OPTUMRx®

OptumRx Drug Pipeline Insights Report

Q3 2021

Looking Ahead: 2021 Pipeline

By Sumit Dutta, Chief Medical Officer at OptumRx

OptumRx is pleased to provide a summary of notable new drug approvals expected for mid-2021.

Before proceeding, we should acknowledge the recent news regarding the Alzheimer's Disease drug aducanumab (Aduhelm™). There are multiple issues regarding its place in therapy, cost and coverage that are being evaluated by payors and providers.

In the context of this report, our role requires us to take a longer view. What does this approval mean for the future of Alzheimer's research and treatment development? Will Aduhelm's approval encourage new approaches, or will it narrow the field to just one mechanism of action?

Our clinical experts are compiling a report that will examine these considerations. Please look for it soon.

For this issue of the Drug Pipeline Insights Report, we will begin by highlighting a first-in-class treatment for those with chronic kidney disease and type 2 diabetes. Developers are applying proven mechanisms of action that may have significant benefits when applied to type 2 diabetes.

Next is a new oral treatment option for preventing migraine attacks. Migraine therapy is a rapidly developing space and it remains to be seen how much of a competitive advantage this new drug will offer.

We close this period with a look at two drugs aimed at similar genetic liver conditions. By preventing the liver from eliminating waste from the bloodstream, patients often experience progressive liver disease. While each of the drugs has a different mechanism of action, the conditions they treat are similar so they may compete against each other in the future.

Readers may recall the discussion of new atopic dermatitis drugs that we discussed in our last report. Some of the expected approvals were delayed (abrocitinib, ruxolitinib). We continue to monitor those drugs and decisions are expected this quarter. For more about atopic dermatitis you can see the previous OptumRx Drug Pipeline Insights Report.

Below are four drugs with FDA approval dates in the middle part of this year. Please refer here for additional technical background and supplemental sources.

Sumit Dutta
Chief Medical Officer, OptumRx

Drug overview

Kerendia® (finerenone). Approved July 9, 2021.

Kerendia treats patients with chronic kidney disease (CKD) and type 2 diabetes mellitus (T2DM).[1]

Chronic kidney disease is a condition in which the kidneys are damaged and cannot filter blood as well as they should. If left untreated, CKD can progress to kidney failure requiring dialysis or kidney transplant. CKD is also associated with increased risk of stroke and heart attack.[2]

Diabetes is one of the leading causes of CKD. There are 26.8 million people diagnosed with diabetes in the U.S. and about 1 in 3 of these people develop some degree of CKD.[3]

Kerendia is a **mineralocorticoid receptor antagonist** (MRA). MRAs such as spironolactone and eplerenone have been used for many years to control high blood pressure and limit damaging inflammation and fibrosis in diabetic kidney disease.[4]

There are safety concerns with existing MRAs that limit their use, including elevated blood potassium levels (hyperkalemia) and poor kidney function (acute renal insufficiency). Drug manufacturer Bayer believes Kerendia will prove to be safer due to its unique non-steroidal structure.[5]

A Phase 3 study (FIDELIO-DKD) demonstrated that Kerendia was effective for delaying the progression of chronic kidney disease and reducing risk for cardiovascular damage in participants with type 2 diabetes.[6]

Trial participants who took Kerendia were more likely to experience elevated blood potassium levels (hyperkalemia). That's a concern since potassium is critical to the function of nerve and muscle cells, including the heart and CKD patients are already at increased risk for high potassium.[7]

You can access an in-depth discussion of safety and trial data here (p. 6).

Competitive environment
As noted, MRAs have been on the market for decades and are available as generics. Kerendia is the first MRA approved for chronic kidney disease.[8]

CKD in diabetic patients
Historically, drugs used to treat CKD in diabetic patients were limited to angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs).[9] More recently, data is emerging regarding SGLT2 (sodium-glucose cotransporter 2) inhibitors and reducing CKD.[10]

For example, the SGLT2 inhibitor Farxiga® (dapagliflozin), has shown benefit in CKD patients with or without diabetes and recently received FDA approval for this indication. Kerendia and SGLT2 inhibitors could compete in this space even though they work differently.[11]

As mentioned above, other drugs used for CKD (eg, ACE inhibitors) are available generically and are very inexpensive. For reference, the wholesale acquisition cost (WAC) for Farxiga is approximately $6,500 per year.[12]

Drug overview

Atogepant *(Brand Name: To be determined).* Expected FDA decision: Q3 2021.

Therapeutic use
Atogepant is in development for the prevention of episodic and chronic migraine in adults.

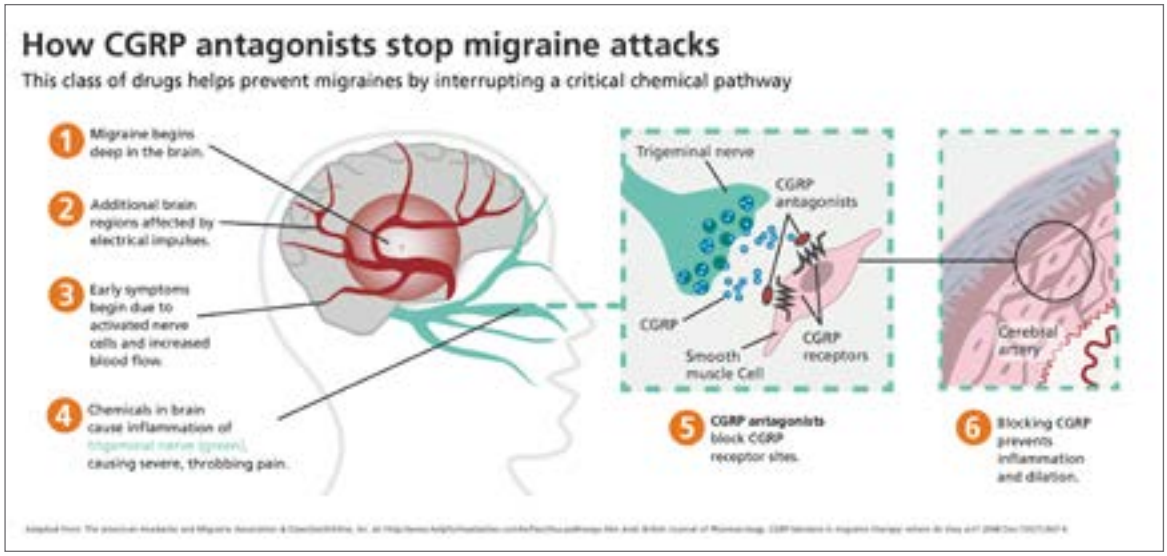
As many people are aware, migraine attacks can be extremely disabling. More than 90% of migraine sufferers are unable to work or function normally while experiencing migraine. Approximately 39 million individuals in the U.S. are affected by migraines. Nearly 72% of all those affected are women.[13]

According to a recent analysis, the annual economic burden of migraine in the United States is approximately $78 billion.[14] Approximately 5 million people are currently receiving therapy for migraine prevention.

Clinical profile
Atogepant is a calcitonin gene-related peptide (CGRP) receptor antagonist. CGRP is a neurotransmitter (or, chemical messenger) that is found throughout the brain and body. Although the mechanism is not completely understood, researchers have known for decades that CGRP is found in high levels in migraine sufferers during an attack. As a result, drugs that block the CGRP receptor have been used to prevent CGRP from contributing to migraine attacks.[15]

The first CGRP drug was approved in 2018. Since then at least six drugs have emerged that block either CGRP or its receptor.[16]

Click on the image below for a CGRP infographic:



Atogepant was evaluated in a Phase 3 study (ADVANCE) among participants who experienced four to 14 migraine episodes per month. Patients took either 10 mg, 30 mg, or 60 mg atogepant, or placebo once daily. Results for all doses found a greater proportion of patients achieving 50% reduction in their mean monthly number of migraine days compared to placebo over a 12-week treatment period.[17]

You can access an in-depth discussion of safety and trial data here (p. 20).

Drug overview

Competitive environment
If approved, atogepant would offer an additional oral treatment option for preventing migraine attacks.

Current oral preventive treatments include beta blockers, antidepressants and anticonvulsants many of which are available as generic products.

Injectable treatments include Botox® (onabotulinumtoxinA) and previously approved CGRP antagonists: Aimovig® (erenumab), Ajovy® (fremanezumab), Emgality® (galcanezumab), Vyepti™ (eptinezumab).[18]

The most direct competition for atogepant could come from Biohaven's Nurtec® ODT (rimegepant). ODT stands for **orally disintegrating tablet.** Previously approved only for acute migraine, the FDA approved Nurtec ODT for preventive treatment of migraine on May 28 of this year. That makes Nurtec ODT the first oral CGRP antagonist option to both prevent and treat migraines.[19]

Atogepant is entering a crowded market and will compete with not only Nurtec ODT but with the other current treatment options for migraine prevention. We lack data comparing atogepant vs. historical migraine prophylaxis agents. While it is difficult to compare across clinical trials, atogepant does appear to have similar or incrementally better efficacy than the injectable CGRP antagonists and Nurtec ODT.[20]

Most of the older oral alternatives (e.g., beta blockers) are available generically and are comparatively inexpensive. For reference, the WAC for Aimovig, and Nurtec are approximately $638 and $1,673 per month, respectively.[21]

Market trend to watch
Liver disease covers a vast field – some 32 different types are listed on the website of the American Liver Foundation.[22] They range from widespread conditions such as alcoholic liver disease and nonalcoholic fatty liver disease to extremely rare conditions, such as those reviewed below.

What these conditions share is the very high cost of treating their long-term effects, which often require extensive inpatient hospitalization. Liver transplants are a frequent occurrence. The total national cost for chronic liver-related hospitalizations over a recent 5-year period was over $81 billion.[23]

Ultimately, the goal is to improve the quality of life for people with these conditions, while also lowering the overall cost of care by slowing or preventing disease progression.

Progress toward new liver disease treatments has been spotty. For example, industry observers are well acquainted with the long – and so far, unsuccessful -- history of Ocaliva® (obeticholic acid), proposed for nonalcoholic steatohepatitis.[24]

Still, researchers continue to bring forward novel treatment strategies against liver diseases.[25] Although treatments targeting common liver diseases like NASH, have been delayed, near-term progress is being made in less common forms of liver disease. This mirrors an ongoing trend in the pipeline focusing on rare disease.

Drug overview

Two examples include:

Bylvay™ (odevixibat). Approved July 20, 2021.

Maralixibat *(Brand Name: To be determined).* Expected FDA decision: September 29, 2021.

Bylvay treats pruritus associated with progressive familial intrahepatic cholestasis (PFIC). PFIC is a group of three related genetic disorders, each type having a different genetic cause.[26]

Maralixibat is in development for the treatment of Alagille Syndrome (ALGS) in patients aged 1 year and older. ALGS is a rare genetic disorder in which bile ducts are abnormally narrow, malformed, and reduced in number.[27]

Both PFIC and Alagille Syndrome damage the liver and cause the accumulation of bile acids, which prevents the liver from working properly to eliminate waste from the bloodstream. Both lead to progressive liver disease and potentially to liver failure.[28]

Both of these conditions are very rare. There is a treatable population of about 600 people with PFIC and approximately 1500 individuals with ALGS in the U.S.[29]

Bylvay and maralixibat work on a similar principle although using different mechanisms. The goal for each is to reduce the amount of bile acids returning to the liver, which reduces the amount of bile acid in the blood.

Trial results for both drugs were promising, with demonstrated improvements in quality of life and bile acid levels. However, neither drug has been assessed for long-term liver benefit such as prevention of liver failure or reducing the need for liver transplantation.[30] These long-term effects will be key to reducing the overall cost of care for these conditions.

Look here for in-depth discussion of safety and trial data:

- Odevixibat (p. 10).
- Maralixibat (p. 13).

Competitive environment

There are high unmet needs for effective treatments for both PFIC and Alagille Syndrome.

PFIC is typically unresponsive to conventional treatments that are used off-label, like ursodeoxycholic acid, antihistamines, or rifampicin. The only proven effective treatments are surgical interventions and transplantation.[31]

ALGS treatment currently focuses on supportive care of subsequent liver disease, pruritus and malnutrition. Cholestyramine, colesevelam, ursodiol and naltrexone have been used off-label to treat pruritus in ALGS, with variable success.[32]

Bylvay is the first FDA approved treatment for PFIC. Similarly, if approved, maralixibat would be the first approved treatment for Alagille Syndrome. It's expected that the cost for these drugs will be high given the rarity of the diseases.

Drug overview

Expanding indications?
As mentioned above, both Bylvay and maralixibat work similarly. Both drugs also being evaluated for use in other rare liver conditions, including biliary atresia. Therefore, while the initial FDA applications for each are for different uses, they could eventually have mirroring indications.[33]

Being approved for use in biliary atresia would substantially expand the eligible population for each drug. While PFIC and ALGS have a combined addressable population of around 2,100, adding biliary atresia would more than double that, with an additional 2,400 individuals.[34]

We can consider a future when these drugs may compete head to head. For example, we note that there are tolerability concerns with maralixibat: 42% of patients experienced diarrhea and 71% experienced gastrointestinal (GI) related adverse events during clinical trials. However, Bylvay was relatively well tolerated and when compared indirectly, did not have the same rates of GI related adverse events. Bylvay could therefore represent a more well-tolerated option for Alagille Syndrome in the future.[35]

As we have noted before, FDA approval is only the first step in the process that leads to the eventual use of any new drug. The next step is an in-depth review by the independent and transparent OptumRx Pharmacy & Therapeutics (P&T) committee. This committee evaluates drugs based on scientific evidence. That assessment then determines the OptumRx strategy for managing each drug as closely as possible through the formulary and utilization management programs.

Your consultant and account manager will keep you abreast of these decisions.

1. RxOutlook. 2nd Quarter 2021. Accessed June 2, 2021.
2. ibid.
3. ibid.
4. Evaluate Vantage. Bayer's big kidney disease readout approaches. Published April 21, 2020. Accessed June 3, 2021.
5. Healio. Finerenone delays diabetic kidney disease progression: FIDELIO-DKD. Published July 10, 2020. Accessed June 2, 2021.
6. ibid.
7. ibid.
8. RxOutlook. 2nd Quarter 2021. Accessed June 2, 2021.
9. ibid.
10. ibid.
11. ibid.
12. ibid.
13. American Journal of Managed Care. Concomitant Medical Conditions and Total Cost of Care in Patients With Migraine: A Real-World Claims Analysis. Published February 18, 2020. Accessed June 9, 2021.
14. ibid.
15. RxOutlook. 2nd Quarter 2021. Accessed June 2, 2021.
16. Nature. A new generation of headache drugs. Published October 14, 2020. Accessed June 9, 2021.
17. AbbVie. AbbVie Announces Positive Phase 3 Data for Atogepant in Migraine Prevention. Published July 29, 2020. Accessed June 3, 2021.
18. RxOutlook. 2nd Quarter 2021. Accessed June 2, 2021.
19. Pharma Letter. FDA nod for Biohaven's Nurtec ODT for migraine prevention. Published May 28, 2021. Accessed June 9, 2021.
20. RxOutlook. 2nd Quarter 2021. Accessed June 2, 2021.
21. ibid.
22. American Liver Foundation. Diseases of the Liver. Accessed July 1, 2021.
23. JAMA Network Open. Trends in the Burden of Chronic Liver Disease Among Hospitalized US Adults. Published April 2, 2020. Accessed July 1, 2021.
24. BioPharma Dive. Intercept shares fall as FDA again delays closely watched NASH drug. Published May 22, 2020.
25. News-Medical.Net. New approach could revolutionize the treatment of liver diseases. Posted May 3, 2021. Accessed July 1, 2021.
26. Johns Hopkins Medicine. Progressive Familial Intrahepatic Cholestasis. Accessed June 9, 2021.
27. RxOutlook. 2nd Quarter 2021. Accessed June 2, 2021.
28. ibid.
29. Albireo Pharma, Inc. Commercial Day: Road to $1 Billion. Posted February 11, 2021. Accessed June 9, 2021.
30. RxOutlook. 2nd Quarter 2021. Accessed June 2, 2021.
31. ibid.
32. ibid.
33. ibid.
34. Albireo Pharma, Inc. Commercial Day: Road to $1 Billion. Posted February 11, 2021. Accessed June 9, 2021.
35. RxOutlook. 2nd Quarter 2021. Accessed June 2, 2021.

optum.com/optumrx

OptumRx is a pharmacy care services company helping clients and more than 59 million members achieve better health outcomes and lower overall costs through innovative prescription drug benefits services.