Optum Rx drug pipeline insights report

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Optum Rx®

Drugs to Watch: Spring 2023

From Sumit Dutta, Chief Medical Officer at Optum Rx

Hello, and welcome to this edition of Drugs to Watch.

2023 is another busy year for new pharmaceutical treatments. We have noted in past editions that the industry continues to direct its attention toward novel technologies, including genetic treatments and rare conditions. As we see in this edition, more common conditions such as respiratory illness and fatty liver disease also have therapeutics in development.

We have chosen four drug pipeline products which have an expected approval decision date by the end of the second quarter of this year.

We review **two respiratory syncytial virus (RSV) vaccines**, one from GSK and one from Pfizer. RSV is one of the most common respiratory infections currently without a specific treatment or vaccine. Both vaccines could be approved for use in the elderly population (age 60 and up) and be available prior to the 2023 RSV season.

Delandistrogene moxeparvovec is under review to treat Duchenne muscular dystrophy (DMD). DMD is a rare genetic disorder with few effective treatments. The condition can lead to progressive disability or death at a young age. If approved, delandistrogene moxeparvovec would be the first gene therapy for DMD.

Obeticholic acid could be the first FDA approved treatment for nonalcoholic steatohepatitis (NASH). NASH has a high prevalence in the U.S. (up to 6.5% of the population) and currently there are no drugs approved for the disease. Obeticholic acid is currently approved under the brand name Ocaliva® for another rare liver disease, primary biliary cholangitis.

As always, Optum Rx will closely monitor and evaluate the drug development pipeline and share upcoming drug approvals.

Please refer here for additional technical background and supplemental sources.

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Respiratory syncytial virus (RSV) vaccines

RSV is a common respiratory virus that usually causes mild, cold-like symptoms, lasting about 1 to 2 weeks. However, some patients may develop severe RSV infection, including pneumonia and bronchiolitis (a common lung infection in young children and infants), which may result in hospitalization.

Infants, young children, and older adults are most at risk for severe RSV infection. In the U.S. and other areas with similar climates, RSV circulation generally starts during the fall and peaks in the winter.

Each year, an average of 58,000 to 80,000 children under the age of 5 are hospitalized in the U.S. due to RSV. In addition, between 60,000 to 120,000 adults over age 65 are also hospitalized. RSV leads to approximately 100 to 300 deaths annually in children younger than 5 years old and 6,000 to 10,000 deaths annually among adults 65 years and older.[1]

Brand name: Arexvy®
Expected FDA decision: May 3, 2023

Arexvy is GSK's investigational RSV vaccine under review for the prevention of lower respiratory tract disease (LRTD) caused by RSV in adults aged 60 years and older.

Clinical profile

Arexvy contains a version of protein F, which is found on the surface of the RSV virus. Protein F helps to position the virus so that it can infect the host cell.[2]

The active protein is combined with a proprietary GSK adjuvant (AS01E). Adjuvants are chemicals added to vaccines to help promote an immune response.

Pivotal trial data

Arexvy was evaluated in a Phase 3, randomized, observer-blind, placebo-controlled study in 24,960 adults aged 60 years and older (AReSVi-006). Patients received either a single dose of the vaccine, or a placebo via intramuscular (IM) injection. The primary endpoint was prevention of RSV LRTD during the first RSV season. LRTD was defined as ≥ 2 lower respiratory symptoms/signs for ≥ 24 hours including ≥ 1 lower respiratory sign or ≥ 3 lower respiratory symptoms for ≥ 24 hours.

The overall vaccine efficacy was 82.6% against RSV LRTD, meeting the trial's primary endpoint.

Safety

The most common local adverse events with Arexvy use were superficial reddening of the skin, pain and swelling. The most common systemic adverse events were joint stiffness, fatigue, fever, headache, and muscle pain.

You can access an in-depth discussion of safety and trial data here (p. 7).

Competitive environment

RSV infection is one of the most common infections without a vaccine or treatment. While typically mild in disease course, severe infections are still a significant driver of morbidity and mortality in at-risk individuals. GSK's vaccine will potentially be the first RSV vaccine approved by the FDA, likely followed shortly thereafter by Pfizer's RSV vaccine.

In the pivotal trial, Arexvy showed significant efficacy against LRTD caused by RSV and appears well tolerated. However, incidence of symptomatic RSV infection was low in the trial, likely due to the atypical RSV season because of the COVID-19 pandemic. The trial was also unable to estimate efficacy against more severe RSV outcomes (i.e., hospitalization, death). The need for revaccination and the frequency of administration is not yet known.

Brand name: Abrysvo™
Expected FDA decision: May 2023

Pfizer's investigational RSV vaccine, Abrysvo, is also under review for the prevention of LRTD caused by RSV in adults aged 60 years and older.

Clinical profile

Abrysvo is also based on the F proteins found on the RSV virus surface. While the GSK version uses one form of the F protein, the Pfizer version is bivalent, which means it uses two forms of F selected to optimize protection against RSV.[3]

Pivotal trial data

Abrysvo was evaluated in a Phase 3, randomized, double-blind, placebo-controlled study in 32,614 adults aged 60 years and older (RENOIR). Patients received a single dose of the vaccine or a placebo via IM injection. The primary endpoint was prevention of RSV lower respiratory tract illness (LRTI) during the first RSV season. LRTI was measured as ≥ 2 or ≥ 3 lower respiratory signs/symptoms lasting more than 1 day.

The overall vaccine efficacy was 66.7% against RSV LRTI ≥ 2 symptoms and 85.7% against RSV LRTI ≥ 3 symptoms, meeting the trial's primary endpoints.

Safety

The most common local adverse events with Abrysvo use were pain at injection site, redness, and swelling; the most common systemic adverse events were fatigue, headache, muscle pain, joint pain, diarrhea, nausea, and fever.

You can access an in-depth discussion of safety and trial data here (p. 9).

Competitive environment

As discussed previously, there is a high unmet need for RSV treatments or vaccines. The FDA approval decision for Pfizer's RSV vaccine in the elderly population is likely to come shortly after the decision for GSK's vaccine. Like the GSK vaccine, Abrysvo showed significant vaccine efficacy against LRTD caused by RSV and it appears well tolerated.

The same trial limitations discussed previously also apply to the Pfizer vaccine. These include low incidence of symptomatic RSV infection, lack of data for more severe RSV infection outcomes, and lack of data on the need for revaccination.

Unlike the GSK vaccine, Pfizer also submitted trial results with positive data for Abrysvo in pregnant patients to help protect newborns and young infants from RSV disease after birth. Pfizer has announced that an FDA submission for use in pregnant patients has been accepted by the FDA with an approval decision expected in August 2023.[4]

Delandistrogene moxeparvovec: Brand name to be determined
Expected FDA decision: May 29, 2023

Delandistrogene moxeparvovec, from Sarepta Therapeutics, is under review for the treatment of ambulatory patients with Duchenne muscular dystrophy (DMD).

DMD is a rare, progressive, neuromuscular disorder. DMD primarily affects boys, but rarely it can affect girls. The age of onset is usually between 3 and 5 years.

DMD is characterized by weakness and wasting of the muscles of the pelvic area followed by the involvement of the shoulder muscles. Historically, boys with DMD did not usually survive beyond their teen years. Today, with advances in cardiac and respiratory care, survival into the early 30s is becoming more common.[5]

DMD is caused by mutations of a protein called dystrophin. The most common mutation in people with Duchenne is a deletion of one or more sections of DNA called exons.6 This causes errors in the instructions for making dystrophin, leading to a lack of dystrophin that causes muscle cells to be fragile and easily damaged.7

The birth prevalence for DMD is estimated to be 1 in every 3,500 live male births.

Clinical profile

Delandistrogene moxeparvovec is a gene therapy that delivers a gene to muscle cells that codes for a functional form of dystrophin (micro-dystrophin).

Pivotal trial data

The FDA submission for accelerated approval for delandistrogene moxeparvovec was based on Study SRP-9001-103 (ENDEAVOR). In addition, data from studies SRP-9001-101 and SRP-9001-102 were used in an integrated analysis across these three early-stage studies. The analysis compared functional results in the treated population against an external control (EC) group weighted to be similar to the study group.

External control is a technique where patients not receiving the new treatment are drawn from another population that is not part of the study. For example, patients from a network of clinics. EC groups can be valuable for rare diseases such as DMD, with few patients available for a study.[8]

ENDEAVOR included 20 ambulatory DMD patients between the ages of 4 to 7. Delandistrogene moxeparvovec was administered via intravenous (IV) infusion.

The primary endpoint is the change from baseline in the quantity of micro-dystrophin protein expression measured at 12 weeks. Key exploratory endpoints were North Star Ambulatory Assessment (NSAA) and certain timed functional tests. At 12 weeks, mean micro-dystrophin expression was 54.2% of normal. At 1 year, NSAA total scores in the treated patients improved 3.9 points and participants in the EC improved 0.8 points.

An integrated analysis of the three studies focused on 1-year functional data from patients who received the target dose of delandistrogene moxeparvovec. NSAA change from baseline 1 year after treatment was 2.4 points higher when compared to the weighted EC group.

Safety

The most common adverse events with delandistrogene moxeparvovec use were vomiting, decreased appetite, nausea, upper respiratory tract infection, pain in extremity, upper abdominal pain, and procedural pain.

You can access an in-depth discussion of safety and trial data here (p. 11).

Competitive environment

The pharmacologic standard of care for DMD are glucocorticoids. Glucocorticoids have been shown to improve motor and pulmonary function, and to delay losing the ability to walk independently.

Several disease-modifying therapies have been approved for DMD. These are exon-skipping therapies such as Exondys 51®, Vyondys 53®, Amondys 45™. As mentioned, in DMD, one or more exons are deleted. Exon skipping allows the cellular machinery to skip over the missing exon and resume the proper sequencing.[9]

But exon skipping treatments can only be used in patients with specific mutations. And while they provide small improvements in dystrophin expression, clinical benefit has not been established. Despite advancements in supportive care for DMD, there is no cure and patients still suffer from significant morbidity and mortality, especially once they reach their teenage years.

The data for delandistrogene moxeparvovec is promising, with improvements in dystrophin expression and functional data that suggests the gene therapy is altering the trajectory of the disease. While long-term data is limited, the two- and four-year results that are available provide some evidence of sustained stabilizing of function.

However, Sarepta's current FDA submission for approval was through the accelerated approval pathway, based on early-stage trial data that relies primarily on a surrogate endpoint of improvement in dystrophin expression. The data is also limited to ambulatory patients between 4 to 7 years of age. A 52-week confirmatory Phase 3 study is currently ongoing, with data expected in 2023.

For reference, the WAC for other one-time gene therapies ranges from $2.1 million (Zolgensma® for spinal muscular atrophy) to $3.5 million (Hemgenix® for hemophilia B).

Obeticholic acid: Brand name to be determined
Expected FDA decision: June 23, 2023

Obeticholic acid, from Intercept Pharmaceuticals, is under review for the treatment of patients with pre-cirrhotic liver fibrosis due to nonalcoholic steatohepatitis (NASH).

NASH is a progressive liver disease caused by excessive fat accumulation in the liver that leads to inflammation and liver injury. Progressive liver scarring (fibrosis) can lead to cirrhosis, liver failure, cancer, and death.

NASH includes the descriptor 'nonalcoholic' because, while it can cause the same kind of liver damage found in long-term alcoholism, it occurs in people who don't abuse alcohol.[10]

The prevalence of NASH in the general population is between 1.5% to 6.45%. Of the patients with NASH, about 20% are estimated to have advanced fibrosis without cirrhosis.

Clinical profile

Obeticholic acid is a potent agonist of the farnesoid X receptor, which regulates the metabolism of bile and cholesterol in the liver. Agonists bind to specific receptors and cause a process in the cell to become more active. By binding to the farnesoid X receptor, obeticholic acid increases liver bile flow, suppresses bile production, and slows the process that normally causes inflammation and cirrhosis of the liver.[11]

Obeticholic acid is currently available under the brand name Ocaliva®, for the treatment of primary biliary cholangitis (PBC).

Pivotal trial data

Obeticholic acid was evaluated in REGENERATE, an ongoing Phase 3 study in 2,477 patients with liver fibrosis due to NASH. Patients were randomized to obeticholic acid 10 mg, obeticholic acid 25 mg administered orally once daily, or placebo. The co-primary endpoints were achieving at least one stage of fibrosis improvement with no worsening of NASH at month 18 on liver biopsy and resolution of NASH with no worsening of liver fibrosis.

Improvement in fibrosis with no worsening of NASH occurred in 22.4% of patients with obeticholic acid 25 mg, 14.1% with obeticholic acid 10 mg, and 9.6% with placebo. The difference vs. placebo was only statistically significant for the 25 mg dose.

Neither dose of obeticholic acid was shown to be superior to placebo for the second primary endpoint of NASH resolution with no worsening of liver fibrosis.

The most common adverse event with obeticholic acid use was itchy skin.

You can access an in-depth discussion of safety and trial data here (p. 14).

Competitive environment

Obeticholic acid would potentially be the first FDA approved treatment for NASH. NASH is a very common chronic condition in the U.S. with millions of patients potentially

eligible for treatment. The current first line treatment for NASH is lifestyle modification – primarily weight loss. A reduction in weight can not only reduce inflammation in the liver but also potentially improve fibrosis. However, only a small subset of patients with NASH can achieve adequate weight loss. In the absence of any approved drugs, treatment guidelines suggest the off-label use of vitamin E, semaglutide, or insulin-sensitizing agents (e.g., pioglitazone), but the data for these therapies for treatment of NASH are very limited.[12]

In the pivotal trial, the overall results for obeticholic acid were modest. Obeticholic acid showed no significant impact with respect to NASH resolutions and only the 25 mg dose demonstrated significant improvements in fibrosis. Long-term data (all-cause mortality and liver-related clinical outcomes) will be included in the end-of-study analysis but are not yet available. Additionally, obeticholic acid is associated with an increase in low-density lipoprotein cholesterol (LDL-C). This could be a concern in patients with NASH as they often have comorbidities that put them at risk for cardiovascular events. Notably, LDL-C levels do return to near baseline by month 12.

Finally, while obeticholic acid may be first to market for treatment of NASH, Madrigal Pharmaceuticals has announced positive Phase 3 trial data (both primary endpoints met) for their investigational oral drug, resmetirom. Madrigal is expected to file for accelerated approval for resmetirom in the first half of 2023.

Financially, as noted, the potential target population may be very large. (However, see here for a closer look at some of the subtleties around NASH population estimates.) As mentioned above, obeticholic acid is currently available under the brand name Ocaliva for treatment of PBC and costs approximately $105,000 per year. However, Intercept is expected to market obeticholic acid for NASH under a different brand name with indication-specific pricing. [13]

References

[Unless otherwise indicated, all sources taken from Optum Rx Outlook® 1st Quarter 2023.]

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