

OptumRx Drug Pipeline Insights Report



Looking ahead: 2020 Pipeline

From Sumit Dutta, Chief Medical Officer at OptumRx

OptumRx is pleased to provide this summary of notable new drug approvals expected for the balance of this year. This is part of our ongoing commitment to provide timely updates designed to increase your understanding of the near-term pharmaceutical pipeline.

In our last report we noted delays in drug development and postponement of FDA submissions due to COVID-19. While delays may be seen in some cases, in this report we outline reasons why delays may be the exception and that the COVID-19 impact to drug development is minimal. (See Market Trend to Watch, below.)

While expected new drug approvals reflect the pharmaceutical industry's continued emphasis on rare diseases, we also see new treatments for more "mainstream" conditions such as hypercholesterolemia and cancer.

The list contains a diverse mix of small and large molecule drugs: three are the first oral option in their respective categories. One drug uses an intriguing RNA-based mechanism to dampen or "silence" genetic signaling in order to correct an underlying genetic condition. Another drug will be the fourth CAR T cell therapy in what will be a rapidly-growing category.



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Drug overview

Here are five drugs with expected FDA approval dates in or near Quarter 4, 2020 that are expected to make significant impact in the market. Please refer [here](#) for additional technical background and the supplemental sources.



Roxadustat (Brand name: To be determined). Expected FDA decision: December 23, 2020.

Roxadustat is intended to treat anemia associated with chronic kidney disease (CKD).¹ Anemia is common in patients with CKD, and occurs when there is insufficient hemoglobin, which carries oxygen in the blood. CKD anemia can be associated with increased risk of hospitalization, cardiovascular complications, and death.²

In the U.S. approximately 4.8 million individuals are affected with anemia associated with CKD; about 500,000 of them receive dialysis. The manufacturer has applied to have roxadustat indicated for both the dialysis and the much larger non-dialysis market.^{1,3}

Roxadustat increases hemoglobin through use of the **hypoxia-inducible factor (HIF)** pathway. HIF is a cluster of genes that is present in all humans, and which helps high-altitude populations adapt to chronic low oxygen levels (i.e., hypoxia). By triggering the HIF factor, roxadustat effectively mimics the body's natural response to hypoxia with increased red blood cells and hemoglobin levels.^{2,3}

In contrast, the standard-of-care for CKD anemia is to inject erythropoiesis-stimulating agents (ESAs), which stimulate the bone marrow to make red blood cells. Branded ESAs available in the U.S. include Procrit®, Epogen® (epoetin alfa), and Aranesp® (darbepoetin alfa).⁴

Phase 3 trials showed that roxadustat resulted in significantly higher hemoglobin levels in dialysis-dependent patients compared with an ESA (i.e., epoetin alfa). In non-dialysis patients, roxadustat was shown to be superior vs. placebo.²

The risks of adverse events were not increased compared to patients receiving ESA therapy. [For additional trial details, see here \(p.25\).](#)

Competitive environment

If approved, roxadustat would be the first novel therapy for CKD-related anemia since 1989. It would offer an oral alternative to the injectable ESA products.¹

In addition to the increased hemoglobin compared to ESAs, roxadustat-treated patients required fewer red blood cell transfusions and less monthly intravenous (IV) iron use. Reduced iron supplementation would be an advantage, as IV iron comes with its own safety concerns.¹

Roxadustat may be associated with an improved cardiovascular (CV) safety profile compared to ESAs, which carry a boxed warning for increased CV risk. However, long term safety data is still pending.¹

Published studies in China (where roxadustat is marketed as Evrenzo®) indicate it is associated with adverse blood chemistry imbalances. This is concerning, since CKD patients are predisposed to these imbalances.¹

Roxadustat will be entering the market at a time when multiple biosimilar ESAs are now available. In addition, until recently roxadustat expected competition from other oral HIF pathway drugs, including

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Akebia Therapeutics' vadadustat. However, in September news came that vadadustat was linked to increased heart risks compared with ESA therapy in nondialysis-dependent CKD patients. Now analysts speculate that roxadustat could hold an early monopoly for HIF pathway drugs in the nondialysis-dependent indication.⁵

A sale price is not yet established for roxadustat. For reference, the average WAC price for Procrit is approximately \$1,500 per 30 days.¹



Relugolix (Brand name: To be determined). Expected FDA decision: December 20, 2020.

Relugolix is intended to treat advanced prostate cancer in men.

[Note that relugolix is also under FDA review as a potential new treatment for symptomatic uterine fibroids, with a projected action date of June 1, 2021.⁶]

Prostate cancer is the second most common cancer in American men. The American Cancer Society estimates that in 2020, there will be nearly 192,000 new cases of prostate cancer and over 33,000 deaths.¹ Advanced prostate cancer is cancer that has spread or has come back after treatment.¹

Testosterone is required for the normal growth and function of the prostate, and is also necessary for prostate cancers to grow. Therefore, the primary treatments for advanced prostate cancer focus on reducing the amount of testosterone in the body.⁷

Drugs called GnRH receptor agonists are considered the standard testosterone-reducing treatment for prostate cancer.⁸ They work by telling the pituitary gland to stop producing a hormone that stimulates testicles to release testosterone in men.⁷ Leuprolide is the leading drug in the class, which includes Eligard[®] and Lupron Depot[®].⁹

In contrast, relugolix is a GnRH antagonist which works by blocking the hormone that stimulates the production of testosterone by the testes.⁸

In a phase 3 trial (HERO), relugolix achieved rapid, sustained suppression of testosterone levels that was superior to leuprolide. In addition, relugolix demonstrated a 54% lower risk of major adverse cardiovascular events.⁸

Overall, the manufacturer notes that the incidence of adverse events in the relugolix and leuprolide trial groups was comparable.¹⁰ [For additional trial details, see here \(p. 23\).](#)

Competitive environment

If approved, relugolix would be the first oral GnRH receptor antagonist for advanced prostate cancer. Despite certain clinical advantages, relugolix is entering a crowded marketplace with generic alternatives available.¹

Leuprolide drugs can cause an initial testosterone surge that may result in a clinical flare of symptoms such as bone pain and obstructive urinary symptoms. One advantage relugolix offers is that it is proven to achieve rapid, sustained suppression of testosterone levels without the accompanying surge in testosterone levels.⁸

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An existing drug, Firmagon® (degarelix) can avoid these flares, however degarelix is not widely used. This is possibly due to the need for monthly injections, and an incidence of injection-site reactions approaching 40%.⁸

Relugolix also demonstrated a better cardiovascular safety profile vs. leuprolide. This is notable because patients with prostate cancer are at increased risk of cardiovascular events which are the leading cause of death in these patients.¹¹

Prices have not yet been announced. For reference, the WAC price of Lupron Depot is approximately \$20,000 per year.



Inclisiran (Brand name: To be determined). Expected FDA decision: December 2020.

Inclisiran was developed to treat elevated low-density lipoprotein cholesterol (LDL-C) in patients with atherosclerotic cardiovascular disease (ASCVD) and familial hypercholesterolemia (FH). FH is caused by genetic mutations that impact the breakdown of LDL-C.¹

Over 29 million people are affected with ASCVD and FH in the U.S. Of these patients, about 22 million are treated with oral lipid lowering therapies (e.g., statins).¹ For those who do not respond adequately to statins there are currently two FDA-approved medications in a relatively new drug class known as PCSK9 inhibitors. These are Repatha® (evolocumab) and Praluent® (alirocumab).¹²

Inclisiran is also a PCSK9 inhibitor, but it works differently than the existing drugs. Inclisiran is a **small interfering RNA (siRNA)**.¹³ Too much PCSK9 can hinder the body from removing LDL. Where currently approved PCSK9 inhibitors, Repatha and Praluent, prevent PCSK9 from circulating, inclisiran uses gene silencing to prevent the production of PCSK9, which leads to lower LDL levels.¹⁴ The term RNA interference describes using a gene's own DNA sequence **to stop its' functioning**, a process that researchers call **gene silencing**. Originally restricted to biomedical research, gene silencing can now be used therapeutically.¹³

Phase 3 trials showed that inclisiran was able to lower LDL levels by an average of 54.1% after about a year and a half compared to placebo in patients already taking their maximum doses of statins.¹⁵

The most common adverse event with inclisiran use occurred at the injection site. [For additional trial details, see here \(p. 28\).](#)

Competitive environment

If approved, inclisiran would provide an additional PCSK9 therapy to reduce LDL-C. Inclisiran would be a relatively late market entry, as both Repatha and Praluent have been available since 2015. All three products are administered via subcutaneous injection. The primary difference for inclisiran is that it can be administered every 6 months while Repatha and Praluent have to be administered every 2 to 4 weeks.¹

Inclisiran will likely require administration by a healthcare provider, while the others can be self-administered.¹

We do not expect inclisiran to compete with statins given their well-documented long-term cardiovascular (CV) outcomes benefit data and low cost. Like existing PCSK9 inhibitors, inclisiran is anticipated to be used as add-on therapy to patients maximized on statin therapy.

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In comparison to the existing PCSK9 drugs, which also have documented CV data, results from inclisiran's long-term cardiovascular outcomes trial (ORION-4) are not expected until 2024. This could make physicians reluctant to choose it over the existing PCSK9s.¹

For reference, the WAC price for Repatha and Praluent is approximately \$5,850 per year.¹



Berotralstat (Brand name: To be determined). Expected FDA decision: December 3, 2020.

Berotralstat is intended to prevent hereditary angioedema (HAE) attacks. HAE is caused by a genetic defect causing a biochemical imbalance that releases fluids outside of the blood vessels into surrounding tissues.¹⁶

HAE symptoms include swelling in various parts of the body, including the hands, feet, face and airway. Airway swelling can lead to death by asphyxiation; before therapies became available, the mortality rate for airway obstruction was as high as 30%.¹⁶

Approximately 7,500 people are diagnosed and treated for HAE in the U.S.¹

The HAE defect interferes with a blood protein (called C1 inhibitor) that helps to regulate blood-based systems involved in disease fighting, inflammation and coagulation.¹⁶ Berotralstat is designed to block a metabolic precursor which is thought to be responsible for the characteristic HAE symptoms.¹⁷

Clinical trial results (from the APeX-2 study) showed that berotralstat reduced HAE attacks in patients over a 24-week period by 30% (low dose) and 44% (high dose) compared to placebo. In addition, the results suggest that berotralstat may reduce attack severity.¹⁷

The treatment was safe and well-tolerated, with the most common adverse events being nausea, indigestion and diarrhea.¹ [For additional trial details, see here \(p. 19\).](#)

Competitive environment

As a relatively late market entry, berotralstat would compete in a crowded market with well-established therapies. Berotralstat would be primarily competing with Cinryze® (C1 esterase inhibitor [human]) and Haegarda® (C1 esterase inhibitor [human]), as well as with Takhzyro® (lanadelumab-flyo). Cinryze requires intravenous (IV) administration and Haegarda is administered via subcutaneous injection every 3 to 4 days. Takhzyro is also SC administered but it is dosed every 2 to 4 weeks.¹ If approved, berotralstat would be the first oral, non-biologic, once daily treatment, which could provide an advantage.¹

When compared indirectly, berotralstat seems to be less effective than the approved injectable alternatives. For instance, Takhzyro reached a much higher numerical reduction relative to placebo in the HAE attack rate (73% to 87% reduction).

For reference, the WAC price for Takhzyro is approximately \$591,000 per year. While specific pricing for berotralstat has not yet been announced, as a late entry into a crowded class competing against products with seemingly better efficacy, the non-biologic berotralstat could potentially be priced less than the biologic alternatives currently in use.¹

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Lisocabtagene maraleucel (Brand name to be determined). An FDA decision for liso-cel was expected by November 16, 2020. Instead, on that day the FDA announced that the date would be delayed.

NOTE: The manufacturer announced that the FDA was unable to conduct an inspection of a third-party manufacturing facility in Texas during the current review cycle due to travel restrictions related to the COVID-19 pandemic. Therefore, the FDA is deferring action on the application until the inspection can be completed. The application remains under review.

Lisocabtagene maraleucel (“liso-cel”) is intended to treat adult patients with diffuse large B-cell lymphoma (DLBCL) that either returns (**relapsed**) or that does not respond to treatment after at least two prior therapies (**refractory**).¹

DLBCL is an aggressive type of non-Hodgkin’s lymphoma (NHL) that specifically affects the B type of white blood cell. DLBCL is the most common type of NHL in the U.S. with more than 18,000 people diagnosed each year. Of these patients, one third will relapse after first-line treatment, and 10% will have refractory disease.¹

Liso-cel is a **chimeric antigen receptor** (CAR T) cell therapy. CAR T treatment takes naturally occurring infection-fighting T-cells, re-engineers them, and puts them back in the body where they can attack cancer cells.¹⁸

According to phase 3 trial results (TRANSCEND NHL 001), 73% of patients who received liso-cel achieved a measurable response while 53% achieved complete response. Long term, 58% of all patients were alive at 1 year, including 86% of those who achieved a complete response to therapy.¹⁸

One risk associated with CAR T therapy is that the patient’s immune response can react in dangerous ways, including a condition called cytokine release syndrome (CRS) and neurotoxicity. In the TRANSCEND trials participants showed relatively low levels of both CRS and neurotoxicity.¹⁸

The most common adverse events with liso-cel use were anemia, decreased platelet count, and decreased white blood cell count, as well as CRS, and neurologic events.¹⁸

Competitive environment

Liso-cel will be competing with Kymriah® (tisagenlecleucel) and Yescarta® (axicabtagene ciloleucel), which are also CAR T therapies approved in 2017 for the same indication.

Like its competitors, liso-cel is a one-time infusion. The early stage data shows promising efficacy as well as a lower rate of CRS compared to its competitors currently on the market, although it is difficult to compare across clinical trials.

Due to the risk of CRS, liso-cel may potentially require a boxed warning and a Risk Evaluation and Mitigation Strategy (REMS) program that requires close monitoring for four weeks post-administration. This would be the same as for Kymriah and Yescarta.

The lack of long-term remission data for CAR T cell therapies is also a concern due to the high cost of the one-time infusion. CAR T cell therapies can also cause treatment delays due to the long preparation process needed to produce the cells for administration.

As the third entry into the DLBCL CAR T market, liso-cel may lead to increased competition and potentially a reduction in CAR T prices. Additionally, an improved safety profile with liso-cel could further lower the total cost of care.

For reference, the WAC prices of the one-time infusion for Kymriah and Yescarta range from \$373,000 to \$475,000.

Industry trend to watch

As soon as the scope of the COVID-19 pandemic became clear, concerns were raised about the potential to slow drug development including during the clinical trials phase, in the FDA review process, and in new drug launches.¹⁹

We discussed concerns in the trial phase last spring [in an interview](#) with Bill Dreitlein, Pharm.D., Senior Director of OptumRx's Pipeline and Drug Surveillance team. He observed that, while we might see temporary delays in recruiting trial subjects or collecting results, in general the pharmaceutical trials process is already quite robust and resilient over the long term.

Overall, while trial schedules have slowed, they have not stopped. For example, just recently Johnson & Johnson and UnitedHealth Group announced a collaboration to accelerate recruitment of 60,000 participants for the drug maker's COVID-19 vaccine trial. More broadly, one tracking service followed more than 2,500 industry-sponsored drug trials that were planned or started in 2020 in the U.S. Of these, approximately 65% experienced some delay, with a mean delay of 2.6 months.²⁰

Regarding new drug launches, we have [previously noted instances](#) where new drugs have received approvals, but manufacturers decided to delay launch due to pandemic related concerns. However, drug makers have adapted and we are now seeing "virtual" drug launches that minimize person-to-person contact by substituting virtual doctor's office visits and advisory boards, instead of in-person.²¹

Turning to the FDA's ability to review and approve new drug applications, in the early part of 2020 staff members at the Center for Drug Evaluation and Research (CDER) were quoted in the media saying that they were not certain they would be able to sustain their customary pace of reviews.²²

However, as the year begins to close, it does not appear that the pandemic has slowed the FDA's approval process. This graph combines approvals in past years with 2020 year-to-date values, and shows that the number of new drugs this year could equal or even exceed prior years:

CDER's novel drug approvals



Source: 2010-2019 FDA Center for Drug Evaluation and Research's (CDER). *New Drug Therapy Approvals 2019*. Published January 6, 2020. YTD 2020: FDA Center for Drug Evaluation and Research's (CDER). *Novel Drug Approvals for 2020*. Content current as of October 15, 2020.

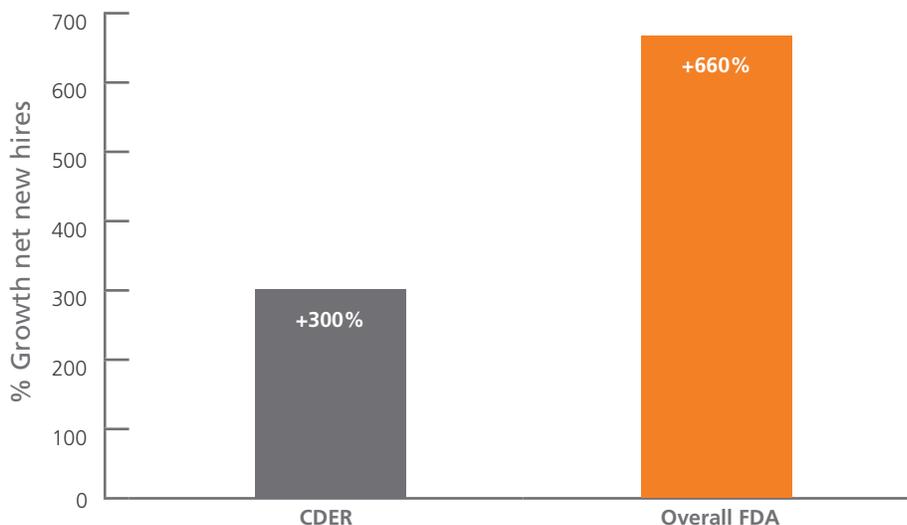
Industry trend to watch

One cause for this productivity is the 21st Century Cures Act. Signed in December 2016, the Act is best known for new research programs like the Cancer Moonshot and a nationwide genomics initiative.²³

A less-well known aspect of the Act is that it allows the FDA a more streamlined hiring process. 2020 has seen the first results of this new hiring strategy.²⁴

The chart below shows some year-over-year results:

FDA hiring YOY 2019/2020



Source: *Regulatory Focus*. Top CDER officials discuss budget priorities, staffing and COVID. Posted October 16, 2020.

This additional staff allows the FDA to advance non-COVID work in parallel with COVID-19 related efforts. Acting CDER Director Patrizia Cavazzoni was recently quoted in *Regulatory Focus*, saying that the pandemic should not prevent them from meeting their non-COVID-19 commitments.²⁴

In summary, the COVID-19 pandemic has had a minor impact on the new drug approval process.²⁵ This is good news for people who need innovative new treatments. As the pandemic approaches a full year's duration and COVID-19 diagnosis is on the rise, OptumRx will continue to monitor drug development and provide timely and relevant updates.

About OptumRx

OptumRx is a pharmacy care services company helping clients and approximately 59 million members achieve better health outcomes and lower overall costs through innovative prescription drug benefits services, including network claims processing, clinical programs, formulary management, specialty pharmacy care and infusion services. OptumRx is part of Optum®, a leading information and technology-enabled health services business dedicated to making the health system work better for everyone. For more information, visit optum.com/optumrx.

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