OPTUMRx®

OptumRx Drug Pipeline Insights Report

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Looking Ahead: 2021 Pipeline

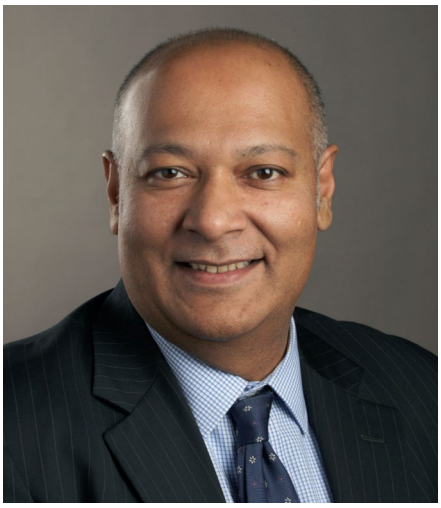
By Sumit Dutta, Chief Medical Officer at OptumRx

On behalf of OptumRx, I am pleased to provide our quarterly edition of notable upcoming drug approvals. These agents have expected FDA approval decisions in the second half of 2021.

We previously reported the number of new novel drug approvals in 2021 could approach a record high, exceeding 53 approvals in 2020 (the most in a year was 59 in 2018). This now seems even more likely. As of October 6, 2021, the FDA's Center for Drug Evaluation and Research (CDER) lists 40 new novel drugs — not including new vaccines[1] — which is slightly ahead of last year's pace.[2]

In this report we will discuss five investigational drugs. Our list includes treatments for moderate-to-severe plaque psoriasis and a new therapy designed to help cancer patients tolerate their cancer fighting medications. We also look at another new cellular based therapy (CAR T cell therapy) for multiple myeloma, plus an unusual pairing of the common over-the-counter cough suppressant dextromethorphan with a standard antidepressant for major depressive disorder.

Here are our featured drugs for the second half of 2021. Please refer here for additional technical background and supplemental sources.



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Drug overview

Bimekizumab *(brand name to be determined).* EFDA decision delayed.

Bimekizumab is in development for the treatment of adults with moderate-to-severe plaque psoriasis.[3]

Psoriasis is a common chronic inflammatory condition that affects an estimated 8 million individuals in the U.S. The most common type is plaque psoriasis, which represents 80–90% of cases. Plaque psoriasis is characterized by thick red patches of skin covered with silvery scales or dry, cracked skin that may bleed.

Psoriasis commonly results in disfiguration and disability. Patients are also challenged by emotional and social burdens caused by psoriasis stigmatization.[4]

Bimekizumab is a **humanized monoclonal antibody.** These are manufactured in the laboratory to bind to the target, while being less likely to be destroyed by the body's immune system.[5]

Bimekizumab selectively inhibits chemical messengers (called interleukin cytokines) that regulate the inflammatory pathways of psoriasis. Bimekizumab is the first therapy that targets both the interleukin-17A and interleukin-17F cytokines. Existing drugs in the class — Cosentyx® (secukinumab) and Taltz® (ixekizumab), only target interleukin-17A.[6]

Bimekizumab was evaluated in four Phase 3 studies: BE VIVID, BE SURE, BE RADIANT, and BE READY. The studies compared bimekizumab against existing standard of care options — Stelara® (ustekinumab), Humira® (adalimumab), Cosentyx® (secukinumab) — or placebo.

All four studies were looking for the proportion of patients with greater reductions in the area and severity of their psoriasis symptoms in standardized psoriasis assessments: Psoriasis Area and Severity Index (PASI 90) and Investigator Global Assessment (IGA) response of clear (0) or almost clear (1). Bimekizumab demonstrated superior results in both assessments against each comparator.[7]

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

Competitive environment
There are several types of existing pharmacotherapy options for plaque psoriasis. These include topical treatments (e.g., corticosteroids, vitamin D analogues, tazarotene) and systemic oral therapies (e.g., Otezla® [apremilast], cyclosporine, methotrexate, and systemic steroids).

Clinical guidelines also recommend biologic agents as options for treatment of moderate-to-severe plaque psoriasis. These include several injectable biologic agents (e.g., Stelara, Humira, Cosentyx) which have been approved for years, with more complete long-term data demonstrating their safety and efficacy.

If approved, bimekizumab would be competing with these products. As noted, bimekizumab demonstrated superiority in direct head-to-head trials vs. existing biologic treatment options.

However, bimekizumab is entering a crowded market and each option has different strengths and weaknesses. For example, there were increased rates of oral thrush with bimekizumab, as compared to Stelara, Humira, Cosentyx and placebo. Also, there are other biologic agents that are dosed

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less frequently (e.g., Skyrizi, Stelara), or that can be used in pediatric populations (Stelara). Finally, biosimilars for Humira are expected to enter the market in 2023 which may decrease cost through increased competition.

For reference, the WAC for Cosentyx is approximately $70,000 per year.[8]

Plinabulin *(brand name to be determined).* Expected FDA decision: November 30, 2021

Cancer chemotherapy drugs can damage normal cells, such as the bone marrow cells that produce white blood cells. This can cause abnormally low amounts of a type of white blood cell called neutrophils. Patients with a low neutrophil count ('neutropenia') are at risk of infection and may need to delay chemotherapy doses until the neutrophils recover.

Plinabulin is in development for the prevention of chemotherapy-induced neutropenia (CIN). It would be used in combination with blood growth proteins called **granulocyte colony-stimulating factors** (G-CSFs) which stimulate the bone marrow to produce more infection-fighting neutrophils.[9]

Plinabulin is thought to reduce neutropenia by triggering the release of the immune defense protein, GEF-H1. This activates a signaling pathway that both increases neutrophil activation and reduces neutrophil destruction. This combination of effects might account for reduced neutropenia.[10]

Plinabulin was evaluated in a Phase 3 study (PROTECTIVE-2). The trial compared plinabulin in combination with a G-CSF, Neulasta® (pegfilgrastim) vs. Neulasta alone in patients with breast cancer undergoing chemotherapy. The combination of plinabulin and Neulasta was 53% more effective in reducing the incidence of CIN vs Neulasta alone.[11]

Plinabulin produced fewer adverse events when combined with Neulasta vs. Neulasta alone.

You can access an in-depth discussion of safety and trial data here (p. 19).

Competitive environment

G-CSFs such as Neulasta are the current standard of care for CIN prophylaxis in patients being treated with certain types of chemotherapy. However, patients can still experience breakthrough neutropenia during the first week after chemotherapy when paired only with Neulasta alone.

Adding plinabulin to Neulasta seems to reduce that vulnerability, which could help patients remain on their existing chemotherapy regimens.[12]

Still, there remain several factors that may limit uptake if plinabulin is approved:

- The initial indication for plinabulin is expected to be limited to use in combination with G-CSFs. his may reduce its uptake as it could be reserved for patients who are at especially high risk for developing CIN.
- G-CSFs like Neulasta are administered via subcutaneous injection, whereas plinabulin requires IV infusion.

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Separately, early-stage trials indicate that plinabulin may have anti-cancer effects. Recently, BeyondSpring announced positive topline results from a Phase 3 study (DUBLIN-3) in the second- and third-line treatment setting for non-small cell lung cancer (NSCLC). BeyondSpring expects to file for treatment of NSCLC in the first half of 2022.

For reference, the WAC for brand Neulasta is approximately $6,500 per dose.[13]

Dextromethorphan/bupropion *(brand name to be determined).* Expected FDA decision delayed (see below).

Dextromethorphan/bupropion (AXS-05) is in development for treatment of adult patients with major depressive disorder.

Major depressive disorder is one of the most common mental health disorders in the U.S. with approximately 7% of adults affected each year.

Dextromethorphan has been approved since 1958 and appears in a myriad of over-the-counter cough medicines. Dextromethorphan has recently drawn attention on its' own as a fast-acting antidepressant.[14]

Similarly, bupropion was approved in 1985. Available either as a generic or a number of brand names (e.g., Wellbutrin®), it is one of the most widely prescribed antidepressant medications in the world.[15]

AXS-05 was evaluated in a Phase 3 study (GEMINI) and a Phase 2 study (ASCEND). Both trials studied patients with moderate-to-severe major depressive disorder. AXS-05 was tested against a placebo in the Phase 3 study, and against bupropion alone in the Phase 2 study. In each case the primary endpoint was change from baseline in a standardized depression rating scale at various times.[16]

The studies showed a statistically significant improvement, both vs. placebo and vs. bupropion monotherapy.[17]

You can access an in-depth discussion of safety and trial data here (p. 3).

Competitive environment

There are several classes of medications currently used in the first line setting. The choice of antidepressant is based upon multiple factors including side effect profile, comorbid illnesses, and patient preference.

Despite many treatment options for major depressive disorder, they're not always effective. Only a third of people respond favorably to the first antidepressant they are prescribed.[18]

The primary differentiator for AXS-05 vs. some of the commonly used treatments for major depressive disorder is that it appears to work faster. Trials have demonstrated improvements in one week compared with several weeks for most antidepressants.

Analysts from GlobalData interpret these results to mean that AXS-05 will meet some of the key unmet needs in the major depressive disorder, for example a rapid onset of action. That leads them to project blockbuster sales status (>$1 billion) for AXS-05 by 2026.[19]

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However, those same analysts do not expect AXS-05 to become a first-line therapy for major depressive disorder. In general, it would be entering a crowded marketplace with well-established standards of care that are available as inexpensive generics.[20] Also, as with any combination of existing drugs, it is at least theoretically possible that they could be combined in their existing generic forms, instead of as the new, branded version. That remains to be seen.

But before anything can happen, the drug maker must address a recent notice from the FDA that AXS-05 will not meet its originally established action date (August 22, 2021) because of deficiencies in the application. FDA review of the application is ongoing.[21]

AXS-05 is also in development for agitation in patients with Alzheimer's disease. There is a high unmet need for treatments in this space, with a lack of FDA approved treatments. Axsome is expecting Phase 3 results in the second half of 2022.

Efgartigimod *(brand name to be determined).*
Expected FDA decision: December 17, 2021.

Efgartigimod is in development for treatment of generalized myasthenia gravis.

Myasthenia gravis is an autoimmune, neuromuscular disorder primarily characterized by muscle weakness and muscle fatigue. Approximately 10% of affected patients develop potentially life-threatening complications involving difficulty breathing.

Approximately 65,000 people in the U.S. are affected by myasthenia gravis. Symptom onset most commonly peaks in women during their 20s or 30s and in men in their 50s or 60s.

Efgartigimod is designed to reduce disease-causing antibodies (immunoglobulin IgG) commonly found in patients with generalized myasthenia gravis.

A Phase 3 study (ADAPT) met its main goal of demonstrating that a greater percentage of patients treated with efgartigimod showed improvement in their daily activities of living compared to those on placebo. Significantly more treated patients showed meaningful improvement than placebo-treated controls (68% vs. 30%).

The most common adverse events with efgartigimod use were headache and cold symptoms (nasopharyngitis). Rates were similar to placebo.[22]

You can access an in-depth discussion of safety and trial data here (p. 22).

Competitive environment
Efgartigimod would offer an additional treatment option for myasthenia gravis with a novel mechanism of action. The current standard of care includes acetylcholinesterase inhibitors (e.g., pyridostigmine) as well as other immunosuppressants like corticosteroids. In patients who fail those types of conventional therapies, biologics such as Alexion's Soliris® (eculizumab) are used.[23]

Current immunotherapy is typically successful, therefore efgartigimod would likely be similar to Soliris in terms of being used in more severe or refractory cases.[24]

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While it is still not known what the final FDA approved dosing recommendation will be for efgartigimod, a potential benefit vs. Soliris might be less frequent injections. Soliris is IV administered every 2 weeks whereas efgartigimod is administered weekly for 4 weeks. However, in the ADAPT study, patients were not re-dosed until clinical benefit was lost (no earlier than 8 weeks).

Alexion's Ultomiris® (ravulizumab-cwvz) is also under development for generalized myasthenia gravis and it is dosed once every 8 weeks. This might dilute any potential convenience advantage for efgartigimod. Alexion plans to file the new indication for Ultomiris in late 2021 or early 2022.[25]

[We should note that Ultomiris has been in the news for two different potential new indications recently: myasthenia gravis and amyotrophic lateral sclerosis (ALS). Recently Alexion announced it was halting the ALS trial.[26, 27]]

For reference, the WAC for Soliris is approximately $565,000 per year, which the Institute for Clinical and Economic Review (ICER) regards as substantially overpriced. ICER is also evaluating efgartigimod while awaiting a final FDA decision.[28]

Ciltacabtagene autoleucel (brand name to be determined).
Expected FDA decision: November 29, 2021

Ciltacabtagene autoleucel is in development for the treatment of patients with relapsed and/or refractory multiple myeloma.

Multiple myeloma is a cancer affecting the white blood cells that produce antibodies. Multiple myeloma is a relatively uncommon cancer with about 34,920 new cases in 2021 and 12,410 deaths expected in the U.S.

While several treatment options are available for multiple myeloma, many patients will eventually relapse and require further therapy. The 5-year survival rate is approximately 50%.

Ciltacabtagene autoleucel is a chimeric antigen receptor (CAR) T cell therapy. CAR T takes naturally occurring infection-fighting cells ('T-cells') and re-engineers them to be more effective. The altered T-cells are put back in the body, where they can attack cancer cells.

Ciltacabtagene autoleucel was evaluated in a Phase 1b/2, open-label study (CARTITUDE-1). Patients were adults with relapsed and/or refractory with multiple myeloma who had received at least 3 prior lines of therapy (median of six lines). The study's primary endpoint was overall response rate.

Patients treated with ciltacabtagene autoleucel had an overall response rate of 98%, with 80% being complete responses. The 18-month progression-free survival rate was 66%. The overall survival rate was 81%.[29]

Cytokine release syndrome (CRS) is a common adverse event associated with CAR T cells. CRS occurred in 95% of ciltacabtagene autoleucel patients, however only 4% were Grade 3 or 4. (The CRS scale ranks 1 least serious, 4 most serious).[30]

You can access an in-depth discussion of safety and trial data here (p. 17).

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If approved, ciltacabtagene autoleucel would be the second of CAR T cell therapy treatment option for patients with multiple myeloma. A similar CAR T cell therapy Abecma™ (idecabtagene vicleucel) was approved in March 2021. Compared indirectly, ciltacabtagene autoleucel does appear to have better efficacy with higher response rates demonstrated in the pivotal trial. However, factors weighing against ciltacabtagene autoleucel include higher rates of neurotoxicity adverse events and that it is not the first therapy to market in this space.

As with all other CAR T cell therapies, ciltacabtagene autoleucel is expected to have a boxed warning for CRS and would require close monitoring post-administration. Furthermore, treatment delays may also occur due to the long preparation process needed to produce the cells for administration to the patient. These delays can often result in disease progression while waiting for the therapy.

CAR T cell therapies come with a high one-time cost and ciltacabtagene autoleucel would not only be competing with Abecma, but also other drugs used for relapsed/refractory multiple myeloma, an increasingly crowded market.

For reference, the WAC for Abecma is $419,500 for a one-time dose.[31]

References

1. FDA. FDA's Center for Drug Evaluation and Research (CDER). Novel Drug Approvals for 2021. Site updated August 26, 2021. Accessed August 26, 2021.
2. Fierce Pharma. Innovation on hold during the pandemic? FDA says no with 29 approvals in first half of 2021. Published July 6, 2021. Accessed August 26, 2021.
3. OptumRx. Rx Outlook: 3rd Quarter 2021. Accessed August 26, 2021.
4. Frontiers in Immunology. The IL-17 Family of Cytokines in Psoriasis: IL-17A and Beyond. Published August 2, 2018. Accessed August 9, 2021.
5. National Cancer Institute. NCI Dictionaries: Humanized monoclonal antibody. Accessed August 9, 2021.
6. Frontiers in Immunology. The IL-17 Family of Cytokines in Psoriasis: IL-17A and Beyond. Published August 2, 2018. Accessed August 9, 2021.
7. OptumRx. Rx Outlook: 3rd Quarter 2021. Accessed August 26, 2021.
8. ibid.
9. JAMA Patient Page. Granulocyte-Colony Stimulating Factor. Published March 1, 2006. Accessed August 20, 2021.
10. Evaluate Vantage. Beyondspring finds a vascular-disrupting niche. Published March 21, 2017. Accessed August 20, 2021.
11. OncLive. Unique Mechanism of Action Positions Plinabulin as a Preventive and Active Therapy in Breast Cancer, NSCLC. Published July 19, 2021. Accessed August 20, 2021.
12. ibid.
13. OptumRx. Rx Outlook: 3rd Quarter 2021. Accessed August 26, 2021.
14. Johns Hopkins University School of Medicine. Perspectives in Research: Is Cough Syrup an Antidepressant? Published April 2, 2019. Accessed August 26, 2021.
15. Medical News Today. What is bupropion, or Wellbutrin? Published October 23, 2017. Accessed August 26, 2021.
16. Clinical Psychiatry News. Dextromethorphan/bupropion combo is remarkably fast-acting antidepressant. Published November 12, 2019. Accessed August 26, 2021.
17. OptumRx. Rx Outlook: 3rd Quarter 2021. Accessed August 26, 2021.
18. Johns Hopkins University School of Medicine. Perspectives in Research: Is Cough Syrup an Antidepressant? Published April 2, 2019. Accessed August 26, 2021.
19. Formulary Watch. Axsome Therapeutics antidepressant drug could become blockbuster. Published April 27, 2021. Accessed August 26, 2021.
20. ibid.
21. Axsome Therapeutics, Inc. Axsome Therapeutics Provides Update on the New Drug Application for AXS-05 for the Treatment of Major Depressive Disorder. Published August 23, 2021.
22. OptumRx. Rx Outlook: 3rd Quarter 2021. Accessed August 26, 2021.
23. ibid.
24. NEJM. Efgartigimod: PLEX in a Bottle — A Quick Fix for Myasthenia Gravis. Published July 12, 2021. Accessed August 25, 2021.
25. OptumRx. Rx Outlook: 3rd Quarter 2021. Accessed August 26, 2021.
26. Fierce Pharma. Alexion's Ultomiris notches myasthenia gravis win amid quest for 3rd Soliris use. Published July 16 2021. Accessed August 26, 2021.
27. AstraZeneca. Update on CHAMPION-ALS Phase III trial of Ultomiris in amyotrophic lateral sclerosis. Published August 20, 2021. Accessed August 26, 2021.
28. [fierce/ef-icer] Fierce Pharma. AstraZeneca's newly acquired Soliris is overpriced in myasthenia gravis, cost watchdog says. Published July 23, 2021. Accessed August 25, 2021.
29. Clinical Trials Arena. ASCO 2021: Compelling data For Ciltacabtagene Autoleucel in multiple myeloma. Last Updated June 11, 2021. Accessed August 25, 2021.
30. Biology of Blood and Marrow Transplantation. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Published April 2019. Accessed August 25, 2021.
31. OptumRx. Rx Outlook: 3rd Quarter 2021. Accessed August 26, 2021.

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