Optum Rx drug pipeline insights report

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Optum Rx®

Two potential treatments for Alzheimer's disease on the horizon

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Greetings and welcome to this year's first issue of Drugs to Watch. These treatments have been approved or have potential FDA approval decisions in the first quarter of 2023.

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Drug overview

We feature two treatments for Alzheimer's disease: **lecanemab**, which was approved on January 6, and **donanemab**. The drugs are beta-amyloid targeted antibodies, similar to Aduhelm® (aducanumab), which was approved in June 2021.

Similar to lecanemab, donanemab was reviewed on the accelerated approval pathway based on a surrogate endpoint – reductions in beta-amyloid in the brain. Recently, the FDA denied the accelerated path, which means approval will rest on phase 3 confirmatory trial results. The FDA's review of the data will be critical for assessing the clinical benefit and the overall evaluation of the beta-amyloid hypothesis in the treatment of Alzheimer's disease.

We also discuss Roctavian™ (**valoctocogene roxaparvovec**), a first-in-class gene therapy for hemophilia A. By providing a functional copy of the Factor VIII gene, it could reduce or eliminate the need for costly clotting factor replacement therapy in some patients. We recently reviewed etranacogene dezaparvovec for hemophilia B, which is now approved with the brand name Hemgenix®.[1]

Finally, **fezolinetant** is a first-in-class, non-hormonal treatment for menopause-associated vasomotor symptoms (VMS) and could represent a better tolerated alternative to the current standard of care (hormone therapy and antidepressants).

Please refer here for additional technical background and supplemental sources.

Leqembi™ (lecanemab): FDA approved January 6, 2023

Lecanemab, from Eisai/Biogen, is under review for the treatment of mild cognitive impairment (MCI) due to Alzheimer's disease and mild, or early, Alzheimer's disease.

Alzheimer's disease is an irreversible brain disorder that progressively destroys memory and cognition. MCI is usually the first sign of Alzheimer's disease, which is characterized by changes in the brain, including the abnormal accumulation of a protein known as amyloid beta.

Alzheimer's disease is the most common form of dementia. It affects about 6.5 million people in the U.S. and is the 5th leading cause of death among adults aged 65 years or older.

Clinical profile

Lecanemab is an antibody that binds to fibrillar amyloid, a soluble, toxic version of beta-amyloid.[2]

By binding, lecanemab can neutralize the fibrillar amyloid and help "tag" it, so the immune system can clear it from the brain.[3]

As part of the Aduhelm accelerated approval process, the FDA approved the drug by using reduction in beta-amyloid plaque as a surrogate endpoint that was reasonably likely to predict a clinical benefit to patients with early Alzheimer's disease.[4]

Pivotal trial data

Eisai/Biogen submitted lecanemab for accelerated approval in mid-2022 based on Phase 2 biomarker data. The trial results at 12 months measured change on the Alzheimer's Disease Composite Score (ADCOMS) versus placebo. A key secondary endpoint was brain amyloid reduction.

The Phase 2 data has been characterized as showing "robust plaque clearance" plus a "modest slowing" in cognitive decline.[5]

Since that time, new Phase 3 trial results (Clarity AD) were published in the *New England Journal of Medicine* on November 29.[6]

The Clarity AD trial studied the effects of lecanemab in patients with early Alzheimer's. Patients were randomized to receive lecanemab or a placebo once every 2 weeks. At 18 months, patients taking lecanemab showed a 27% slower cognitive and functional decline compared to placebo in the Clinical Dementia Rating-Sum of Boxes (CDR-SB) score. This corresponded with a -0.45-point difference vs. placebo on the 18-point CDR-SB scale.[7]

Safety

Lecanemab is subject to similar adverse event concerns as other amyloid-targeting drugs: brain swelling, or bleeding associated with amyloid-related imaging abnormality (ARIA). This effect has been seen in other Alzheimer's studies involving drugs designed to eliminate beta-amyloid in the brain.[8]

In the Clarity AD trial, 22% taking lecanemab experienced ARIA, while under 10% in the placebo group did. In most, the effect was asymptomatic.[9]

You can access an in-depth discussion of safety and trial data here (p. 1).

Competitive environment

There is a high unmet need for treatments for Alzheimer's disease since it is a leading cause of illness and death among the elderly and existing treatment options have been ineffective.

Currently available medications such as cholinesterase inhibitors (e.g., Aricept®) and the NMDA inhibitor Namenda® are considered symptomatic therapies of limited benefit and do not change the underlying course of the disease.

In June 2021, the FDA approved Aduhelm® (aducanumab), the first amyloid beta-directed antibody, via the accelerated approval pathway based on reductions in amyloid beta plaques. Subsequently, a CMS National Coverage Determination limited Medicare coverage for Aduhelm and other beta-amyloid targeted therapies to patients enrolled in clinical trials because of unknown clinical benefit.

Lecanemab would be the second drug in the class with FDA approval through the accelerated approval pathway that was followed to approve Aduhelm, based on the surrogate of reductions in beta-amyloid plaques. The recently announced Phase 3 data demonstrated that lecanemab showed slowing of cognitive decline, but the benefit, while statistically significant, was generally less than what would be considered clinically meaningful. As noted, the full Phase 3 study results are now available. Eisai is planning to discuss this data with the FDA in order to file for traditional (full) approval by the end of the first quarter in 2023.

Like Aduhelm, lecanemab is associated with ARIA-related side effects, including edema and microhemorrhages which would require additional provider monitoring. It may also face competition from Eli Lilly's donanemab (see below). Unlike Aduhelm or donanemab, lecanemab requires biweekly IV infusions as opposed to monthly dosing.

The wholesale price for Leqembi has been set at $26,500 per patient per year. For reference, the Wholesale Acquisition Cost (WAC) for Aduhelm is approximately $28,000 per year.

Donanemab: Brand Name: TBD
Expected FDA decision: Delayed

Donanemab, from Eli Lilly, is under review for the treatment of MCI due to Alzheimer's disease and mild, or early, Alzheimer's disease. On January 19, 2023, the FDA denied accelerated approval for donanemab due to insufficient data. Eli Lilly says that expanded data will be available by the second quarter of 2023, when they expect to apply for full approval.

Clinical profile

Like lecanemab (and Aduhelm), donanemab is a type of beta-amyloid targeted antibody. It works slightly differently than lecanemab in that it is designed to bind to beta-amyloid proteins that have already aggregated into plaques. Donanemab works by stimulating the immune system to attack beta-amyloid plaques and clear them from the brain.[10]

Pivotal trial data

The FDA submission for accelerated approval for donanemab was based on TRAILBLAZER-ALZ, a Phase 2, randomized, double-blind, placebo-controlled study in 257 patients with early symptomatic Alzheimer's disease.

Donanemab met its primary study objective, slowing the clinical decline of Alzheimer's disease by 32% relative to placebo on the Integrated Alzheimer's Disease Rating Scale (iADRS) at 76 weeks.

Also, there was a "substantial reduction" of amyloid plaque, with 68% of patients who received donanemab achieving complete amyloid clearance.[11]

It's worth noting that on December 1, Lilly released results for a small study (TRAILBLAZER-ALZ 4) that compared donanemab against Aduhelm. 148 patients with early symptomatic Alzheimer's disease received one of the two drugs. At 6 months, patients receiving donanemab had cleared amyloid from the brain in approximately 38% of those treated, compared to approximately 2% for those given Aduhelm.[12]

Safety

Like the other drugs in the class, the most common adverse event with donanemab use was ARIA.

You can access an in-depth discussion of safety and trial data here (p. 4).

Competitive environment

Like lecanemab, donanemab would be another beta-amyloid targeted therapy for the treatment of Alzheimer's disease. As previously noted, there is a high unmet need for treatments for Alzheimer's disease.

Like lecanemab, Eli Lilly was pursuing an accelerated approval for donanemab based on Phase 2 data demonstrating improvements in the surrogate marker of amyloid plaque levels. Eli Lilly expects data from the Phase 3 TRAILBLAZER-ALZ-2 study by mid-2023.Now, Lilly will rely on

the Phase 3 study to serve as the confirmatory trial for a traditional (full) approval. Until this data is available, the clinical benefit with donanemab is uncertain.

Like the other drugs in the class, donanemab is associated with ARIA-related side effects which would require additional provider monitoring. It must be administered via IV infusion.

In a head-to-head comparison, donanemab demonstrated superiority vs. Aduhelm for beta-amyloid clearance, but improved clinical outcomes is unknown.

For reference, the WAC for Aduhelm is approximately $28,000 per year.

Valoctocogene roxaparvovec: Brand Name: Roctavian™
Expected FDA decision: March 31, 2023*

**Target date may be delayed if the FDA incorporates a new phase 3 analysis (GENEr8-1) into the application.[13] See below.*

Valoctocogene roxaparvovec, from BioMarin, is under review for the treatment of adults with severe hemophilia A.

Clinical profile

Hemophilia A is caused by mutations in the Factor VIII (FVIII) gene. The mutations cause the clotting protein, FVIII, to not function correctly or be underproduced. People with hemophilia can experience bleeding episodes that can cause pain, irreversible joint damage and life-threatening hemorrhages.

Roctavian uses a viral vector (AAV5) to deliver functional copies of the FVIII gene to the liver, where clotting factors are produced. The intention is for the added genes to spread and restore effective FVIII production. This should lower the risk of bleeds, and potentially reduce or eliminate the need for routine preventive treatments.[14]

Pivotal trial data

Valoctocogene roxaparvovec was evaluated in a Phase 3 study (GENEr8-1). It enrolled 134 patients with severe hemophilia A who had been treated continuously with prophylactic FVIII replacement therapy for a minimum of 1 year. The study delivered a single infusion of valoctocogene roxaparvovec. At approximately 1 year (49-52 weeks), participants experienced substantially reduced annualized bleeding rates, reduced factor VIII utilization, and increased factor VIII activity compared to the year prior to the study.[15]

Additionally, BioMarin has collected data up to 6 years from a smaller Phase 1/2 study. In the follow-up period, valoctocogene roxaparvovec has demonstrated sustained efficacy.

Safety

The most common adverse events with valoctocogene roxaparvovec use were liver enzyme elevation, nausea, headache, and fatigue.

You can access an in-depth discussion of safety and trial data here (p. 18).

Competitive environment

If approved, valoctocogene roxaparvovec would be the first gene therapy for hemophilia A. It would reduce, and potentially eliminate, chronic and as-needed factor replacement therapy. Factor replacement therapy has a high treatment burden and can be costly, particularly in severe cases requiring high doses or prophylactic use of FVIII.

Treatment will be limited to 50% of patients with severe hemophilia A. Adults who do not have inhibitors (antibodies) against factor VIII and no antibodies against its adeno-associated virus would not be candidates for treatment.

Like other gene therapies, particularly for hemophilia, the primary question is the unknown durability of response. Sustained efficacy is important with gene therapies because of the high projected cost for a one-time dose.

Other gene therapies for hemophilia A are in development, but not expected to reach the market in the next 2 years. There may be some patients who are eligible and willing to be treated with gene therapy, but could wait until data is available for competitors and not early adopters for valoctocogene roxaparvovec.

For reference, the WAC for Hemgenix for is $3.5 million for a one-time dose.[16] You can learn more about etranacogene dezaparvovec here.

Fezolinetant: Brand Name: TBD
Expected FDA decision: February 22, 2023

Fezolinetant, from Astellas Pharma, is under review for the treatment of moderate-to-severe vasomotor symptoms (VMS) associated with menopause.

At about age 40, most women begin the transition to perimenopause and menopause, as their levels of estrogen and progesterone start to fall. During this transition, some women experience vasomotor symptoms (VMS). These are frequently experienced as hot flashes and/or night sweats.[17]

For most women, VMS symptoms are manageable. However, there is a significant subset for whom these symptoms can negatively affect sleep, mood, and quality of life.[18]

In the U.S., about 60% to 80% of women experience these symptoms during or after the menopausal transition.

Clinical profile

VMS are thought to result from changes in the hypothalamus caused by falling levels of estrogen. The neurokinin B (NKB) signaling pathway has been implicated in the development of vasomotor symptoms.[19] NKB is a neuropeptide associated with regulating female reproduction that serves as a chemical messenger in the hypothalamus.[20]

Stimulating NKB-neurokinin 3 receptor (NK3R) signaling can induce hot flashes, therefore fezolinetant acts as an antagonist of this signaling pathway to mitigate menopausal symptoms.[21]

Pivotal trial data

The efficacy of fezolinetant was evaluated in two Phase 3 studies (SKYLIGHT 1 and SKYLIGHT 2) in 1,028 women aged 40 to 65 years with moderate-to-severe VMS. The co-primary endpoints were mean change from baseline to week 4 and week 12 in frequency and severity of moderate-to-severe VMS.

No data is published at this time, but results from abstracts and press releases indicate that both trials met all four co-primary endpoints. Women treated with fezolinetant reported, on average, 1.8 to 2.5 fewer episodes of moderate-to-severe VMS per day at week 4 and week 12 for vs. a placebo. While the percent of responders was not available, the severity of VMS episodes appeared to be reduced in responders.[22]

Safety

The most common adverse event with fezolinetant use was headache.

You can access an in-depth discussion of safety and trial data here (p. 12).

Competitive environment

If approved, fezolinetant would provide an additional non-hormonal treatment for VMS that appears to be well tolerated. VMS is a very common symptom associated with menopause and represents a large potential target population. The current standard of care is usually hormone therapy which is effective, but may not be an appropriate option in some women due to risks associated with breast cancer, heart disease, or stroke. Historically, the most used alternative to hormone therapy are antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs).

While fezolinetant provides an alternative, potentially well-tolerated treatment option for VMS, there are no head-to-head trials comparing it to existing standards of care, which are mostly available generically. Fezolinetant may also face future competition as Bayer's elinzanetant, a dual neurokinin-1,3 receptor antagonist, is currently being reviewed across three Phase 3 trials.

For reference, the WAC for Osphena® (ospemifene), a branded drug used for severe dyspareunia and vaginal atrophy associated with menopause, is approximately $3,000 per year.

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[Unless otherwise indicated, all sources taken from Optum Rx Outlook® 4th Quarter 2022.]

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