2024 FDA Approvals: A Wave of Innovation in Treating Serious Diseases

In 2024, the Food and Drug Administration Center for Drug Evaluation (CDER) approved 50 new small molecules, biologics, and oligonucleotide therapies (1). The approvals — the second largest in 30 years — include an oligonucleotide therapy for blood cancer, an antisense oligonucleotide shown to significantly drop triglyceride levels, and an mRNA vaccine targeting the respiratory syncytial virus.

IMETELSTAT: a first-in-class telomerase inhibitor

On June 6, 2024, Imetelstat (RYTELO) was approved by the Food and Drug Administration (FDA) for adults with low- to intermediate-1 risk myelodysplastic syndromes (MDS). Those eligible for the therapy must have transfusion-dependent anemia requiring four or more red blood cell units over eight weeks and have not responded to, lost response to, or are ineligible for erythropoiesis-stimulating agents (ESAs).

Created by the biopharmaceutical company Geron Corporation, the drug reduces the need for red blood cell transfusions, increasing quality of life.

What it treats:

Myelodysplastic syndrome (MDS) includes an assorted group of disorders caused by poorly formed or malfunctioning blood cells. MDS affects all ages but is more common in older adults (2). Most MDS diagnoses are "lower-risk" diseases (LR-MDS), meaning there's a lower risk of

death or evolution to acute myeloid leukemia. However, the most common complication of LR-MDS is progressive anemia, which eventually leads to a need for regular red blood cell transfusions (2). Anemia and the resulting transfusions, as well as a complication related to cytopenias and inflammation, have been shown to reduce the quality of life and increase mortality compared to the general population (2).

Erythropoiesis-stimulating agents (ESAs), which increase RBC production in the bone marrow, are the first line of therapy for those with LR-MDS and symptomatic anemia. However, ESAs are not curative, and patients eventually stop responding to them as a form of treatment (2). Therefore, there is a high unmet need for those with LR-MDS, which Imetelstat may just fill.

How Imetelstat works:

Imetelstat, or RYTELO, is an aptamer oligonucleotide telomerase inhibitor, meaning it blocks the activity of the telomerase enzyme by binding to the template region of its RNA component. Telomerases — the ribonucleoprotein complexes that elongate the telomeres at the end of chromosomes — are associated with cancer and aging-related diseases (1). The recommended dosage for Imetelstat is 7.1mg/kg, administered intravenously over two hours every 28 days.

Clinical trial results:

The FDA approval of Imetelstat was based on results from the IMerge Phase 3 clinical trial, which demonstrated significantly higher rates of red blood cell transfusion independence compared to placebo, increases in hemoglobin levels, and a reduction in transfusion burden compared to placebo.

The most common adverse reactions were neutropenia and thrombocytopenia, which lasted less than two weeks and were generally manageable.

TRYNGOLZA: first-ever treatment for adults living with familial chylomicronemia syndrome (FCS)

The end of 2024 also saw the FDA approval of Tryngolza, the first-ever treatment shown to significantly and substantially reduce triglyceride levels in adults with familial chylomicronemia syndrome (FCS) and meaningfully reduce acute pancreatitis events when paired with an appropriate diet.

What it treats:

FCS is caused by the lack of functional lipoprotein lipase (LPL) which is the enzyme responsible for breaking down fats, impairing the body's ability to remove triglycerides from the bloodstream. Typically, triglyceride levels are below 150 mg/L, but these levels are greater than 880mg/dL for those with FCS.

Due to the accumulation of triglycerides, people with FCS have a high risk of acute pancreatitis, a painful and potentially fatal swelling of the pancreas. According to a new study from the University of Montreal, 67% of patients with the disease have had an acute pancreatitis episode requiring a hospital visit.

FCS affects around 3,000 people in the U.S. and 5,000 people globally, and currently, the only treatment is a strict fat-restricted diet and lifestyle modifications, like exercise and eliminating alcohol and simple carbohydrates, but Tryngolza may provide a more effective option.

The treatment is recommended for adults with FCS regardless of a genetically or clinically confirmed diagnosis and is to be used alongside a low-fat diet. It is unknown if Tryngolza is safe and effective in children.

How TRYNGOLZA works:

Tryngolza, also known as olezarsen, is a GalNAc conjugated antisense oligonucleotide (ASO) that specifically targets and binds to and degrades the RNA that encodes the protein apolipoprotein C-III (APOC-III). This protein typically slows the breakdown of fats and by decreasing APOC-III levels, Tryngolza enables the body to more efficiently break down and eliminate triglycerides, resulting in a substantial reduction of fat levels in the bloodstream and a significantly lower risk of debilitating and potentially life-threatening acute pancreatitis.

Clinical trial results:

The FDA approval of Tryngolza was based on a successful Phase 3 clinical trial in 66 adult patients with FCS and very high triglyceride levels (3). Participants received 80 or 50 mg of Tryngolza or a placebo every four weeks for 53 weeks. The reduction in APOC-III was dose dependent and significant compared to placebo, with 77% and 81% reduction at 12 months for 50 and 80 mg, respectively. After six months, those taking 80mg of Tryngolza had a significant placebo corrected 42.5% reduction in triglyceride levels, and after 12 months, a 57% reduction was observed. The lower 50 mg dose did not lead to a significant decrease in triglycerides at 6 months.

Importantly, patients on the drug were less likely to develop acute pancreatitis: only 5% of patients on Tryngolza experienced an episode compared to 30% in the placebo group experiencing one or more episodes. Additionally, a substantial reduction in hospitalization as well as time in hospital was observed for patients on Tryngolza (3).

Tryngolza had a favorable safety profile. The most common side effects were skin reactions from the injection, low platelet count, and joint pain.

Importantly the approved dose form is a low volume (0.8 mL), single dose autoinjector for at home use. Tryngolza is continuing to be studied in multiple Phase 3 studies in the much larger severe high triglyceride (sHTG) population, with a readout planned for the second half of this year.

mRESVIA (mRNA-1345): first mRNA vaccine for respiratory syncytial virus (RSV)

In May 2024, the FDA approved the first-ever mRNA vaccine for respiratory syncytial virus (RSV). Created by Moderna and using the same lipid nanoparticles (LNPs) as the company's COVID-19 vaccine, the mRNA-1345 vaccine is designed to protect adults 60 years and older from lower respiratory tract disease caused by RSV infection. The European Commission and Health Canada approved the vaccine in August and November, respectively.

How it works:

MRNA-1345, or mRESVIA, works by preparing the body to defend itself against RSV. It includes an mRNA sequence containing instructions for making a stabilized prefusion F glycoprotein — a protein expressed on the virus's surface that is needed for it to enter and infect the host cells. After receiving the vaccine, some cells will read the mRNA instructions and temporarily produce the RSV F glycoprotein. The immune system will then recognize this protein as foreign and produce antibodies and activate T cells to attack it. This immune response will also recognize a similar protein called RSV-B glycoprotein F, which is found on the RSV-B subtype. If a vaccinated individual later comes into contact with RSV, their immune system will recognize it and be ready to defend the body. After vaccination, the mRNA from the vaccine is broken down and removed from the body.

What mRESVIA treats:

Respiratory syncytial virus (RSV) leads to infections of the lungs and respiratory tract. Infecting both children and adults, it's so common that almost all children will have had an RSV infection by their second birthday. In adults and older, healthy children, symptoms are mild and often resemble the common cold. However, in severe cases, RSV can spread to the lower respiratory tract, causing pneumonia or bronchitis.

While most children and adults recover in a few weeks, severe infections require hospitalization. In the U.S., there are over 2 million RSV infections in children, more than 86,000 of which result in hospitalization every year. Amongst older adults, 177,000 are hospitalized in the U.S. due to RSV and 14,000 die annually. The combined medical costs of children and older adults is greater than $5 billion annually in the U.S. alone.

Clinical trial results:

The approval of mRESVIA was based on the Phase 3 ConquerRSV trial, which included more than 37,000 adults aged 60 or older in 22 countries (1). The vaccine demonstrated 83.7% protection from lower respiratory tract disease (LRTD) with at least two signs or symptoms after a median follow-up of four months. The vaccine was similarly effective at 82.4% against LRTD with at least three signs or symptoms (4). An additional analysis, which followed up with participants eight months later, found the vaccine was still effective, with an efficiency of 74.6%

against RSV-LRTD with at least two symptoms and 63% against RSV-LRTD with three or more symptoms.

Systemic adverse reactions were more likely in those who received the vaccine compared to the placebo group, with fatigue, headache, myalgia, and arthralgia being the most typical. Serious adverse events were experienced in 2.8% of participants in both groups. Most reactions were transient and mild to moderate in severity, with less than 0.1% related to the shot (4).

The drug does have competition in the field, with Pfizer and FSK receiving FDA approval in 2023 for their non-mRNA vaccines protecting older adults against RSV.

FDA approvals: addressing unmet needs

The recent FDA approvals of RYTELO (Imetelstat), TRYNGOLZA, and mRESVIA are helping to address the pressing unmet needs of patients facing conditions with limited treatment options and offer hope for improved quality of life. As these therapies are integrated into clinical practice, they not only highlight the progress in biopharmaceutical research but also underscore the importance of continued innovation in addressing complex medical challenges.

In the past decade, the FDA has approved an average of 46.5 novel therapies each year (1). Among the FDA approvals to watch for in 2025 include an antisense oligonucleotide therapy for treating hereditary angioedema. An upcoming article will look more in-depth at some of the oligonucleotide therapies that will potentially be approved this year.

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