sodium-glucose co-transporter 2 (SGLT2) inhibitor Invokana (canagliflozin) specifically carries an indication to reduce the risk of end-stage kidney disease, doubling of serum creatinine, cardiovascular death and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria. *(Also see "Keeping Track: US FDA, Industry Roar Into Fourth Quarter With Bevy Of Regulatory Announcements" - Pink Sheet, 5 Oct, 2019.)*

Jardiance (empagliflozin), the SGLT2 inhibitor from Eli Lilly/Boehringer Ingelheim, was the first drug in the class approved to reduce cardiovascular risk in type 2 diabetes based on the EMPA-REG outcomes trial in 2017.

Dobber said that studies conducted on the three SGLT2 inhibitors at the behest of regulators "show that Farxiga and its two other competitors in the class are not only safe, but that they also

have a protective effect on the heart, leading to less death in patients with diabetes … And we have also shown that Farxiga very substantially reduced hospitalization for heart failure, not only in type 2 diabetic patients but also in non-diabetic patients."

He said Farxiga had also shown itself to have a profound effect on the kidney, "by curbing the slowdown of kidney function."

"We are gradually moving to a space where SGLT2 inhibitors – and Farxiga in particular – are renal protective when compared with other products that are only focusing on lowering glucose in the body," Dobber said.

AstraZeneca still plans a US filing for its hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) roxadustat for the treatment of anemia in chronic kidney disease. Dobber declined to say whether AstraZeneca would use a priority review voucher which it acquired from Swedish Orphan Biovitrum AB for $95m earlier this year for roxadustat's filing.

"We have a priority review voucher, but so far we haven't decided yet which product we are going to use it for. We are now in a situation that the pipeline is now performing so extremely well that we have multiple choices where we could use the voucher," the executive said. He also declined to say what assets might be front runners in possibly using the priority review voucher.

Published online 29 October 2019

David Hung Launches Start-Up Nuvation With Old Medivation Team And $275m

MANDY JACKSON mandy.jackson@informausa.com

Former Medivation Inc. CEO David Hung is returning to oncology with the new cancer drug company Nuvation Bio Inc., which has raised $275m in series A venture capital and reassembled members of the team that developed and launched the prostate cancer blockbuster Xtandi (enzalutamide) before selling Medivation to Pfizer Inc. for $14.3bn in 2016.

With offices in New York and San Francisco, Nuvation describes itself as a "stealth biotechnology company" as it keeps the details of its pipeline close to the vest, but the start-up noted that it is working on "next-generation therapies that will target the foremost unmet needs," including "seven novel and mechanistically distinct oncology programs," each of which involves multiple drug candidates.

Otello Stampacchia, founder and managing director of lead series A investor Omega Funds, said in the company's announcement about the financing that "the breadth and depth of Nuvation Bio's innovative pipeline demands a large initial investment." Nuvation will use its newly raised venture capital to expand its development activities and advance multiple programs.

Aisling Capital, Altitude Life Science Ventures, The Baupost Group, Boxer Capital of the Tavistock Group, EDBI, ECOR1 Capital, Fidelity Management and Research Co., Pavilion Capital, Perceptive Advisors, Redmile Group, Surveyor Capital (a Citadel Company) and other institutional investors joined Omega in the series A round. Nuvation president and CEO Hung recruited former Medivation vice presidents Michele Bronson as the start-up's chief development officer and Melanie Morrison as VP of clinical operations, while former Medivation senior vice president Thomas Templeman is the new company's SVP of pharmaceutical operations and quality. Chief scientific officer Gary Hattersley joins Nuvation from Radius Health Inc., where he was CSO; chief medical officer Sergey Yurasov was CMO at Immune Design Corp. when it was acquired by Merck & Co. Inc. earlier this year. *(Also see "Merck Strengthening Vaccine Capabilities By Acquiring Troubled Immune Design" - Scrip, 21 Feb, 2019.)*

Hung initially launched Medivation to pursue development of an Alzheimer's drug before the company's focus switched to Xtandi.

Hung initially launched Medivation to pursue development of an Alzheimer's drug before the company's focus switched to Xtandi, the prostate cancer drug that attracted Astellas Pharma Inc. as a development partner in 2009 and Pfizer as an acquirer in 2016. The serial CEO was recruited to lead the Roivant Sciences Inc. neurology subsidiary Axovant Sciences Ltd. in 2017. *(Also see "Full Circle: David Hung Looks Forward To Axovant's Alzheimer's Data, Reflects On Medivation" - Scrip, 27 Jun, 2017.)*

But after Axovant's high-profile lead drug candidate for Alzheimer's disease flopped in Phase III, Hung left the company in February 2018 to pursue other endeavors. Nuvation apparently was born soon after, since the start-up has been operating since 2018.

Nuvation's leadership also includes two board members who previously sat on Medivation's board of directors – Anthony Vernon and Kim Blickenstaff – increasing the number of people overseeing the start-up who are familiar with the Medivation team and its previous oncology endeavors.

Vernon is a former CEO of Kraft Foods Group Inc. and worked in consumer brands at Johnson & Johnson for more than two decades. Blickenstaff is the former president and CEO, and current executive chairman and board member, at the insulin pump maker Tandem Diabetes Care Inc.

Published online 28 October 2019

US FDA Puts IT Zolgensma Studies On Partial Clinical Hold

ALEX SHIMMINGS alex.shimmings@informa.com

A year of highs and lows for Novartis AG's gene therapy product Zolgensma continues with the US Food and Drug Administration now placing on partial clinical hold studies looking at intrathecal administration of the product following troubling results from an animal study.

Novartis's AveXis Inc. unit reported to regulators findings from a small preclinical trial showing development of dorsal root ganglia (DRG) mononuclear cell inflammation, which was sometimes accompanied by neuronal cell body degeneration or loss, with the product, which is also known as AVXS-101 or onasemnogene abeparvovec-xioi.

DRG inflammation can be associated with sensory effects but Novartis said it did not know the clinical significance of the inflammation seen in the study. It did note that it had not been seen in any previous AVXS-101 animal studies. "We have completed a thorough review of human safety data from all available sources to date and no adverse effects related to sensory changes have been seen in AVXS-101 intrathecal or Zolgensma," it added.

The partial hold, which Novartis stressed would have no impact on the sale of intravenous Zolgensma or on current studies of the IV version, will mainly affect enrollment into the high-dose cohort of the Phase I/II STRONG study. This open-label, dose-comparison trial is designed to evaluate the efficacy, safety and tolerability of one-time intrathecal administration of AVXS-101 in patients with type 2 spinal muscular atrophy (SMA); the low and mid-dose cohort enrollment was already complete and with promising interim results.

Zolgensma, which uses an adeno-associated virus vector, was approved in May for the treatment of pediatric patients less than two years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron 1 (*SMN1*) gene. The label did not specify the type of SMA – the disease varies in severity according to the number of copies of the back-up *SMN2* gene patients have (from zero to eight, with more copies being associated with less severe symptoms and later age of symptom onset). Type 1 is the most severe with symptoms evident from birth to six months, while type 2 symptoms usually begin between seven and 18 months. Type 3 occurs in childhood and type 4 in adults.

Zolgensma taking Novartis on a wild ride.

Intrathecal administration is being developed for use in older patients, where the current IV administration is unsuitable. The IV product is dosed according to patient weight and as children age, the viral load required increases to unacceptable levels – the two main side-effects of IV administration are liver toxicity and platelet inhibition. Intrathecal (IT) administration is targeted to the spinal column where it takes effect, requiring less product: it is expected to be a safer and more direct route for older patients.

IT ZOLGENSMA DELAYS?

Analysts on the whole were not too concerned that the development would prevent the approval of the IT version of Zolgensma, but said it raised the risk that resulting discussions may delay proceedings and dampen peak sales.

According to Deutsche bank analysts, the study in question was not a safety trial but was assessing biodistribution of the product at a dose comparable to the maximum planned clinical trial dose, and did not include the use of prednisone prior to administration, something done in human trials.

"Although the news does not seem to have any relation to the previous issues over manipulated data at AveXis, this may make the FDA particularly cautious over its investigations," they said.

The recently reported better than expected sales for the product's first full quarter on the market came as a welcome relief following bad publicity surrounding the manipulation of other preclinical safety data for the gene therapy that came to light in August. The company had been aware of the issue in March but investigated the matter internally before informing the FDA in June, a month after Zolgensma received its US approval. Shortly after, AveXis co-founder and CSO Brian Kaspar and his brother, SVP of R&D Allan Kaspar, left the company, replaced as SVP and chief scientific officer by Page Bouchard, who was previously global head of preclinical safety for Novartis Institutes of Biomedical Research. *(Also see "Novartis Swaps Two AveXis Executives For One Following Zolgensma Data Manipulation" - Scrip, 14 Aug, 2019.)*

In the meantime, Zolgensma's EU approval process has dragged as it first lost

its accelerated assessment status and then Novartis had to ask for more time to answer questions raised by the CHMP during its review. A CHMP opinion is not now expected until the first quarter 2020, having previously been slated for late this year.

The main risk for Novartis is that animal studies may need to be repeated, causing a lengthier delay. In a worst case more serious safety concerns could prevent approval or limit the dose that can be safely administered intrathecally, the Deutsche Bank analysts said.

Evercore ISI analyst Umer Raffat said in a reaction note that other intrathecal gene therapies have shown MNC inflammation, citing a *Cell* paper on AAV9 dose-related neuronal degeneration in type 2 mucopolysaccharidosis. "Overall, a possible neuronal degeneration signal dampens the profile of Zolgensma IT and provides a counter-detailing point… Perhaps they could consider dosing into cisterna magna instead of broad IT? This could obviate the need to go higher in dose given better AAV biodistribution," he said.

Any delay to the IT version would have a material impact for Novartis, as it competes with Biogen/Ionis's intrathecal SMN2 splicing modifier Spinraza (nusinersen), the first product approved for this disease, and with Roche's similar oral investigational product, risdiplam. (Novartis also has an oral splicing modifier in Phase II development.)

"Delay of IT AVXS-101 approval is a near-term positive for persistence of Spinraza in the prevalent Type 2/3 population, though further delays may also provide an opening for risdiplam to become further established in the later-onset SMA market," noted analysts at SVB Leerink in an 30 October research note.

Deutsche Bank analysts said that if sales of Zolgensma were limited to incident patients with the current intravenous formulation they believe it would likely limit sales to ~$1.0-1.4bn (assuming broad adoption of screening). "The news thus directly puts at risk ~$500m to $900m of consensus sales (currently $1.9bn by 2022E) equal to 1-3% of Core EPS with a small risk concerns spill over to the currently approved formulation further impacting future sales."

Published online 30 October 2019

Mirati's First KRAS Data Look At Least As Good As Amgen's

MANDY JACKSON mandy.jackson@informausa.com

Mirati Therapeutics Inc.'s first-in-human results for the KRAS G12C inhibitor MRTX849 appear to be at least as good as data disclosed to date for Amgen Inc.'s similarly targeted AMG 510 in lung and colorectal cancer patients with KRAS-expressing tumors that have G12C mutations, according to data presented on 28 October at an early stage research meeting hosted by the American Association for Cancer Research, the National Cancer Institute and the European Organisation for Research and Treatment of Cancer.

Mirati's results have been closely watched because MRTX849 is only the second drug against KRAS to show efficacy in patients whose tumors harbor this relatively common oncogene, which is a marker of poor prognosis and previously was deemed an undruggable target.

The data are also notable because a small San Diego-based biotechnology firm is going up against a biotech giant in this potentially lucrative market. Mirati rose as much as 32% in after-hours trading, ending the night up 14.2% at $93 per share in after-hours trading on 28 October, while Amgen's stock was unmoved at $205.01.

Mirati estimates that KRAS G12C inhibition is a $7bn market opportunity in the US and EU with 68,000 patients eligible for treatment in the two regions. KRAS G12C mutations are detected in 14% of non-small cell lung cancer (NSCLC) cases (44,400 patients, a $4.9bn market in the US and EU), 4% of colorectal cancer (CRC) cases (19,600 patients, $2.2bn) and 2% of pancreatic cancer cases (4,000 patients, $400m).

Amgen has a head start with AMG 510, having presented clinical trial results primarily in lung and colorectal cancer patients at the American Society of Clinical Oncology (ASCO) meeting in June. The company followed with updated results at the World Conference on Lung Cancer (WCLC) and European Society for Medical Oncology (ESMO) in lung cancer and CRC, respectively, in September. *(Also see "Amgen KRAS Inhibitor Less Effective In Colorectal Cancer Than Lung" - Scrip, 28 Sep, 2019.)*

While it is difficult to compare two drugs across early human studies that have tested the agents at various doses in small numbers of patients, the data presented by Mirati in Boston at the "triple meeting" – so-called because of the AACR/NCI/EORTC joint sponsorship – seem to show that MRTX849 and AMG 510 have a similar efficacy profile.

DIFFERENT DOSE ESCALATION DESIGNS, SIMILAR RESULTS

The dose-escalation studies have different designs, with Mirati testing MRTX849 in the ongoing Phase I portion of its Phase I/II clinical trial in single-patient cohorts with intra-patient dose escalation. The dose-escalation portion of Amgen's trial has been completed, but in that stage of the study each dose cohort enrolled a few patients who stayed at that dose, meaning Amgen has more patients treated at lower doses of AMG 510.

However, Amgen determined that the maximum tolerated dose (MTD) of its drug is 960mg once daily for additional Phase I and II modules of the Phase I/II study, and in separate Phase I and II studies.

Meanwhile, Mirati still is seeking its MTD for MRTX849 after testing once-daily doses of 150mg, 300mg, 600mg and 1,200mg as well as 600mg given two times per day in 17 patients as of the cutoff date for the triple meeting presentation (10 with NSCLC, four with CRC and three in other tumor types). The twice-daily 600mg dose of MRTX849 has been deemed most likely to fully inhibit KRAS G12C signaling and dose expansion with that dose is ongoing.

Three out of five evaluable NSCLC patients treated with 600mg of MRTX849 twice daily had a partial response (PR) and one out of two CRC patients treated with that dose had a PR. The company did not provide overall response rate (ORR) data given the small patient numbers, but the data equate to a 60% ORR in lung cancer and 50% ORR in colorectal cancer. That is similar to responses seen at the highest dose of Amgen's AMG 510.

MRTX849 ON PAR WITH AMG 510, FOR NOW

Jefferies analyst Michael Yee said in a note to Amgen investors on 28 October that both Amgen and Mirati appear to have active KRAS G12C inhibitors, but MRTX849 "is not clearly better or worse in any way." He conceded that Mirati's data are "at least similar or better than" AMG 510, but on a smaller number of patients than Amgen has presented data for to date.

Yee noted that "based on the 'waterfall' plot and footnotes, it appears at least two of the responses (one lung, one colorectal) had deepening responses (some more shrinkage) on the second scan, so that could suggest maybe better durability or continued improvement with more treatment (one patient went from 37% to 47% and one went from 33% to 43%)."

However, with early data in a small number of patients, Mirati's data could change significantly as more results are presented further into its study. Also, Yee pointed out, one of the two dose-limiting toxicities (DLTs) was due to the treatment burden – 12 pills per day for the once-daily 1,200mg dose – suggesting that the pill burden could put Mirati's drug at a disadvantage.

The other DLT that Mirati reported was grade 3/4 isolated amylase/lipase increase at the twice-daily 600mg dose. However, treatment-related adverse events primarily were grade 1, the company said.

Prior to the MRTX849 data at the triple meeting, SVB Leerink analyst Andrew Berens said in an 18 October note to Mirati investors that there was about a 15% probability the drug would show better efficacy than AMG 510, a 10% chance MRTX849 would show inferior efficacy and/or problematic safety issues, and a 50% likelihood that the Mirati drug was on par with AMG 510, "de-risking the clinical program and suggesting the drug is competitive in the G12C mutant population."

"Given the skepticism ahead of the data … we believe Mirati shares would react favorably in this [latter] scenario as the worst case would be avoided, with shares increasing about 20-30% to about $110 toward the previous 52-week high," Berens continued. "We believe that there would still remain the possibility that with more mature data, '849 could better '510 as some of the drug's attributes may impact durability, a metric that is unlikely to be apparent in this dataset" at the triple meeting.

COMBINATION STUDIES COMING SOON

Future opportunities to improve on MRTX849 efficacy include combination trials pairing the drug with other mechanisms of action. Mirati has identified inhibition of PD-1, SHP2, CDK4/6 and EGFR as mechanisms of interest for MRTX849 drug combination trials, which it intends to begin initiating in the second half of 2019, the company said in a September investor presentation.

Mirati and Novartis AG announced an agreement in July to test MRTX849 in combination with Novartis's SHP2 inhibitor TNO155. Mirati will sponsor combination studies of the two agents, but the companies will share clinical trial costs. *(Also see "Deal Watch: Genentech Inks New Collaborations With Skyhawk, Convelo" - Scrip, 16 Jul, 2019.)*

Novartis also said recently that it is making a direct investment in KRAS inhibition for its own portfolio, partnering with Cancer Research UK on KRAS inhibitor research. *(Also see "Novartis Snaps Up KRAS Inhibitor R&D" - Scrip, 24 Oct, 2019.)*

"Mirati believes that the Novartis partnership is the best way to access a SHP2 inhibitor (as there is no way to acquire a SHP2 commercially). Cost-sharing was not the driver of the partnership, but is a 'nice to have,'" Credit Suisse analyst Evan Seigerman said in a 17 October note. "For other combinations, including PD-1, the company does not see the need to partner as these assets can be purchased commercially. As of now the company is not pursing combination with a MEK inhibitor, [signaling] a somewhat divergent path from the Amgen development plan for '510."

Amgen's preclinical research has identified PD-1, MEK, SHP2, EGFR and PI3K as targets of interest for combination studies with AMG 510. A Phase I study testing the drug with a PD-1 inhibitor in NSCLC is under way and fourth quarter clinical trial initiations will include a PD-1 combination study in CRC as well as a MEK inhibitor combination study in solid tumors. Data from a Phase II monotherapy study in lung cancer and the Phase I PD-1 combination study in NSCLC are expected in 2020.

Mirati's stock has risen as Amgen's program has advanced, with the smaller firm's investors hoping for at least similar efficacy to the larger company's drug. Mirati closed at $67.79 on 31 May, the last trading day before Amgen's AMG 510 presentation at ASCO, and rose as high as $109.60 a month later. Even at its $81.47 closing price on 28 October – minutes before the triple meeting data release – Mirati remained well above its pre-ASCO value.

Published online 29 October 2019

KRAS G12C Clinical Trial Results Presented To Date For MRTX849 And AMG 510

MRTX849 at the triple meeting	Three of five evaluable NSCLC patients (60%) and one of two evaluable patients with CRC (50%) treated with 600mg two times daily had a PR and the others achieved stable disease (SD) for a 100% disease control rate (DCR). Across all doses, three out of six NSCLC patients (50%) and one out of four with CRC (25%) had a PR; one with lung and one with colorectal cancer had a confirmed PR with tumor shrinkage. The other two NSCLC patients with PR continue to be treated with MRTX849, but haven't had confirmatory scans.
AMG 510 at ASCO	A 50% ORR in lung cancer with five out of 10 evaluable patients responding, including four PRs and one complete response (CR), with another four achieving SD the DCR was 90% across all doses tested. In colorectal cancer, 13 out of 18 evaluable patients had SD (72%).
AMG 510 at WCLC	In 13 evaluable NSCLC patients treated with the 960mg dose, seven patients had a PR (54%) and six had SD for a DCR of 100%.
AMG 510 at ESMO	Among 12 CRC patients treated with 960mg daily, one had a PR (8%) and 10 achieved stable disease (83%) for a DCR of 92%.

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

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

PIPELINE WATCH, 25–31 OCTOBER 2019

Event Type	Lead Company/Partner	Drug Name	Indication	Comments	Change To LOA (%)	LOA (%)
Phase III Updated Results	Advicenne	ADV7103	Distal Renal Tubular Acidosis	Non-Inferiority vs. Standard-Of-Care	0	62
Phase III Updated Results	Actinium Pharmaceuticals, Inc.	Iomab-B	Acute Myeloid Leukemia	SIERRA; Positive Results	0	37
Phase III Updated Results	Almirall Prodesfarma, S.A.	tirbanibulin	Actinic Keratosis	Recurrence Rates Promising	0	70
Phase III Updated Results	RedHill Biopharma Ltd.	RHB-104	Crohn's Disease	MAPUS Study; Early Onset Responses	0	61
Phase III Top-Line Results	Catalyst Pharmaceuticals Inc.	Firdapse (amifampridine phosphate)	Congenital Myasthenic Syndromes	CMS-001; Missed Endpoints	0	52
Phase II/III Top-Line Results	TG Therapeutics, Inc.	umbralisib	Follicular Lymphoma	UNITY-NHL; Met Primary Endpoint	4	39
Phase II/III Top-Line Results	MorphoSys AG	MOR208	Diffuse Large B-Cell Lymphoma	Re-MIND; Met Primary Endpoint	0	39
Phase III Trial Initiation	GlaxoSmithKline plc	gepotidacin (GSK2140944)	Urinary Tract Infections	EAGLE-2 (vs. nitrofurantoin); In Females	34	61
Phase III Trial Initiation	Axsome Therapeutics, Inc.	AXS-07 (meloxicam/rizatriptan)	Acute Migraine	INTERCEPT (Early); Dual Action Product	0	52
Phase III Trial Initiation	Pfizer/Sangamo	SB-525, gene therapy	Hemophilia A, Severe	Lead-In Study	30	61
Phase III Trial Initiation	GlaxoSmithKline/AnaptysBio	dostarlimab	Uterine Cancer	RUBY, w/Chemo; First-Line	29	39
Phase III Trial Initiation	Acadia Pharmaceuticals/Neuren	trofinetide	Rett Syndrome	LAVENDER; In Females	35	52

Source: Biomedtracker | Informa, 2019

Galapagos Hit By Atopic Dermatitis Drug Fail

KEVIN GROGAN kevin.grogan@informa.com

Galapagos NV's winning run in the clinic has suffered a blip with the news that development of an investigational atopic dermatitis treatment partnered with MorphoSys AG and Novartis AG has been halted.

The three partners have terminated the clinical program on MOR106, an interleukin-17C inhibitor, following an interim analysis for futility performed in the Phase II IGUANA trial. The analysis detected a low probability of meeting the primary endpoint of the study, defined as the percentage change in the eczema area and severity index (EASI) score. The companies stressed that the decision was based on a lack of efficacy and not on safety concerns.

Piet Wigerinck, chief scientific officer at Galapagos, said, "We are obviously disappointed with this result with MOR106 in atopic dermatitis. Together with our collaboration partners, we will explore the future strategy." As well as IGUANA, the development program included another Phase II trial called GECKO, a Phase I bridging study for subcutaneous formulation and a Japanese ethno-bridging study. MOR106, the first publicly disclosed human monoclonal antibody designed to selectively target IL-17C in clinical development worldwide, was generated using MorphoSys's Ylanthia antibody platform and is based on a target discovered by Galapagos. Novartis paid €95m up front (split 50/50) to get rights to the drug in July 2018.

Analysts at Credit Suisse issued a note on 28 October saying that "from a valuation perspective, we do not include any estimates for this clinical program in our model for Galapagos." They added that "while this is a small setback" for the Belgian biotech, they see it as positive news for Sanofi and Regeneron Pharmaceuticals Inc.'s blockbuster IL-4 and IL-13 inhibitor Dupixent (dupilumab), which is approved for moderate-to-severe atopic dermatitis.

Galapagos will now be even more firmly focused on its flagship product filgotinib. The selective JAK1 inhibitor has been filed for rheumatoid arthritis (RA) by partner Gilead Sciences Inc. in Europe, where Galapagos has the kept the commercialization rights, and will be submitted to the US Food and Drug Administration by the end of the year.

In terms of safety, very much a key issue for the JAK class, filgotinib has been shown to have a good profile. Nevertheless, analysts are concerned that like the currently marketed JAK inhibitors for RA – Pfizer Inc.'s Xeljanz (tofacitinib), Eli Lilly & Co.'s Olumiant (baricitinib) and AbbVie Inc.'s recently-approved Rinvoq (upadacitinib) – filgotinib will be hit by a black box label warning for thrombosis.

On a conference call to discuss the firm's third-quarter financials on 25 October, Galapagos chief medical officer Walid Abi-Saab said it was very difficult to predict what position the FDA would take. "All we can do is share the data that we have, which…continues to be very favorable and we can articulate scientifically why we believe we do have a differentiated profile when it comes to safety and also the low rates of thromboembolic events," he added.

Published online 30 October 2019

APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
Tim Oldham	AdAlta Ltd	Chief Executive Officer	Tijan Ventures	Executive Leader	9-Oct-19
Rabia Gurses Ozden	Akouos	Chief Development Officer	Nightstar Therapeutics plc	Chief Medical Officer	24-Oct-19
Thomas J. Russo	Assembly Biosciences	Chief Financial Officer	Gilead Sciences	Head, Commercial Finance and Vice President	28-Oct-19
Philip Ashton-Rickardt	AZTherapies Inc	Senior Vice President, Immunology	Smith Therapeutics	Chief Executive Officer	24-Oct-19
Wendy McDermott	Rafael Pharmaceuticals Inc	Chief People Officer	Sanofi	Vice President, Human Resources	2-Oct-19
Will Downie	Vectura Group plc	Chief Executive Officer	Catalent Inc	Senior Vice President, Global Sales and Marketing	7-Nov-19

Click here for all appointments: https://bit.ly/2oHWRYn

Source: Medtrack | Informa, 2019

Meddevicetracker

Informa Pharma Intelligence

Meddevicetracker: Medical Device Intelligence and Forecasts

Stay up-to-date and get a complete view of the continually evolving medtech landscape with access to real-time market intelligence on product and company developments across the medical devices, diagnostics and advanced delivery systems markets.

Anticipate upcoming filings, clinical trials dates and data, and access market size information and expert forecasts all in one place, helping you assess the competition, track key events and make better-informed decisions.

To find our more visit:
pharmaintelligence.informa.com/Meddevicetracker