PRIME THERAPEUTICS®

Specialty Pipeline **MONTHLY UPDATE**

Critical updates in an ever changing environment

October 2021

NEW DRUG INFORMATION

- **Livmarli™ (maralixibat):** The U.S. Food and Drug Administration (FDA) has granted approval of Mirum Pharmaceuticals' Livmarli for treatment of cholestatic pruritus in patients with Alagille syndrome one year of age and older. Alagille syndrome (ALGS) is a rare genetic disorder in which bile ducts are abnormally narrow, malformed and reduced in number, which leads to bile accumulation in the liver and ultimately progressive liver disease. ALGS affects 2,000 to 2,500 children in the United States. Livmarli is an oral solution that works as a minimally absorbed ileal bile acid transporter (IBAT) inhibitor. Livmarli was approved based on Phase 3, ICONIC study that demonstrated statistically significant reductions in pruritus compared with placebo. Pruritus is one of the most common and arduous symptoms associated with the disease; the reductions were maintained through four years.[1] Livmarli has launched with a wholesale acquisition cost (WAC) of $46,500 per bottle (30ml) or $31,620 per 30 days for a 17kg child.

- **Tavneos™ (avacopan):** ChemoCentryx's Tavneos has been approved by the FDA for oral adjunctive treatment of adults with severe active anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis, specifically granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), in combination with standard therapy including glucocorticoids. ANCA-associated vasculitis is a rare systemic disease in which over-activation of the complement pathway further activates neutrophils, leading to inflammation and destruction of small blood vessels. This results in organ damage and failure, with the kidney as the major target, and is fatal if not treated. Tavneos is an orally administered selective complement 5a receptor inhibitor. The FDA-approved Tavneos is based on the Phase 3 ADVOCATE trial that met its primary endpoint of disease remission at week 26, and sustained remission at 52 weeks, compared with prednisone. Eligible study subjects were randomized to receive either rituximab or cyclophosphamide (followed by azathioprine/mycophenolate) and either Tavneos or study-supplied oral prednisone. Subjects in both treatment groups could also receive non-protocol glucocorticoids if needed.[2]

A committee of the FDA narrowly supported the approval of Tavneos for the treatment of ANCA-associated vasculitis (AAV). In the final segment of a public meeting, the committee voted:

- 9–9 split on whether the efficacy data supported approval of Tavneos
- 10–8 that the therapy's safety profile adequately supported approval
- 10–8 on whether the benefit-risk profile supported approval at the proposed dose of 30mg twice daily[3]

Tavneos is launching through Amber Specialty Pharmacy and one other specialty pharmacy as part of a limited distribution network. It will have an upcoming launch with an annual WAC between $150,000 and $200,000.

- **Rethymic™ (allogeneic processed thymus tissue-agdc):** Enzyvant's Rethymic has been approved by the FDA to treat pediatric patients with congenital athymia. Rethymic is a one-time regenerative tissue-based therapy derived from cultured human thymus tissue and implanted in a single surgery for immune reconstitution. Pediatric congenital athymia is ultra-rare with an estimated incidence of about 17 to 24 live births each year in the United States. Children who have this condition are born without a thymus and therefore have profound immunodeficiency, life-threatening immune dysregulation, and high susceptibility to potentially fatal infections. With only supportive care, children with congenital athymia typically die by age two or three. The FDA approved Rethymic based on clinical trials that demonstrated Kaplan-Meier-estimated survival rates were 77% at year one and 76% at year two. For patients alive at one year post implantation, the Kaplan-Meier estimated long-term survival rate was 94% at a median follow-up time of 10.7 years.[4] Rethymic launch and price are pending.

NEW INDICATIONS

- **Keytruda® (pembrolizumab):** Merck's Keytruda was granted approval by the FDA to expand its indication to be used in combination with chemotherapy, with or without bevacizumab, for the treatment of patients with persistent, recurrent or metastatic cervical cancer whose tumors express PD-L1, as determined by an FDA-approved test.
- **Verzenio® (abemaciclib):** The FDA expanded the indication of Lilly's Verzenio to include the use in combination with physician's-choice endocrine therapy to cut the risk of relapse in patients with high-risk HR-positive, HER2-negative breast cancer.
- **Tecartus® (brexucabtagene autoleucel):** Gilead Sciences' Tecartus has a new indication granted by the FDA for treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) as well as for adjuvant treatment for patients with stage II-IIIA non-small cell lung cancer (NSCLC) with PD-L1 scores greater than or equal to one.
- **Repatha® (evolocumab):** Amgen's Repatha has been approved by the FDA as an add-on treatment to diet alone or together with certain other therapies for patients aged 10 years and older with heterozygous familial hypercholesterolemia (HeFH) and homozygous familial hypercholesterolemia (HoFH).

- **Jakafi® (ruxolitinib):** The FDA expanded the indication for Incyte's Jakafi to include the treatment of steroid-refractory chronic graft versus host disease (SR chronic GVHD) in adults and pediatric patients 12 years and older (approved for chronic GVHD after failure of one or two lines of systemic therapy in people 12 years and older).
- **Cabometyx® (cabozantinib):** Exelixis and Ipsen Cabometyx has a new indication granted by the FDA to include treatment of patients aged 12 and older with locally advanced or metastatic differentiated thyroid cancer (DTC) that has progressed following prior vascular endothelial growth factor receptor (VEGFR)-targeted therapy and who are radioactive iodine-refractory or ineligible.
- **Brukinsa® (zanubrutinib):** The FDA has expanded Beigene's Brukinsa indication to include the treatment of adults with marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based therapy and a new indication for the Bruton's tyrosine kinase (BTK) inhibitor for treatment of adults with the rare indolent B-cell lymphoma Waldenstrom's macroglobulinemia (WM).
- **Tibsovo® (ivosidenib):** Servier Pharmaceuticals' Tibsovo received a new indication from the FDA for adult patients with previously treated, locally advanced or metastatic cholangiocarcinoma with an isocitrate dehydrogenase-1 (mIDH1) enzyme to include IDH1 mutation, as detected by an FDA-approved test. Cholangiocarcinoma is a rare type of cancer in the bile ducts in the liver. Servier purchased Agios Pharmaceuticals in April 2021, which originally developed Tibsivo.[5]

OCTOBER NEWS

- "As one of the biggest players in an increasingly packed gene therapy space, Pfizer has taken an early lead over specialists like Sarepta in taking a Duchenne muscular dystrophy (DMD) candidate into late-stage testing. But new safety fears have led Pfizer to scale back that trial, cutting out patients with certain genetic mutations. Pfizer has amended its enrollment protocol for a Phase 3 test for gene therapy fordadistrogene movaparvovec in DMD after investigators flagged severe side effects tied to specific mutations, according to a letter the drugmaker sent to Parent Project Muscular Dystrophy, a patient advocacy group. The amended CIFFREO study plans to enroll 99 DMD patients without any mutations affecting exons 9 through 13, or a deletion that affects both exon 29 and exon 30. Exons are portions of a gene that code for specific amino acids. Pfizer said three cases of muscle weakness, two of which included heart inflammation, forced the trial amendment. The drugmaker said the proposed changes are currently being reviewed by regulators and ethics committees, with trial site-specific changes set to roll out on a country-by-country basis. This isn't the first time fordadistrogene movaparvovec has hit a roadblock on its late-stage path, with the company reporting in May that it was meeting headwinds from the FDA on the quality of its potency assays. That hurdle appears to be in the past, but given how closely watched safety data are in the gene therapy space, this may not be the last hiccup for Pfizer's plans in DMD."[6]

- "Biogen — together with partners at Eisai — will be the first to breeze down that Alzheimer's trail it blazed with the FDA's historic and controversial accelerated approval of Aduhelm. Eisai disclosed it's initiated a rolling BLA submission for lecanemab, or BAN2401, the anti-amyloid beta antibody that Biogen has long touted as a follow-on to Aduhelm (then aducanumab). Following the precedent that the agency has now set, the two companies are gunning for an OK based on data suggesting that the drug could lower amyloid beta plaques. They won't be alone in the queue for long. Roche and Eli Lilly are hot on their heels to join the gold rush, with the latter having also pledged to file by the end of the year. Unlike with Aduhelm, whose approval was cemented by mixed data viewed negatively by the FDA's advisory committee, the lecanemab filing only comes with Phase IIb data, including those from the open-label extension. The trial, dubbed Study 201, enrolled 856 patients with early Alzheimer's and confirmed amyloid pathology."[7]
- "Merck said it is seeking U.S. Food and Drug Administration emergency use authorization for its experimental antiviral Covid-19 treatment, molnupiravir. If authorization is granted, the drug, made by Merck and Ridgeback Biotherapeutics, would be the first oral antiviral treatment to fight Covid-19. It comes in capsule form. Merck said it is asking for authorization for the capsules to treat infected adults who are at risk of progressing to severe Covid-19 disease or hospitalization. Its submission is based on a study that was stopped at the interim point because the drug was working so well in more than 700 patients randomly assigned to take either molnupiravir or a placebo. '7.3% of patients who received molnupiravir were either hospitalized or died through Day 29 following randomization, compared with 14.1% of placebo-treated patients,' the company said in a statement."[8]

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