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OptumRx Drug Pipeline Insights Report

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Looking Ahead: 2022 Pipeline

By Sumit Dutta, Chief Medical Officer at OptumRx

As we welcome a new year, expect a steady cadence of new drug approvals in 2022. So, it's time to highlight key pipeline drugs with an expected FDA decision by the end of the first quarter.

In this selection we review several potential first-in-class therapies, including tezepelumab for the treatment of severe asthma. It will bring new competition with existing biologics used for treatment of severe asthma.

Cabotegravir is in development for pre-exposure prophylaxis (PrEP) of HIV-1 infection in at-risk individuals. It will be the first long-acting PrEP treatment for HIV. In clinical trials, cabotegravir has been associated with higher compliance and improvement in reducing the HIV incidence rate vs. the existing standard of care.

Vadadustat is novel treatment for anemia associated with chronic kidney disease. A similar drug (roxadustat) was rejected by the FDA in August 2021 for safety concerns. If vadadustat can overcome lingering questions about cardiovascular safety, it could be the first oral alternative to the existing injectable treatments.

Finally, we expect 2022 to bring new authorizations, full approvals, and additional uses for COVID-19 vaccines and treatments. Due to the rapidly changing nature of the pandemic, these drugs are out of scope for this report. However, please look for this detailed discussion from our Pipeline Surveillance team on COVID-19 vaccines and treatments.

Here are our featured drugs for the first quarter of 2022. Please refer here for additional technical background and supplemental sources.

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Drug overview

Tezepelumab *(Brand Name to be determined.)* Expected FDA decision: 1Q 2022.

Tezepelumab is in development for treatment of patients with severe asthma. It is administered subcutaneously once every four weeks.[1]

There are an estimated one million people in the U.S. with severe, uncontrolled asthma. Severe, uncontrolled asthma is debilitating, with patients experiencing significant limitations in lung function and a reduced quality of life.

Epithelial cells protect the airway from allergens, viruses and other airborne particles by releasing protective molecules including thymic stromal lymphopoietin (TSLP). Overexpression of TSLP can play a key role in airway inflammation, causing asthma symptoms and exacerbations.[2]

Tezepelumab works to block TSLP, which may prevent asthma exacerbations for improved asthma control.

Tezepelumab was evaluated in two Phase 3 studies: NAVIGATOR and SOURCE.

In the NAVIGATOR study, tezepelumab reduced the annual asthma exacerbation rate vs. placebo by 56% in the entire trial population. Results were also tracked for patients with differing baseline blood eosinophil counts (a predictive biomarker). Tezepelumab reduced the exacerbation rate for each group, although results varied.[3]

The SOURCE study evaluated tezepelumab in adults with severe, daily oral corticosteroid-dependent asthma. Results demonstrated that use of Tezepelumab did not lead to a significant reduction in steroid use compared to placebo, however it did reduce the annual asthma exacerbation rate vs. placebo in the entire trial population.[4]

The most common adverse events with tezepelumab use were cold symptoms, upper respiratory tract infection, and headache.

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

Competitive environment

Tezepelumab would be a relatively late market entry in the severe asthma category and will be competing with well-established treatments. Several different biologic treatment options are currently available, including Nucala® (mepolizumab), Cinqair® (reslizumab), Fasenra® (benralizumab) and Dupixent® (dupilumab). However, existing treatments focus on specific asthma subtypes, which are characterized by different baseline blood eosinophil counts, and on whether the patient is dependent on a daily oral corticosteroid.

If approved, tezepelumab would offer a first-in-class biologic treatment for patients with severe, uncontrolled asthma shown to reduce asthma exacerbations, regardless of baseline blood eosinophil counts.

A novel mechanism of action and broad indication means tezepelumab could be used in a large target population. However, there are no head-to-head data comparing tezepelumab vs. existing therapies like Dupixent.

Drug overview

Tezepelumab is also in Phase 2 and 3 trials for the treatment of nasal polyps, chronic spontaneous urticaria, and chronic obstructive pulmonary disease. If approved, these could expand the target patient population and sales.

For reference, the wholesale acquisition cost for Dupixent is approximately $41,000 per year.

Cabotegravir *(Brand name to be determined.)* Expected FDA decision: January 24, 2022.

Cabotegravir is in development for pre-exposure prophylaxis (PrEP) of HIV-1 infection in at-risk individuals. Cabotegravir is administered orally for five weeks and then via intramuscular injection once every two months.

There are an estimated 200,000 people in the U.S. using PrEP therapy to prevent possible HIV infection.

Cabotegravir belongs to a class of antiretroviral drugs that block HIV replication called integrase strand transfer inhibitors.

Cabotegravir is formulated as an extended-release injection. It is currently approved as part of a combination regimen with rilpivirine for the treatment of HIV-1 infection (under the brand name Cabenuva®).

Cabotegravir was evaluated in a Phase 2/3 study including cisgender men who have sex with men and transgender women who have sex with men. Patients received PrEP therapy using either cabotegravir or oral daily Truvada® (emtricitabine/tenofovir disoproxil fumarate), a current standard of care treatment option. The primary endpoint was the HIV incidence rate, which was 0.41% with cabotegravir vs. 1.22% with Truvada. Overall, cabotegravir was 69% more effective than Truvada in preventing HIV acquisition in the study population. This was due to a higher rate of compliance with cabotegravir vs. Truvada in the trials.

Cabotegravir was also evaluated in a Phase 3 study including cisgender women from seven countries in sub-Saharan Africa. These patients also received either cabotegravir or Truvada. In this study the HIV incidence rate was 0.21% with cabotegravir vs. 1.86% with Truvada. Overall, cabotegravir was 89% more effective than Truvada.

Most adverse events were mild or moderate in severity and largely balanced between both treatment arms. Injection site reactions were more frequent with cabotegravir.[5]

You can access an in-depth discussion of safety and trial data here (p. 5).

Competitive environment
If approved, cabotegravir would be the first long-acting PrEP for HIV infection in at-risk individuals. The current standard of care includes daily oral administration of Truvada or Descovy® (emtricitabine/tenofovir alafenamide).

The primary differentiator for cabotegravir is maintenance dosing once every two months instead of daily oral administration of Truvada and Descovy. The longer dosing cycle with cabotegravir led to a higher rate of compliance and the demonstrated superiority vs. Truvada in the trials.

Drug overview

While cabotegravir provides an alternative with infrequent administration, it must be administered via intramuscular injection by a healthcare provider. This drug can be an option in patients who have difficulty swallowing or who have adherence issues.

Truvada and Descovy are far less expensive, well-established PrEP treatments that are highly effective when taken as directed. Both Truvada and Descovy performed similarly in their pivotal trials as Truvada did in the head-to-head vs. cabotegravir.

We are also watching lenacapavir, another long-acting HIV-1 treatment that is administered every six months. It is in development for the treatment of multidrug resistant HIV-1 infection and is also being evaluated for HIV PrEP. Should lenacapavir be approved, having two injectables may lead to a competitive market for long acting PrEP therapy.

For reference, the wholesale acquisition cost for Descovy is approximately $23,000 per year while branded Truvada retails at about $21,600 per year. Notably, in late March, 2020 generic Truvada first became available in the U.S. By April there were multiple generic manufacturers entering the market, and the retail price for the generic had dropped to less than $600 per year.[6]

Vadadustat *(Brand Name to be determined.)* Expected FDA decision: March 29, 2022.

Vadadustat is in development for treatment of anemia associated with chronic kidney disease (CKD) in adult patients on dialysis as well as adult patients not on dialysis. Vadadustat is administered orally once daily.

Anemia is a common complication of CKD and occurs because patients with the disease do not produce enough erythropoietin, a hormone that helps regulate production of red blood cells. More than 37 million American adults may have CKD and about 1 in 7 develop anemia

Current treatments for the CKD-associated anemia include iron, erythropoiesis-stimulating agents (ESAs), and, if necessary, red blood cell transfusions.

Vadadustat increases hemoglobin through use of the **hypoxia-inducible factor (HIF)** pathway. HIF is a cluster of genes which help high-altitude populations adapt to chronic low oxygen levels (i.e., hypoxia). By triggering the HIF factor, vadadustat effectively mimics the body's natural response to hypoxia with increased red blood cells and hemoglobin levels.

The efficacy of vadadustat was evaluated in four Phase 3 studies. Two trials involved patients with anemia and **dialysis-dependent** chronic kidney disease, while another two studies evaluated vadadustat in anemia patients with **non-dialysis-dependent** CKD. All studies compared vadadustat against Aranesp® (darbepoetin alfa), an ESA.

The two sets of trials yielded different results. First, among patients who **were** undergoing dialysis, vadadustat was noninferior to darbepoetin alfa in its ability to correct and maintain hemoglobin concentrations, as well as with respect to cardiovascular safety.[7] (Non-inferior means that the test product is not worse than the comparator by more than a small pre-specified amount.)

Drug overview

However, among patients who **were not** on dialysis, vadadustat was noninferior to darbepoetin alfa in managing hemoglobin but did not meet the prescribed noninferiority criterion for cardiovascular safety.[8]

The most common adverse events with vadadustat use were similar to darbepoetin alfa.

You can access an in-depth discussion of safety and trial data here (p. 23).

Competitive environment
If approved, vadadustat would be the first novel therapy for the treatment of CKD-related anemia since the introduction of ESAs and would offer an oral alternative to injectable products. In the head-to-head trials vs. an ESA, vadadustat provided similar improvements in hemoglobin in both dialysis and non-dialysis dependent patients.

Vadadustat is the second drug using the HIF pathway reviewed by the FDA. FibroGen and AstraZeneca's roxadustat received a Complete Response Letter in August 2021, following a negative FDA Advisory Committee meeting. The primary reason for roxadustat's rejection was concern around cardiovascular safety. This could also jeopardize the approval of vadadustat, particularly in the non-dialysis CKD population.

If vadadustat is approved but use is limited to dialysis-dependent CKD, this would significantly limit the market potential for the drug. Only a fraction of the chronic kidney disease population is dialysis dependent. Of the nearly six million people in the U.S. with anemia-associated chronic kidney disease, approximately 550,000 are estimated to be on dialysis.

Finally, vadadustat may also face future competition. It would enter the market at a time when biosimilars are now available for ESAs. For example, the biosimilar Retacrit® (epoetin alfa-epbx) was approved in 2018 with a wholesale cost 57.1% below Procrit® (epoetin alfa) and 33.5% below Epogen® (epoetin alfa).[9] A biosimilar for Aranesp is also in development.

In addition, GlaxoSmithKline has its own HIF pathway drug (daprodustat). It is in late-stage development, with a filing expected in the first half of 2022.

References

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