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12 Approvals To Look Out For In Q4

Sanofi, Pfizer, MacroGenics, BMS Expecting

by Alex Shimmings

The end of the year should see a flurry of new products reaching the market to break new commercial ground or shake up their respective therapeutic areas. Here, *Scrip* takes a look at 12 of the more interesting approvals expected in the coming months, with the help of analysts at Biomedtracker.

Supernus Pharmaceuticals' SPN-812

Indication: Attention Deficit Hyperactivity Disorder

PDUFA Date: 8 November NDA - First Review

Supernus Pharmaceuticals, Inc. should hear by 8 November whether the US Food and Drug Administration will approve SPN-812 (viloxazine hydrochloride), its novel non-stimulant treatment for the treatment of children and adolescents with attention deficit hyperactivity disorder (ADHD). The serotonin norepinephrine modulating agent (SNMA) inhibits noradrenergic reuptake transporters and has been approved for many years in Europe for the treatment of depression.

If approved by the FDA, SPN-812 will be the first novel therapy to treat ADHD in a decade. Nearly 6.1 million children and adolescents in the US are in need of a treatment that is a noncontrolled substance and that works differently from currently available therapies.

The new drug application (NDA) is based on data from a development program that included four Phase III trials that studied the pediatric patient population from the age of 6 to 17 years.

Each of the four pivotal clinical trials showed a reduction in ADHD Rating Scale-5 (ADHD-RS-5) total score as early as week 1 and continuing until the end of the clinical study, as well as improvement in both hyperactivity/impulsivity and inattention subscales. SPN-812 had an

acceptable safety profile with low incidence of adverse events and low discontinuation rates. (Also see "*Supernus' ADHD Drug Hits Phase III Endpoint As Filing Beckons*" - Scrip, 21 Dec, 2018.)

The FDA has assigned a Prescription Drug User Fee Act (PDUFA) target action date of November 8, 2020. As this date falls on a weekend, the PDUFA decision is expected to come on the Friday before.

Sanofi's sutimlimab (BIVV009)

Indication: Cold Agglutinin Disease (Autoimmune Hemolytic Anemia)

PDUFA date: 13 November BLA - First Review

If approved, *Sanofi*'s sutimlimab will be the first marketed treatment for patients with cold agglutinin disease (CAD). The monoclonal antibody inhibitor of C1s in the classical complement pathway of the immune system, is under priority review by the FDA as a treatment for C1-activated hemolysis in CAD patients.

CAD is a chronic rare blood disease that affects approximately 5,000 people in the US alone and the drug has been granted orphan and breakthrough therapy designations. The biologics license application (BLA) is supported by clinical data from the single-arm Phase III CARDINAL trial, in which sutimlimab met the primary composite efficacy end point, with 54% of patients having an increase from baseline in hemoglobin levels, 62% of patients achieving normalization of hemoglobin levels ⩾12 g dl−1 at week 26, and 71% remaining transfusion-free after week five. (Also see "*Sanofi's Sutimlimab Shows Promise In Rare Blood Disorder* " - Scrip, 22 Nov, 2019.)

CAD is one of a number of auto-immune hemolytic anemias – which also include warm or mixed reactive – and is so called as the autoantibody agglutinins are activated when the patient's blood is goes below core temperature. CAD occurs in about 16 people per million, including an estimated 12,000 people in the US, Europe and Japan.

MacroGenics' Margetuximab

Indication: Breast Cancer

PDUFA action date: 18 December BLA - First Review

MacroGenics, Inc.'s investigational, Fc-engineered, monoclonal antibody that targets human epidermal growth factor receptor 2 (HER2), margetuximab, has US fast-track status to for the treatment of patients with metastatic or locally advanced HER2-positive breast cancer who have previously been treated with anti-HER2-targeted therapy.

If successful, margetuximab could provide an alternative therapy option for patients with HER2-

positive metastatic breast cancer, although it will likely face significant competition from recently approved drugs, *AstraZeneca PLC*/*Daiichi Sankyo Co., Ltd.*'s Enhertu (trastuzumab deruxtecan) and *Seattle Genetics, Inc.*'s Tukysa (tucatinib).

The BLA is supported by results from the Phase III SOPHIA study which met the primary endpoint of prolongation of progression-free survival (PFS) in patients treated with the combination of margetuximab plus chemotherapy compared to trastuzumab plus chemotherapy, with comparable safety and tolerability. SC125384

While margetuximab failed to significantly improve overall survival (OS) at the second interim analysis, the trend in OS in the intention-to-treat population and, particularly, in the CD16A 158F allele populations, was encouraging, said Biomedtracker analysts. "The established PFS benefit over trastuzumab from the previous data release is likely sufficient for approval of MacroGenics' BLA submission."

Margetuximab was filed in the US for use in combination with chemotherapy in December 2019, with an expected PDUFA date of 18 December.

Bristol Myers Squibb's lisocabtagene maraleucel

Indication: Diffuse Large B-Cell Lymphoma

PDUFA action date: 16 November BLA - First Review

A third CD19-targeted CAR-T therapy, *Bristol Myers Squibb Company*'s lisocabtagene maraleucel (expected to be marketed as Breyanzi), could receive US approval by mid-November, to rival *Gilead Sciences, Inc.*'s Yescarta (axicabtagene ciloleucel) and *Novartis AG*'s Kymriah (tisagenlecleucel).

The therapy, which was gained by BMS through the $74bn acquisition of *Celgene Corporation* in 2019, is under regulatory review in the US, EU and Japan as a treatment for third-line or later relapsed or refractory large B-cell lymphoma.

Its US review was delayed when BMS submitted additional information to the FDA, which was deemed to constitute a major amendment to the application, with a new PDUFA target action date of November 16.

Breyanzi differs from its rivals in the separate preparation of purified CD4+ and CD8+ cells which are then administered as sequential infusions at equal target doses; although this complicates manufacturing, it is thought to reduce product variability and improve safety which may allow for administration in the outpatient setting.

The filings are based on the TRANSCEND trial in 269 patients with relapsed/refractory large B-cell lymphoma, demonstrated an overall response rate (ORR) of 73% and a complete response (CR) rate of 53% in the efficacy-evaluable population. These results compare well with historical data from Yescarta's ZUMA-1 trial and Kymriah's JULIET trial, which reported CR rates of 51% and 32%, respectively. Only six patients (2%) experienced grade 3/4 cytokine release syndrome with Breyanzi, compared with 13% with Yescarta and 23% with Kymriah. SC141322

Kala Pharmaceuticals' Eysuvis

Indication: Dry Eye

PDUFA action date: 30 October NDA - Second Review

Following a complete response letter in August 2019, *Kala Pharmaceuticals, Inc.* is hoping for better luck with this second review for Eysuvis (loteprednol etabonate ophthalmic suspension) for the short-term treatment of the signs and symptoms of dry eye disease. (Also see "*Kala Needs Big STRIDE To Get Dry Eye Drug OK*" - Scrip, 12 Aug, 2019.)

Currently Eysuvis is positioned to be a short-term treatment of dry eye disease rather than as a maintenance therapy. Since Novartis' Xiidra (lifitegrast) and C#11116:Allergan AG]'s Restasis (cyclosporine ophthalmic emulsion) are both used as long-term treatments, this should allow Eysuvis to differentiate itself within this competitive indication.

The CRL indicated that efficacy data from an additional clinical trial would be needed to support a resubmission, which led to the Phase III STRIDE 3 trial to supplement the previously completed Phase II trial and the first two Phase III efficacy and safety trials, STRIDE 1 and STRIDE 2. (Also see "*Kala's Third Phase III Trial Should Line Up Approval In Dry Eye*" - Scrip, 9 Mar, 2020.)

Kala resubmitted its application in April with the STRIDE 3 trial data and this was accepted as a Class 2 response with a PDUFA target action date of 30 October. The study met both of its primary symptom endpoints, showing a significant improvement in ocular discomfort severity in both the overall ITT population and in a predefined subgroup of ITT patients with more severe ocular discomfort at baseline.

Regeneron's REGN-EB3

Indication: Ebola

PDUFA action date: 23 October BLA - First Review

If approved, *Regeneron Pharmaceuticals, Inc.*'s Ebola therapy REGN-EB3 would be a positive example of how synergy between a government agency, the Biomedical Advanced Research and Development Authority (BARDA) of the US Department of Health and Human Services (HHS) and

a biopharmaceutical company can expedite the drug development process, analysts at Biomedtracker say.

The product, a cocktail of three human IgG1 mAbs (REGN3470, REGN3471, and REGN3479) directed against different epitopes on the Ebola virus glycoprotein, was developed under an agreement announced in 2015 between the two parties for the treatment of Ebola virus infection.

Regeneron initiated a rolling BLA submission for REGN-EB3 for the treatment of Ebola virus infection based on the pivotal Phase II PALM trial, which tested four potential therapies for Ebola: REGN-EB3, Mapp Biopharmaceutical Inc.'s ZMapp and mAb114 (a single monoclonal antibody which was developed by scientists at the US NIH's National Institute of Allergy and Infectious Diseases); and one small-molecule antiviral, Gilead's remdesivir. (Also see "*Ebola Success For Regeneron's Triple Antibody Cocktail* " - Scrip, 13 Aug, 2019.)

Eiger's Zokinvy

Indication: Hutchinson-Gilford Progeria Syndrome

PDUFA action date: 20 November NDA - First Review

Having previously failed in treating myelodysplastic syndrome (MDS), breast cancer, brain cancer, and non-small cell lung cancer, an approval for *Eiger BioPharmaceuticals, Inc.*'s Zokinvy (lonafarnib) for Hutchinson–Gilford progeria syndrome the (HGPS) would be the breakthrough the drug needs, say Biomedtracker analysts. (Also see "*Eiger Shifts Focus After Phase II Failure In PAH*" - Scrip, 16 Jan, 2018.)

HGPS is a rare genetic disorder with symptoms that resemble aspects of aging but at an early age. Though there is a heritable form, progeria usually occurs as a new point mutation in the LMNA gene, with a frequency of one per 8 million live births.

Eiger began a rolling NDA for Zokinvy, a farnesyl transferase inhibitor (FTI), last December, which it completed in March; the FDA has given a 20 November PDUFA date. The product also has breakthrough therapy designation for the treatment of HGPS.

Results from the ProLon1 and ProLon2 trials, which evaluated Zokinvy's impact on mortality in progeria patients compared with non-treatment in contemporaneous untreated patients, were published in the *Journal of the American Medical Association* in April 2018. The combined data from the two studies showed that treatment with Zokinvy was associated with a lower mortality rate (HR 0.23; 95% CI, 0.06-0.90; p=0.04) after 2.2 years of follow-up.

Zokinvy is also in Phase III trials for the treatment of hepatitis D, with promising results from a Phase II trial released in October 2019. "Having one FDA approval under its belt would bode well

for Zokinvy when Eiger eventually pursues approval of the drug for HDV. In addition, as the only approved product in the US for HGPS, Zokinvy would strengthen the company's revenue stream to help fund future clinical trials and regulatory submissions for HDV," said the Biomedtracker analysts.

Alnylam's Lumasiran

Indication: Hyperoxaluria

PDUFA action date: 3 December NDA - First Review

If approved, *Alnylam Pharmaceuticals Inc.*'s lumasiran will be the first marketed therapy for the ultra-rare disease primary hyperoxaluria type 1 (PH1), and the third RNAi therapy to be approved, following the company's pioneering success with patisiran in 2018.

The siRNA therapeutic targets hydroxyacid oxidase 1 (HAO1), which encodes glycolate oxidase. It has been granted breakthrough designation and is currently under priority review as a treatment for PH1, an ultra-rare disease that is estimated to have a prevalence of approximately 3,000–5,000 patients across the US and the EU. The disease is characterized by overproduction of liver oxalate, causing accumulation of oxalate in the kidneys, with progressive decline in kidney function, typically culminating in kidney failure.

Results from the Phase III ILLUMINATE-A study showed that at six months, lumasiran lowered patients' urinary oxalate levels by 65% compared with baseline and by 54% compared with placebo. In addition, 52% of lumasiran-treated patients achieved urinary oxalate levels within normal range and 84% achieved near normal levels, whereas none of the patients on placebo achieved normal or near-normal levels.

Although a clinical benefit was not seen, the trial may have been too short, and with longer follow-up, the strong reduction in oxalate is hoped to have a favorable impact on kidney function and disease progression. (Also see "*Alnylam's Full Lumasiran Dataset Seen As Confirming Approvability*" - Scrip, 8 Jun, 2020.)

Top-line data were recently released for the ILLUMINATE-B study in children under six, which will also be presented at the American Society of Nephrology meeting this month. (Also see "*Alnylam Shows Efficacy, Safety With Lumasiran In Vulnerable Pediatric Patients*" - Scrip, 30 Sep, 2020.)

Y-mAbs Therapeutics' Danyelza

Indication: Neuroendocrine Tumors

PDUFA action date: 30 November BLA - First Review

Danyelza (naxitamab) could represent a first new treatment for neuroblastoma since the approval of *Roche Holding AG*'s Avastin (bevacizumab) in 2009 and become *Y-mAbs Therapeutics Inc.*'s first commercial product.

Y-mAbs developed the humanized 3F8 monoclonal antibody targeting GD2 was developed its MULIT TAG protein platform.

The FDA accepted the rolling BLA started last November for Danyelza for the treatment of relapsed/refractory high-risk neuroblastoma for priority review and set a 30 November action date.

The submission is based on results of the pivotal Phase II studies 201 and 12-230. In the Phase I/II study 12-230, naxitamab produced a 73% overall response rate in the primary refractory patient group, and 42% response rate in the secondary refractory group.

From the Phase II study 201, the dataset from the 24 patients included in the BLA filing showed 79% ORR and 71% CR. In 13 of 14 patients with bone marrow disease, bone marrow was cleared after treatment.

Of note, in 2018, the FDA granted breakthrough therapy designation to naxitamab for the treatment of high-risk neuroblastoma refractory to initial therapy or with incomplete response to salvage therapy in patients older than 12 months of age, complementing a rare pediatric disease designation granted in 2017.

Y-mAbs has a second candidate, omburtamab, for which it has just received a refusal to file letter from the FDA for a BLA filed in August for the treatment of pediatric patients with CNS/leptomeningeal metastasis from neuroblastoma. (Also see "*Y-mAbs Faces Delay In Pediatric Neuroblastoma With Refuse-To-File Letter*" - Scrip, 6 Oct, 2020.)

Pfizer/Lilly's Tanezumab

Indication: Osteoarthritis and Osteoarthritis Pain

PDUFA action date: December BLA - First Review

A verdict on *Pfizer Inc.* and *Eli Lilly and Company*'s surprise filing for the novel painkiller tanezumab is expected from the FDA in December. The product has reported mixed clinical data making its path to market uncertain, but following discussions with the FDA, the US agency saw fit to accept for review a BLA for the lower 2.5mg dose for patients with chronic pain due to moderate-to-severe osteoarthritis (OA) who have experienced inadequate pain relief with other analgesics in March 2020. (Also see "*Surprise! Pfizer And Lilly File Tanezumab For Pain With FDA Despite Safety Questions* " - Scrip, 28 Jan, 2020.)

The monoclonal antibody works by selectively inhibiting nerve growth factor (NGF), to keep pain signals produced by muscles, skin and organs from reaching the spinal cord and brain. This peripheral action differs from opioids and other analgesics, including nonsteroidal anti-inflammatory drugs (NSAIDs).

The submission encompasses data from 39 Phase I-III clinical studies evaluating the safety and efficacy of tanezumab among more than 18,000 patients, including three Phase III studies evaluating SC administration of tanezumab in patients with moderate-to-severe OA.

Safety issues have long plagued the drug's development and will likely be a featured topic of discussion in the planned advisory panel meeting before tanezumab's PDUFA goal date. "Rates of adverse joint safety events have been higher with tanezumab compared to NSAIDs but perhaps more importantly, incidence rates of rapidly progressive osteoarthritis were also found to be significantly elevated in tanezumab arms versus comparator arms," the Biomedtracker analysts said.

Urovant's Vibegron

Indication: Overactive Bladder

PDUFA action date: 25 December NDA - First Review

In December 2019, *Urovant Sciences, Inc.* submitted an NDA to the FDA for once-daily 75mg vibegron supported by efficacy and safety data from the pivotal Phase III EMPOWUR study, and a PDUFA decision expected on 25 December. Given the pool of positive long-term efficacy and safety data for the product, a positive PDUFA review is to be expected, Biomedtracker analysts said. (Also see "*Urovant's Vibegron Faces Tough Commercial Climb Despite Phase III Success*" - Scrip, 19 Mar, 2019.)

Originally developed by *Merck & Co., Inc.*, vibegron is a selective beta-3 adrenergic receptor agonist developed for the treatment of overactive bladder (OAB), including patients with symptoms of urge urinary incontinence, urgency, and urinary frequency. Beta-3 adrenergic receptors are the most prevalent subtype on the smooth muscle around the bladder and their selective activation results in an increased bladder capacity and reduced OAB symptoms.

The once-daily small molecule was licensed to Urovant in 2017 worldwide, excluding Japan and some Asian territories. The product was marketed in Japan as Beova in 2018 after an agreement between Merck, *Kyorin Pharmaceutical Co., Ltd.* and *Kissei Pharmaceutical Co., Ltd*.

Vibegron's main competitor will be *Astellas Pharma, Inc.*'s beta-3 adrenergic receptor Myrbetriq (mirabegron), which has been available in the US since 2012.

Alkermes' ALKS 3831

Indication: Schizophrenia And Bipolar 1 Disorder

PDUFA action date: 15 November NDA - First Review

Alkermes plc' combination product, ALKS 3831, composed of the new molecular entity samidorphan co-formulated with olanzapine in a single bi-layer tablet, is awaiting US approval for schizophrenia and bipolar 1 disorder, with a PDUFA action date of 15 November.

The ALKS 3831 NDA included data from the ENLIGHTEN clinical development program in patients with schizophrenia. (Also see "*Is Alkermes' Schizophrenia Data Enough To Drive Demand?*" - Scrip, 29 Nov, 2018.)

The NDA submission is supported by data from 27 clinical studies, including 18 studies evaluating ALKS 3831 and nine studies evaluating samidorphan alone. Throughout the clinical development program, ALKS 3831 showed evidence of antipsychotic efficacy, safety and tolerability, including attenuation of olanzapine-associated weight gain.

However, ALKS 3831 will not launch until the first quarter of 2021 at the earliest, because it will require US Drug Enforcement Administration (DEA) scheduling, since samidorphan is an opioid receptor antagonist. It also remains to be seen whether the olanzapine/samidorphan combination's better weight-gain profile will be enough to drive use of a new branded product in a generic-heavy indication.

For more information, see the Biomedtracker/Meddevicetracker Q4 Outlook Report here.