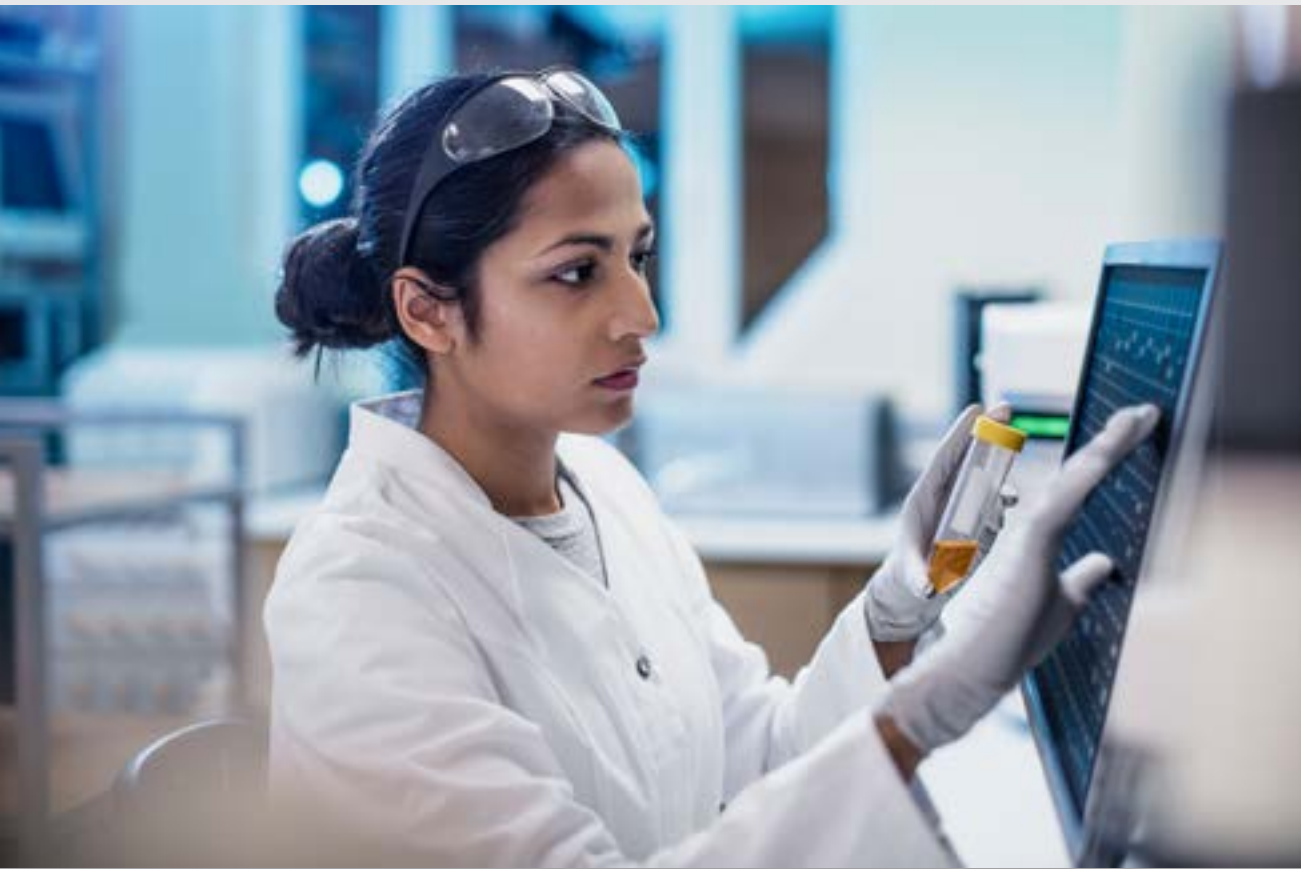
OPTUMRx®

OptumRx Drug Pipeline Insights Report



Q2 2022

Looking Ahead: 2022 Pipeline

By Sumit Dutta, Chief Medical Officer at OptumRx

Greetings and welcome to this edition of the OptumRx Drug Insights report. We have chosen four key drugs to highlight here that may be approved by the end of the second quarter 2022.

Despite the very real disruptions caused by COVID-19, 2021 saw 50 new therapies approved by the U.S. Food and Drug Administration (FDA). That is actually more than the last pre-COVID-19 year, 2019, when 48 new drugs were approved.[1] For 2022, we expect the number of approvals to be similar to the past few years.

The drugs in this report include:

Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (HCM). Mavacamten would be the first disease-specific medication approved for this condition.

Vutrisiran for treatment of a rare inherited condition (polyneuropathy of hereditary transthyretin-mediated amyloidosis). This is a high-cost category as drugs used for this condition are about $500,000 per year.

Tirzepatide for managing type 2 diabetes. It combines an older and newer mechanism that may result in greater effects on glucose and body weight.

Tapinarof for topical treatment of plaque psoriasis. Tapinarof is just one of four new plaque psoriasis therapies that may be approved by the end of this year. In our Market Trends section, we explore this large and growing category in greater detail.

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

Sumit Dutta
Chief Medical Officer, OptumRx

Drug overview

Mavacamten (Brand name to be determined) Expected FDA decision: April 28, 2022.

Mavacamten is in development for treatment of symptomatic obstructive hypertrophic cardiomyopathy (HCM). Mavacamten is administered orally once daily.

HCM is most frequently due to mutations in heart muscle proteins that causes the muscle to enlarge, or "hypertrophy." People with HCM are at higher risk for developing atrial fibrillation and heart failure.

It's estimated that 1 in every 500 people have HCM, but a large percentage of patients are undiagnosed.[2] Of those diagnosed, two-thirds have obstructive HCM. Bristol Myers Squibb estimates that there are currently approximately 160,000 to 200,000 people diagnosed with symptomatic obstructive HCM across the U.S. and EU.

HCM obstruction is caused when the enlarged (hypertrophied) part of the heart contracts too strongly, which creates abnormal blood flow. All types of muscle contraction are caused by repeated attachments of two proteins - actin and myosin. These attachments are called actin-myosin cross-bridges.

Mavacamten is thought to work by decreasing the number of actin-myosin cross-bridges, which reduces the heart muscle's ability to contract.

Trial results
Mavacamten was evaluated in a Phase 3 trial (EXPLORER-HCM) that compared it against placebo among patients with obstructive HCM. Mavacamten was found to be superior to placebo at improving a composite endpoint of exercise capacity (peak VO2) and health status (New York Heart Association [NYHA] functional class).[3]

Overall, 37% patients on mavacamten met the primary composite endpoint vs. 17% of patients receiving placebo.

The safety and tolerability of mavacamten were similar to placebo in the pivotal trial.

You can access an in-depth discussion of safety and trial data here (p.11).

Competitive environment
The current standard of care for HCM includes off-label use of various products. These offer limited relief of symptoms. Non-drug alternatives include surgical and nonsurgical procedures, and surgically implanted devices (e.g., pacemakers). But patients who undergo these procedures can continue to experience hypertrophy.

Mavacamten offers a novel mechanism of action and would be the first disease-specific medication approved for treating HCM. Trial results for mavacamten were promising. While the safety profile for mavacamten appears reasonable, we still lack long-term data on improvements in cardiovascular death or all-cause mortality.

If approved, mavacamten will be limited to patients with symptomatic, obstructive forms of HCM. Potentially it could be reserved for patients who have tried treatment options such as generic beta blockers, given the lack of long-term cardiovascular clinical outcomes data.

Drug overview

While there has been no announcement on price, some industry analysts forecast an annual cost of $75,000. This contrasts with a health-benefit price for mavacamten of between $12,000 and $15,000 per year based on Institute for Clinical and Economic Review (ICER) estimates.[4]

Vutrisiran (Brand name to be determined.) Expected FDA decision: April 14, 2022.

Vutrisiran is in development for treatment of polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis in adults. hATTR amyloidosis is a rare inherited condition caused by mutations that cause abnormal proteins to accumulate and damage different organs and tissues in the body.

This is a physically debilitating disease with multiple effects on the heart, nervous system, gastrointestinal tract, kidney, and others.[5] hATTR amyloidosis affects approximately 50,000 people worldwide.

Trial results
The efficacy of vutrisiran was evaluated in a Phase 3 trial (HELIOS-A). Patients received either vutrisiran via subcutaneous injection or Onpattro® (patisiran) via intravenous infusion for 18 months. The primary endpoint was the change from baseline in modified Neuropathy Impairment Score (mNIS+7) score at 9 months, relative to placebo. Higher scores of mNIS+7 indicate more neurologic impairment (range: 0 to 304).

The HELIOS-A trial did not include a placebo group and so vutrisiran was compared against placebo data taken from the Phase 3 trial for Onpattro (Onpattro is developed by Alnylam, same manufacturer as vutrisiran, and uses the same mechanism).[6]

Vutrisiran treatment resulted in a **2.24-point improvement** in mNIS+7 score at 9 months vs. 1**4.76-point worsening** reported for the placebo group. For reference, Onpattro resulted in a 1.41-point improvement in mNIS+7 score from baseline at 9 months.

Adverse events with vutrisiran occurred at a similar or lower rate as with placebo.

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

Competitive environment
If approved, vutrisiran would provide an additional treatment option for hATTR. Its primary differentiation would be more convenient dosing.

Vutrisiran is administered quarterly via subcutaneous injection. But its predecessor product, Onpattro, is dosed every three weeks via intravenous infusion. Onpattro also requires pre-medications to prevent infusion-related reactions. The only other therapy approved for this use is Ionis' Tegsedi® (inotersen). Tegsedi is also administered subcutaneously but carries known safety issues.

There is yet another hATTR product in development, eplontersen. Data from its Phase 3 trial in patients with polyneuropathy expected in mid-2022.

The initial target population indicated for vutrisiran is expected to be small. For context, as of December 31, 2021, there were just over 2,000 patients using Onpattro globally.

However, vutrisiran is also being evaluated for a considerably larger patient population. This is called **wild-type ATTR amyloidosis with cardiomyopathy** and is found mainly in males aged 80 and up.[7] Based on its presumed prevalence (~1%), wild-type ATTR may be present in more than 50,000 people, just in the U.S.[8, 9] Currently the only drug approved for this use is Pfizer's Vyndamax™ (tafamidis).

Drug overview

Phase 3 trial data for vutrisiran use in cardiomyopathy-associated with ATTR amyloidosis is expected in early 2024.

No pricing information on vutrisiran is available. For reference, the wholesale acquisition cost for Onpattro is approximately $500,000 per year.

Tirzepatide (Brand name to be determined.) Expected FDA decision: May 2022.

Tirzepatide is in development to supplement diet and exercise to improve glycemic control in adults with type 2 diabetes.

Over 30 million people in the U.S. have type 2 diabetes and 78% of these patients may also have obesity, so there is an ongoing need to help patients manage both their blood sugar and weight.[10]

Tirzepatide has a novel dual mechanism of action as a glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist. Several GLP-1 receptor agonists (e.g., semaglutide) are currently on the market. GIP has been shown to decrease food intake and increase energy expenditure, resulting in weight reduction. Paired with a GLP-1 receptor agonist, the combination may result in greater effects on glucose and body weight.

Trial results
Tirzepatide was evaluated across five Phase 3, randomized studies (SURPASS 1 to 5). The primary endpoint was the mean change in glycated hemoglobin (HbA1c). A key secondary endpoint was mean weight reduction.

Tirzepatide demonstrated superiority for the primary and key secondary endpoints of sustained HbA1c reduction and weight loss vs. the comparator arms in (e.g., placebo, basal insulins, GLP-1 receptor agonist) in each trial. This included a trial vs. Ozempic® (semaglutide) 1 mg, a commonly used GLP-1 receptor agonist.[11]

The most common adverse events with tirzepatide use were nausea, diarrhea, and vomiting.

You can access an in-depth discussion of safety and trial data here (p. 9).

Competitive environment
Tirzepatide would provide an additional treatment option for type 2 diabetes with a unique dual mechanism of action. Tirzepatide would primarily be competing with other GLP-1 receptor agonists such as Ozempic.

Based on the head-to-head study vs. Ozempic 1 mg, tirzepatide does have favorable A1c reduction and weight loss. However, **a higher strength formulation of semaglutide** (2.4 mg, sold under the brand name Wegovy®) is currently approved specifically for weight loss. Therefore, to some extent the weight loss benefits of tirzepatide vs. semaglutide may be less pronounced.

Treatment guidelines recommend choosing a type 2 diabetes therapy based on comorbid conditions and risk factors beyond glucose control (e.g., atherosclerotic cardiovascular disease, heart failure, chronic kidney disease). Several drugs have shown benefits for these conditions, including proven cardiovascular outcomes. But cardiovascular outcomes for tirzepatide are not expected until 2025.[12]

Drug overview

Looking further out, tirzepatide is also in development for other conditions, including obesity, heart failure, and nonalcoholic steatohepatitis.

For reference, the wholesale acquisition cost for Ozempic is approximately $10,000 per year.

Tapinarof (Brand name to be determined.) Expected FDA decision: May 26, 2022.

Tapinarof is in development for topical treatment of plaque psoriasis, a chronic (long-term) skin disease that causes red, itchy, scaly patches.[13] Psoriasis is caused by a dysfunction of the immune system that leads to inflammation.[14]

Plaque psoriasis is the most common form of psoriasis, and affects approximately six million people in the U.S.[15, 16]

Tapinarof inhibits two pro-inflammatory pathways implicated in psoriasis.[17]

Trial results
Tapinarof was evaluated in two Phase 3 studies. Patients used either tapinarof cream or vehicle cream (i.e., placebo) once daily for 12 weeks. The primary endpoint of both studies was the proportion of patients who achieved a Physician's Global Assessment (PGA) score of clear (0) or almost clear (1) with a minimum 2-grade improvement from baseline at week 12. The PGA score is on a scale from 0 to 4, with higher scores indicating more severe psoriasis.

- In study 1, 35.4% of the patients in the tapinarof group achieved a PGA response vs. 6.0% of those in the vehicle group.
- In study 2, 40.2% in the tapinarof group achieved a PGA response vs. 6.3% in the vehicle group.

The most common adverse events with tapinarof use were folliculitis, colds, contact dermatitis, headache, upper respiratory tract infection, and itching.

You can access an in-depth discussion of safety and trial data here (p. 7).

Competitive environment
If approved, tapinarof would provide a first-in-class topical treatment for plaque psoriasis. Tapinarof was evaluated in a broad patient population (mild to severe disease). It may also be used as an add-on therapy since systemic side effects are unlikely due to topical administration.

Tapinarof will be entering a topical marketplace that is dominated by corticosteroids and vitamin D analogs, which are available generically. These products are considered first-line agents for the condition and there is a lack of robust head-to-head trial data comparing tapinarof against them.

Tapinarof will also potentially be competing with Arcutis Biotherapeutics' novel topical formulation of roflumilast (see below). An FDA decision for topical roflumilast is expected by July 29, 2022.

Finally, tapinarof is also being evaluated for atopic dermatitis. This would significantly expand the potential target population for tapinarof. Trial data is expected in the first half of 2023.

Drug overview

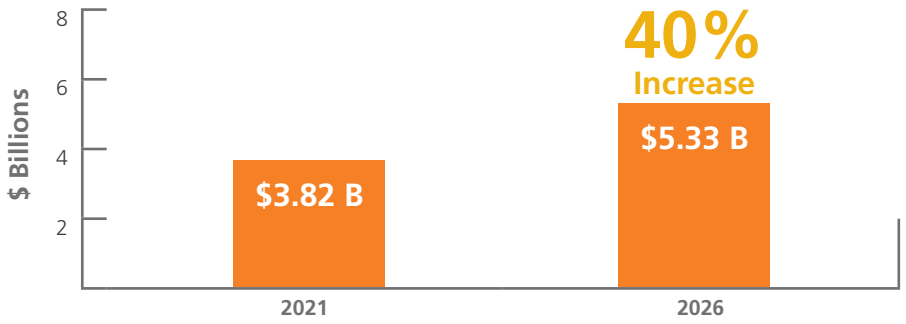
For reference, the wholesale acquisition cost for Wynzora® (calcipotriene/betamethasone dipropionate), a branded combination cream containing a vitamin D analog and corticosteroid, is approximately $1,000 per 30 days.

Industry trend to watch

Plaque psoriasis

The market for psoriasis treatments is big and growing fast. With plenty of treatment options, market projections see sales for psoriasis treatments rising 40% - to over five billion dollars in the U.S. and Canada in just four years.[18]

This graph shows the expected 40% sales growth in the psoriasis market from $3.82 billion in 2021 to $5.33 billion by 2026.



Source: Market Data Forecast. North America Psoriasis Drugs Market Research Report (2021 to 2026). Published January, 2022.

But the cost of medicines is only part of the cost picture. Actually, the total direct cost of treating psoriasis has been estimated at up to $63 billion in the U.S.[19]

2022 could turn out to be a very big year for new **plaque psoriasis** treatments in particular. Earlier we reviewed tapinarof, a new drug for plaque psoriasis. And there are still three more new plaque psoriasis drugs that could also be approved in 2022. So, it seems like a good moment to take a closer look at this important drug class.

Psoriasis basics

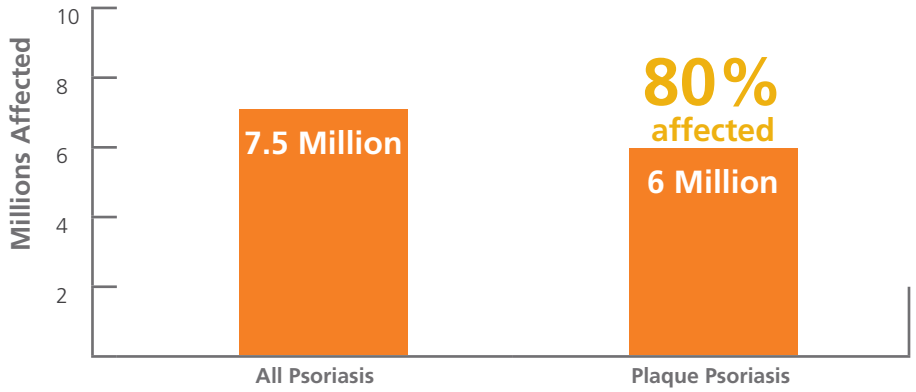
We don't know exactly what causes psoriasis. We do know that the immune system and genetics play major roles, and that an overactive immune system speeds up skin cell growth.[20]

Normal skin cells grow and shed in about a month. With psoriasis, skin cells complete this growth cycle in only three or four days. This causes skin cells to accumulate on the surface of the skin, forming plaques and scales that can appear on any part of the body.[21]

Approximately 7.5 million Americans experience one of the five types of psoriasis.[22] Of these, up to 80% have the **plaque psoriasis** form - around six million people.[23]

Industry trend to watch

This graphic depicts 7.5 million Americans with all forms of psoriasis. 80% of them have plaque psoriasis, or, 6 million.



Source: JAMA Network. Psoriasis Prevalence in Adults in the United States. Published June 30, 2021.
National Psoriasis Foundation. Locations and Types. Last updated March 10, 2021.

Current treatments

Psoriasis comes in several degrees of severity. Approximately 80% of psoriasis patients have mild to moderate disease, while 20% have moderate to severe psoriasis.[24]

For all degrees of severity, the object of psoriasis treatment is to slow skin cell growth and to remove scales. Options include creams and ointments, light therapy (phototherapy), and oral or injected medications.[25]

Topical therapies are considered the first line of treatment for plaque psoriasis. Phototherapy and systemic agents follow in utilization since they are usually prescribed only when topical therapy is not effective.[26]

Research into other autoimmune diseases have brought psoriasis treatments that specifically target the immune system. These **biologic drugs** opened a new class of psoriasis treatments.[27]

There are now at least a dozen biologic medicines approved by the FDA to treat moderate to severe psoriasis. These include such familiar names as Humira® (adalimumab), Remicade® (infliximab), and Skyrizi® (risankizumab-rzaa).[28]

Pending new treatments

In addition to tapinarof, there are three additional new drugs in queue for plaque psoriasis during 2022.

Industry trend to watch

Topical roflumilast (Brand name to be determined.) Expected FDA decision: July 29, 2022.[29]

Topical roflumilast cream manages an enzyme called phosphodiesterase-4 (PDE4). PDE4 helps to regulate inflammation in the body.[30] There is one other PDE4 inhibitor for plaque psoriasis already on the market: the oral drug Otezla® (apremilast).[31]

In Phase 3 trials, topical roflumilast significantly improved both the severity and burden of itch. Itch is the most frequently reported symptom with plaque psoriasis.[32]

In addition to providing an additional treatment option, a topical formulation of roflumilast may have a better tolerability profile compared to the existing drug in the class, Otezla, due to reduced systemic exposure.

No price information was available at the time of writing.

Bimekizumab (Brand name to be determined.) Expected FDA decision: TBD.

Bimekizumab selectively inhibits two interleukins, which belong to a category of small proteins important in cell signaling. Bimekizumab is focused on simultaneously targeting interleukins IL-17A and IL-17F, which are considered to be the most biologically active in psoriasis.[33]

In Phase 3 trials, bimekizumab showed high levels of response in patients with moderate to severe plaque psoriasis, with superiority demonstrated vs. several existing injectable biologics.

Bimekizumab previously had an FDA decision date set for October 15, 2021. But the FDA could not inspect the manufacturing facility due to COVID-19 related travel restrictions. A new date has not yet been set.[35]

Deucravacitinib (Brand name to be determined.) Expected FDA decision: September 10, 2022.[36]

Deucravacitinib is a Janus kinase (JAK) inhibitor in development to treat moderate to severe plaque psoriasis. It focuses on the JAK inhibitor tyrosine kinase 2 (TYK2), also known as JAK4. [37]

In two Phase 3 studies, deucravacitinib demonstrated superiority compared with placebo and Otezla® (apremilast) over the course of one year.[38]

As part of the JAK family, TYK2, could potentially fall within the FDA's safety concerns for oral JAK inhibitors as a class. These concerns include heart risks, liver dysfunction, anemia, abnormal blood platelet count or cholesterol level.[39]

However, so far deucravacitinib has not shown similar effects as the existing JAK inhibitors.[40] The manufacturer (Bristol Myers Squibb) claims this is because deucravacitinib is designed to block TYK2 **without** also inhibiting other JAK inhibitors (JAK1, JAK2, or JAK3), thus preventing the adverse events associated with the larger JAK class.[41]

No pricing information has been released. For comparison, the wholesale acquisition cost for Otezla is approximately $48,000 per year.[42]

Industry trend to watch

Discussion

There seem to be two themes present among the four new compounds described here. One is the innovation in the topical class that until recently has been lacking. Industry observers point out that the plaque psoriasis pipeline has been dominated by injectable biologics for a decade, while topical therapies have seemingly stagnated.[43] However, by the end of 2022 we could have two new novel topical treatments with tapinarof and roflumilast.

The second theme is how well-established mechanisms are being massaged and tweaked to make them safer or more targeted. For example, by blocking just TYK2 without also inhibiting the other JAK enzymes, deucravacitinib hopes to prevent the safety issues associated with the larger JAK class.

Similarly, roflumilast is a reformulation of the PDE4 inhibitor found in an approved oral treatment for chronic obstructive pulmonary disease, Daliresp®. The intention is that reformulating into a topical cream could improve the risk-benefit profile of other PDE4 skin disease treatments.[44]

Price is the great unknown for all of these drugs, as is whether their claimed efficacy will turn out to bear closer scrutiny. Given the variety of existing treatments, these novel therapies will need superior efficacy or safety in order to justify any significant price premium.

Unless otherwise noted: OptumRx RxOutlook® 1st Quarter 2022.

1. U.S. Pharmacist. Recent Trends in Approvals of Novel Drugs. Published October 15, 2021. Accessed February 10, 2022.
2. BioPharma Dive. MyoKardia pops as heart drug passes most important test. Published May 11, 2020. Accessed March 8., 2022.
3. American College of Cardiology. Mavacamten for Treatment of Symptomatic Obstructive Hypertrophic Cardiomyopathy - EXPLORER-HCM. Published July 7, 2021. Accessed November 22, 2021.
4. The Pharma Letter. ICER puts fair mavacamten price at between $12,000 to $15,000 despite $75,000 forecasts. Published October 7, 2021. Accessed November 22, 2021.
5. Akcea Therapeutics, Inc. What Is Hereditary ATTR Amyloidosis (hATTR)? Accessed February 16, 2022.
6. FAP News Today. Vutrisiran's Benefits Sustained Over 18 Months in HELIOS-A Trial. Published November 8, 2021. Accessed February 16, 2022.
7. Amyloidosis Foundation. Wild-type ATTR. Updated March 2021. Accessed February 21, 2022.
8. ibid
9. Statistica. Resident population of the United States by sex and age as of July 1, 2020. Published September 10, 2021. Accessed February 23, 2022.
10. American Diabetes Association. Latest Data From SURPASS Trials Demonstrate Tirzepatide Provided Meaningful Blood Sugar Reductions. Published June 29, 2021. Accessed February 23, 2022.
11. ibid
12. ICER. ICER Publishes Final Evidence Report and Policy Recommendations on Tirzepatide for Type 2 Diabetes. Published February 15, 2022. Accessed March 8, 2022.
13. Mayo Clinics. Psoriasis. Published May 2, 2020. Accessed March 2, 2022.
14. National Psoriasis Foundation. About Psoriasis. Last updated on November 19, 2021. Accessed February 23, 2022.
15. JAMA Network. Psoriasis Prevalence in Adults in the United States. Published June 30, 2021. Accessed March 2, 2022.
16. National Psoriasis Foundation. Locations and Types. Last updated March 10, 2021. Accessed March 2, 2022.
17. Practical Dermatology. In the Pipeline: What to Know About Tapinarof. Published July, 2020. Accessed February 23, 2022.

Market Trends References

18. Market Data Forecast. North America Psoriasis Drugs Market Research Report - Segmented By Drug Type, Route of Administration, Target, & Country (The United States, Canada & Rest of North America) - industry Analysis on Size, Share, Trends, COVID-19 Impact & Growth Forecast (2021 to 2026). Published: January, 2022. Accessed March 2, 2022.
19. Journal of the American Academy of Dermatology. The burden of skin disease in the United States. Published May 1, 2017. Accessed March 3, 2022.
20. National Psoriasis Foundation. About Psoriasis. Last updated on November 19, 2021. Accessed February 24, 2022.
21. ibid.
22. JAMA Network. Psoriasis Prevalence in Adults in the United States. Published June 30, 2021. Accessed March 2, 2022.
23. National Psoriasis Foundation. Locations and Types. Last updated March 10, 2021. Accessed March 2, 2022.
24. American Academy of Dermatology. Skin conditions by the numbers. Accessed March 3, 2022.
25. Mayo Clinics. Psoriasis. Published May 2, 2020. Accessed March 2, 2022.
26. Mordor Intelligence. Psoriasis Drugs Market - Growth, Trends, COVID-19 Impact, And Forecasts (2022 – 2027). Accessed February 24, 2022.
27. WebMD. The Latest in Psoriasis Treatment. Published January 7, 2022. Accessed February 28, 2022.
28. ibid.
29. Dermatology Times. Roflumilast Cream Data Show Positive Outcomes for Plaque Psoriasis. Published October 13, 2021. Accessed February 24, 2022.
30. Arcutis Biotherapeutics. Topical Roflumilast Cream. Accessed March 2, 2022.
31. Healthline. What Everyone with Psoriasis Needs to Know About PDE4 Inhibitors. Updated April 20, 2020. Accessed March 2, 2022.
32. Dermatology Times. Roflumilast Cream Data Show Positive Outcomes for Plaque Psoriasis. Published October 13, 2021. Accessed February 24, 2022.
33. Therapeutic Advances in Chronic Disease. Dual inhibition of IL-17A and IL-17F in psoriatic disease. Published August 12, 2021. Accessed March 2, 2022.
34. The Lancet. Bimekizumab efficacy and safety in moderate to severe plaque psoriasis (BE READY): a multicentre, double-blind, placebo-controlled, randomised withdrawal phase 3 trial. Published February 6, 2021. Accessed February 24, 2022.
35. Formulary Watch. FDA Misses PDUFA Date for Bimekizumab. Published October 19, 2021. Accessed March 2, 2022.
34. Healthline. What Everyone with Psoriasis Needs to Know About PDE4 Inhibitors. Updated April 20, 2020. Accessed March 2, 2022.
35. Therapeutic Advances in Chronic Disease. Dual inhibition of IL-17A and IL-17F in psoriatic disease. Published August 12, 2021. Accessed March 2, 2022.
36. Fierce Pharma. Bristol Myers Squibb's next-gen autoimmune med starts high-stakes FDA review amid classwide JAK scrutiny. Published November 30, 2021. Accessed March 2, 2022.
37. Dermatology Times. Deucravacitinib Safe, Effective for Psoriasis. Published April 28, 2021. Accessed February 24, 2022.
38. ibid.
39. Fierce Pharma. Bristol Myers Squibb's next-gen autoimmune med starts high-stakes FDA review amid classwide JAK scrutiny. Published November 30, 2021. Accessed March 2, 2022.
40. ibid.
41. Dermatology Times. Deucravacitinib Safe, Effective for Psoriasis. Published April 28, 2021. Accessed February 24, 2022.
42. OptumRx Pipeline Surveillance. March, 2022.
43. Pharmaceutical Technology. Arcutis may face challenges when marketing roflumilast despite commercial advantage. Updated October 15, 2021. Accessed March 3, 2022.
44. Fierce Pharma. Arcutis' topical cream hits goal in psoriasis phase 3, setting up FDA filing and market showdown. Published February 9, 2021. Accessed March 8, 2022.

OPTUM®

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.