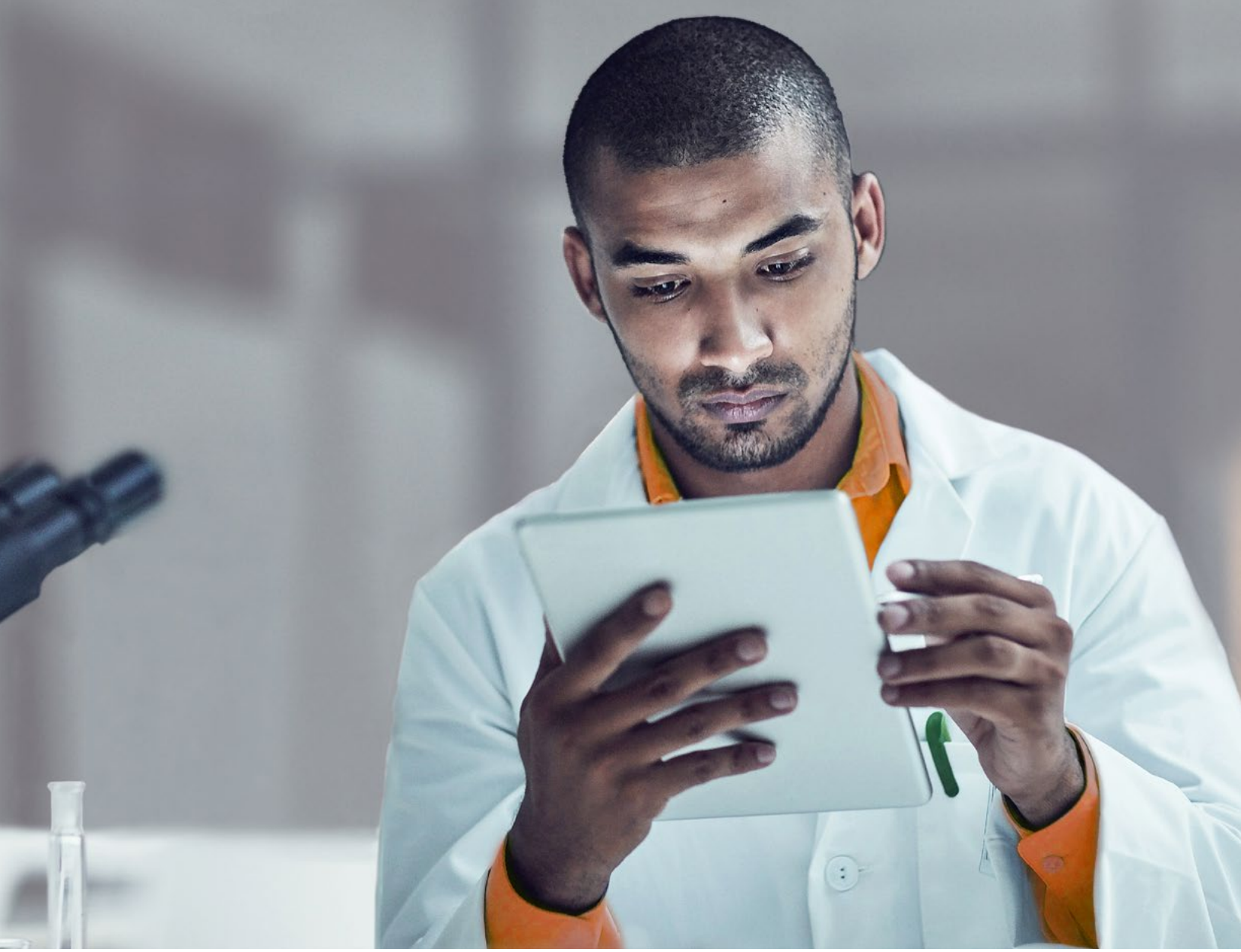

Optum Rx Drug Pipeline Insights Report™

September 2024

Optum Rx®

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From Sumit Dutta, Chief Medical Officer Optum Rx

Hello, and welcome to this edition of the Optum Rx Drug Pipeline Insights Report.

This issue highlights two drugs with expected approval dates before the end of third quarter 2024.

The drugs reviewed in this report include:

Dupixent®(dupilumab), for treatment of chronic obstructive pulmonary disease (COPD). Dupixent is already on the market for several indications, including asthma and atopic dermatitis. If approved, Dupixent would be the first biologic approved for COPD.

Xanomeline/trospium is an alternative treatment for schizophrenia. Due to its novel mechanism, xanomeline/trospium may avoid many of the common side effects found in the existing standard of care.

As always, we will continue to monitor and evaluate drugs in the pipeline and share notable upcoming drug approvals.

Please refer here for additional technical background and supplemental sources.

Sumit Dutta
Chief Medical Officer, Optum Rx

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Dupixent® (dupilumab)

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Expected FDA decision: September 27, 2024

Dupixent is seeking a new indication for treatment of moderate-to-severe chronic obstructive pulmonary disease (COPD) with eosinophilic COPD.

Dupixent is **currently approved** for atopic dermatitis, asthma, chronic rhinosinusitis, eosinophilic esophagitis, and prurigo nodularis.

Key points

Why this drug matters: Potentially the first biologic approved for COPD and the first treatment specifically for type 2 inflammation.

Estimated cost: ~$49,000 per year (based on current cost of Dupixent).

Trial notes: Promising efficacy with significant reduction in COPD flare-ups; favorable safety profile.

Route of administration: Subcutaneous injection every two weeks.

Manufacturer: Regeneron/Sanofi

Condition

COPD is a group of lung diseases including emphysema and chronic bronchitis. These conditions limit airflow and lead to chronic and progressive breathing-related problems. COPD was the sixth leading cause of death in the U.S. in 2023.[1]

There is a significant unmet need for therapies to address disease progression, such as eosinophilic COPD.[2]

Regeneron/Sanofi estimate that approximately 300,000 people in the U.S. have uncontrolled COPD with evidence of type 2 inflammation.

Clinical profile

Interleukin (IL)-4 and IL-13 are related **cytokines** that regulate many aspects of allergic inflammation. These cytokines play a key role in the development of type 2 inflammation in COPD.[3,4]

Dupixent is a biologically engineered antibody that blocks the signaling of the IL-4 and IL-13 pathways to reduce inflammation caused by COPD.

Trials

Dupixent was evaluated in two identical Phase 3 studies. Participants were adults who were current or former smokers with uncontrolled COPD and evidence of type 2 inflammation. Patients were randomized to Dupixent or placebo which was added to standard-of-care inhaled triple therapy.[5]

Findings showed Dupixent significantly reduced moderate to severe acute COPD flare-ups over 52 weeks compared with placebo. Dupixent was also associated with significant improvements in lung function.[6]

Dupixent® (dupilumab) *continued...*

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In one study, the annualized rate of moderate or severe COPD exacerbations was reduced by 30%. In the second study, moderate or severe exacerbations were reduced by 34%.

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

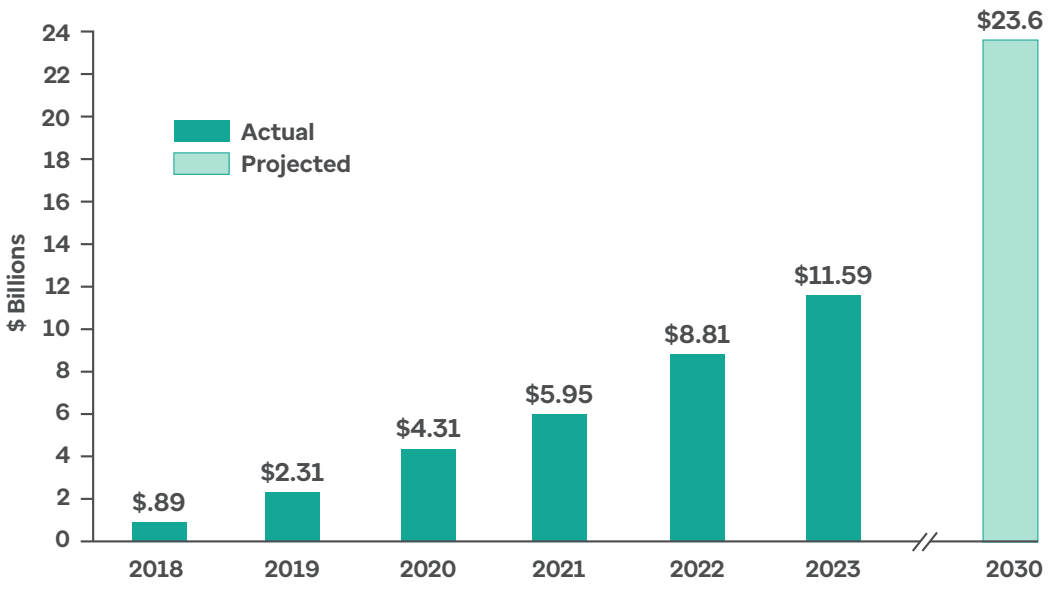
You can access an in-depth discussion of safety and trial data here (p. 1).

Competitive environment

The current standard of care for maintenance treatment of COPD includes inhaled long-acting medications that relax muscles that tighten around airways (bronchodilators) and corticosteroids. In patients who continue to have symptoms, there are limited treatment options available.

Dupixent would potentially be the first biologic approved for COPD and the first treatment specifically for type 2 inflammation. In studies, Dupixent demonstrated significant improvement in reducing COPD flare-ups when used as an add-on therapy. Dupixent was generally well tolerated in the studies. Side effects were consistent with Dupixent in its currently approved indications.

Analysts expect that adding COPD to its list of indications could add $3.5 billion in total sales for Dupixent[7], sales territory previously seen with Humira® (adalimumab).[8] Humira sales peaked at $21.2 billion in 2022, before adalimumab biosimilars became available in the U.S. Analysts believe that Dupixent total sales could exceed of $23 billion by 2030:



2018-2022: Pharma Shots. Top Performing Drug – Dupixent. April 26, 2023.
2023-2030: Pharmaceutical Technology. Dupixent "addresses current gap" in COPD biologics landscape. Published July 5, 2024.

Dupixent® (dupilumab) *continued...*

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Dupixent will be limited to patients with type 2 inflammation who have exhausted traditional inhaler therapies. In this population, Dupixent may also face future competition, as several other biologics are currently being studied in COPD, including GlaxoSmithKline's IL-5 antagonist, Nucala® (mepolizumab).

Administration by injection may represent a barrier in for some patients, especially since COPD is currently treated with inhaled and oral therapies.

The Wholesale Acquisition Cost (WAC) for Dupixent is approximately $49,000 per year.

Xanomeline/trospium (Brand name to be determined)

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Expected FDA decision: September 26, 2024

Xanomeline/trospium (also referred to as KarXT), is a novel treatment for schizophrenia and an alternative to atypical antipsychotics. Due to its novel mechanism, xanomeline/trospium may avoid many of the common side effects found in the existing standard of care.

Key points

Why this drug matters: Provides an alternative to existing front-line therapies. Potential use as an add-on therapy for schizophrenia. Potential use for psychosis in Alzheimer's disease could widen its market.

Estimated cost: ~$20,000 per year [based on pricing for Caplyta® (lumateperone)].

Trial notes: Efficacy appears comparable to existing treatments with fewer side effects compared to current treatment options.

Route of administration: Oral twice daily.

Manufacturer: Bristol Myers Squibb

Condition

The National Institute for Mental Health describes schizophrenia as "…a serious mental illness that affects how a person thinks, feels, and behaves. People with schizophrenia may seem like they have lost touch with reality, which can be distressing for them and for their family and friends."[9]

Schizophrenia occurs more often among men than in women and is usually diagnosed between age 16 and 30. An estimated 2.8 million people have schizophrenia in the U.S.

Clinical profile

Xanomeline/trospium is an agonist drug that works to activate two particular receptors (M1/M4) found in the signaling pathways of the central nervous system (M1/M4). Research has demonstrated that activating the M1 and M4 receptors can reduce the severity of schizophrenia symptoms.[10]

Xanomeline is a synthetic version of the compound **arecoline,** which is found in the betel nut. Chewing betel nut has been associated with less severe symptoms of schizophrenia.[11]

In the 1980s, xanomeline was trialed in patients with treatment-resistant schizophrenia. It produced "rapid and robust" antipsychotic effects, and did not display the common side effects of first- and second-generation antipsychotics. However, it did cause different adverse events like nausea and vomiting, therefore it was not pursued for further development.[12]

Xanomeline must cross into the brain to produce an antipsychotic effect. However, it also spreads to the rest of the body, where it causes the adverse gastrointestinal effects. Trospium acts by cancelling the effects of xanomeline, but it **does not** cross the blood/brain barrier. That means xanomeline can continue to work in the brain while trospium prevents xanomeline from causing adverse effects in the rest of the body.[13]

Xanomeline/trospium *continued...*

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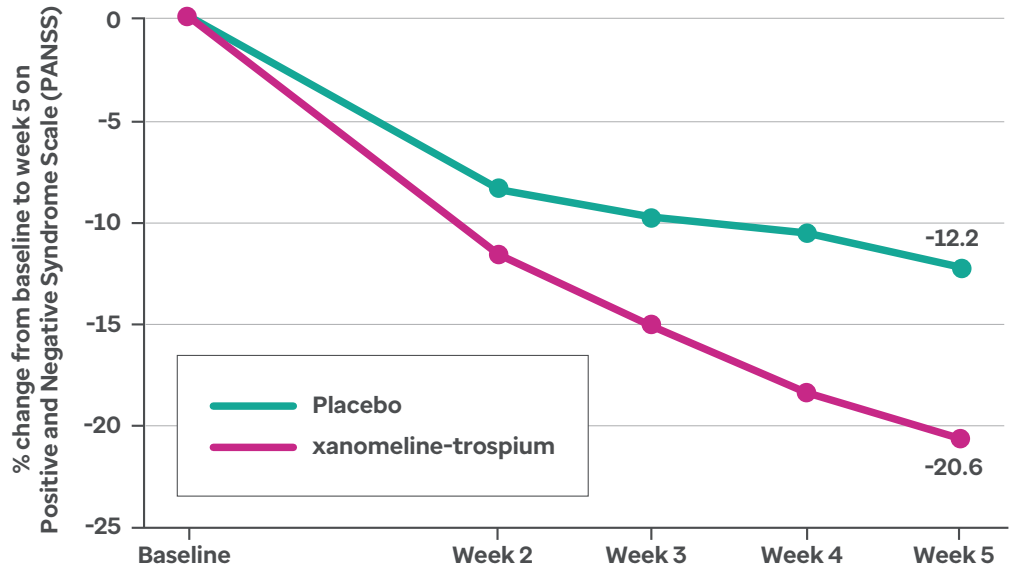
Trials

Xanomeline/trospium was evaluated in two Phase 3 studies in acutely psychotic adults with schizophrenia. Patients were randomized to receive xanomeline/trospium or placebo.

The studies measured the change from baseline in a standardized test used to measure symptom severity in schizophrenia (PANSS) at week 5. As the graph shows, xanomeline/trospium produced a 51% greater reduction from baseline compared with placebo (-20.6 vs. -12.2).[14]



Citation: JAMA Network. Efficacy and Safety of Xanomeline-Trospium Chloride in Schizophrenia: A Randomize Clinical Trial. Published. May 1, 2024.

The most common adverse events with xanomeline/trospium use were constipation, upset stomach, headache, nausea, vomiting, hypertension, dizziness, gastroesophageal reflux disease, and diarrhea.

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

Competitive environment

The current standard of care for schizophrenia is atypical antipsychotics. These drugs can provide significant benefit for some of the symptoms associated with schizophrenia. Generally, antipsychotics are associated with adverse events including involuntary movements, tremors, and muscle contractions. Additional side effects include sedation, weight gain, and hormonal imbalances.

Xanomeline/trospium *continued...*

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Xanomeline/trospium appears to be as effective as atypical antipsychotics. The main difference is that it produces less weight gain and drug-induced movement disorders compared to current treatment options. Still, in clinical trials, the discontinuation rate for xanomeline/trospium appears similar to atypical antipsychotics.

Xanomeline/trospium will enter a treatment landscape among well-established oral treatments available as generics. Also, long-acting injectable antipsychotics are available for patients who struggle with nonadherence. While xanomeline/trospium may offer some advantages, it has not yet faced head-to-head trials against its competitors.

Xanomeline/trospium is also in development as adjunctive therapy in schizophrenia and as a treatment for psychosis with Alzheimer's disease. If the results are positive in these uses, that could significantly increase its market potential.

For reference, the wholesale acquisition price for Caplyta® (lumateperone), a branded atypical antipsychotic, is approximately $20,000 per year.

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