STONEGATE HEALTHCARE

Transformative Therapies for Pruritus Management

Addressing Critical Unmet Need in Primary Biliary Cholangitis (PBC)

November 2023

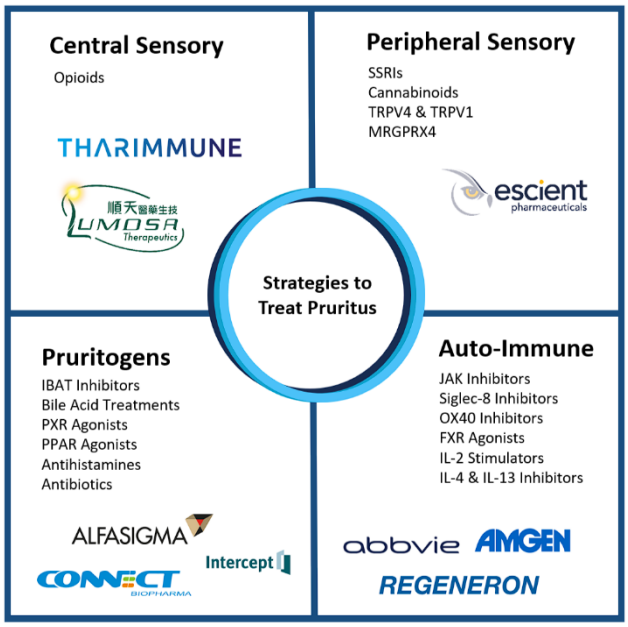
www.stonegatehealthcarepartners.com

Executive Summary

Pruritus, or itch, impacts approximately 8.2% of the global population. Chronic pruritus is reported by 42% of patients diagnosed with skin conditions and 40% of those with liver disease. We believe the highest unmet pruritus need is in Primary Biliary Cholangitis (PBC), an autoimmune liver disease that predominantly damages the small bile ducts, resulting in severe chronic nocturnal pruritus in 72% of PBC patients. This nocturnal itching leads to sleep deprivation, significantly impairing daily and social activities for affected individuals.

Current front-line treatments prove ineffective in relieving pruritus for approximately 50% of PBC patients. While various strategies aim to be disease-modifying, they fall short in providing relief to PBC patients. The primary concern for patients lies in the management of chronic and severe nocturnal itch.

Our research focused on 164 companies in the pruritus space, identifying 23 companies with significant potential to address the specific needs of PBC patients (see Appendix A & B). Through an evaluation of their regulatory approaches, differentiated mechanisms of action, and potential for nocturnal use, we have identified the most promising programs to address this unmet medical need. We believe that these innovative therapies will revolutionize the treatment of pruritus, consequently reshaping the landscape of PBC management.



	EP547	CNP-104	Volixibat	TH104
Nocturnal Use	No	NA	Unknown	8 hours
Targets Pruritus	1st Outcome	2nd Outcome	1st Outcome	1st Outcome
Reduces Inflammation	No	Yes	Yes	Yes
Mechanism of Action	MRGORX4	PDC-E2	IBAT	Opioid Receptor Antagonist
Company	Escient Pharma	Ironwood Pharma	Mirum Pharma	Tharimmune

Note: Figures and tables are deveoped from primary research done by Stonegate Heatlhcare

Large Population of Pruritus Patients

Pruritus (itch) affects approximately 8.2% of the human population. 42% of patients diagnosed with skin conditions and 40% of patients with liver disease report chronic pruritus. Risk for developing chronic severe pruritus increases with age and prevalence is greater in women. There are several diseases that result in chronic moderate to severe pruritus including:

- Lymphoma
- Kidney Disorders
- Liver and Biliary Diseases
- Metabolic Disorders
- Dermatological Disorders
- Rare Genetic Disorder

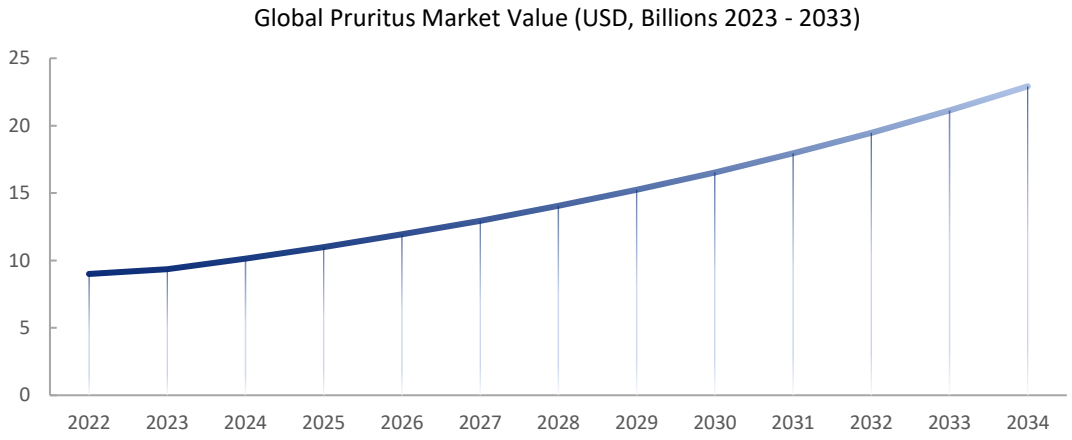


Figure 1: The global pruritus market is expected to grow at 3.8% annually reaching over 20 billion by 2033.
Source: Stonegate Healthcare Research

Need in Primary Biliary Cholangitis is Severe

Primary biliary cholangitis (PBC) is an autoimmune liver disease that primarily affects the small bile ducts within the liver. In PBC, the immune system mistakenly targets and destroys these bile ducts, leading to a disruption and imbalance in the flow of bile. Over time, this damage can lead to inflammation, fibrosis, and ultimately cirrhosis of the liver.

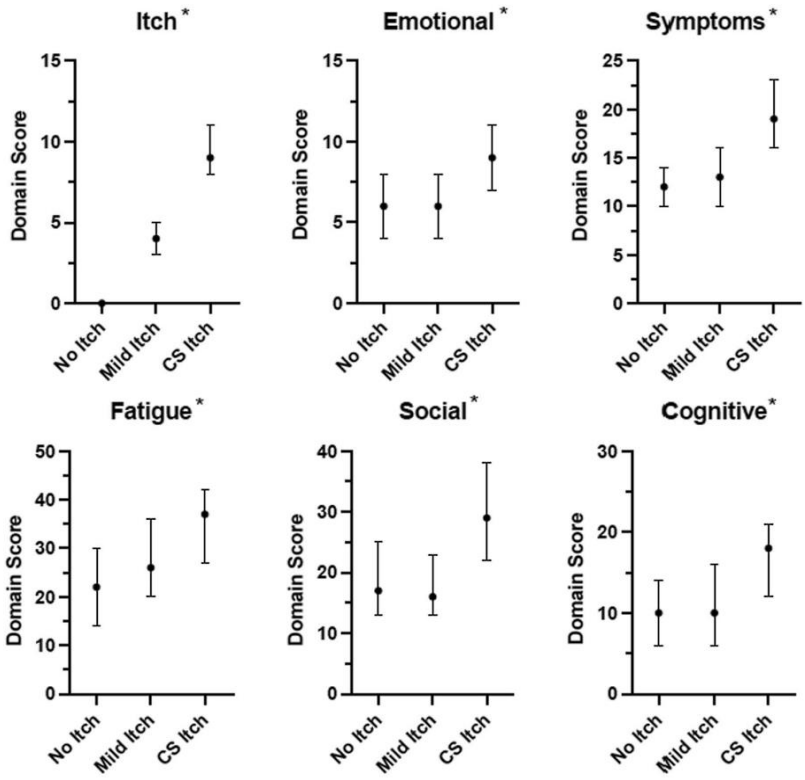


Figure 2: Impact of chronic pruritus in PBC patients.
Source: Mayo, Marlyn J, et al. Digestive Diseases and Sciences (2022)

The need in PBC is severe with 72% of patients suffering from severe nocturnal pruritus resulting in a serious drop in quality of life. Nocturnal pruritus causes sleep deprivation and by proxy impairs all daily and social activities for patients. These symptoms are also known to cause chronic depression. PBC is an orphan disease in the United States affecting approximately 60,000 patients. Women are mainly affected, at a 9:1 ratio.

Current Therapies Fail to Show Efficacy in Treating Pruritus in PBC

Current front-line treatments such as Ursodeoxycholic Acid (UDCA) are ineffective in relieving itch in approximately 40 - 50% of patients. A 2022 study including 671 patients with PBC found that 81% reported itch, 37% reported severe itch. Patients who are unresponsive to UDCA are given Obeticholic Acid (OCA), an FXR agonist. The efficacy of OCA, assessed in the POISE study, showed significant improvement in cholestasis, hepatocellular damage, inflammation, and apoptosis. However, pruritus emerged as a common side effect.

Current front-line treatments fail to address severe pruritus need, while second-line drugs like OCA are increasing itch. A recent review concluded that, "There is a lack of consistent and reproducible evidence available on efficacy of pruritus treatments, leaving physicians to rely on clinical experience rather than evidence-based medicine for treatment selection" (Digestive Diseases and Sciences, 2023). To properly address itch developers, need to look at pruritus scores with equal importance to biomarkers showing disease modifying efficacy such as Alkaline Phosphatase (ALP) levels and liver stiffness scores.

Listed below are some common mechanisms to treat pruritus in PBC.

1. Bile Acid Sequestration:

Excess bile acid accumulates in the bloodstream and subsequently the skin in PBC patients causing itch. Cholestyramine can be used to bind bile acid in the intestine and prevent its leakage into tissue.

2. Ursodeoxycholic Acid (UDCA):

Ursodeoxycholic acid is a naturally occurring bile acid that helps restore the balance of bile acids in the liver. By promoting the secretion of less toxic bile acids, it can also reduce inflammation and pruritus.

3. Antihistamines:

Histamine release can cause itching by binding to histamine receptors in the skin. Antihistamines like hydroxyzine block histamine receptors, preventing histamine from triggering the itching response.

4. Opioid Receptor Antagonists:

Opioid receptor antagonists like naltrexone block opioid receptors. In some cases, activation of these receptors can induce itching sensations.

5. Antibiotics:

Rifampin has been used off-label to manage pruritus in PBC patients. Its exact mechanism of action in alleviating itching is not fully understood, but it may involve effects on the liver metabolism of bile acids.

6. Serotonin Receptor Antagonists:

Serotonin, when released in peripheral tissues, including the skin, can contribute to itching sensations. SSRIs (selective serotonin reuptake inhibitors) work by increasing serotonin levels in the brain by blocking its reuptake.

Strategic Approach to Addressing Severe Unmet Need in Primary Biliary Cholangitis

Most of the therapies listed below aim to be disease modifying but they do not provide relief to PBC patients. The patient need surrounds treating chronic and severe nocturnal itch. In our opinion, to address the patients' needs, successful programs will look to relieve itch as a primary outcome in addition to being long-lasting and enabling nocturnal use. The importance of sleep to overall health cannot be overstated, and for patients with moderate to severe pruritus, a drug that allows for proper rest will have a large positive impact on quality of life.

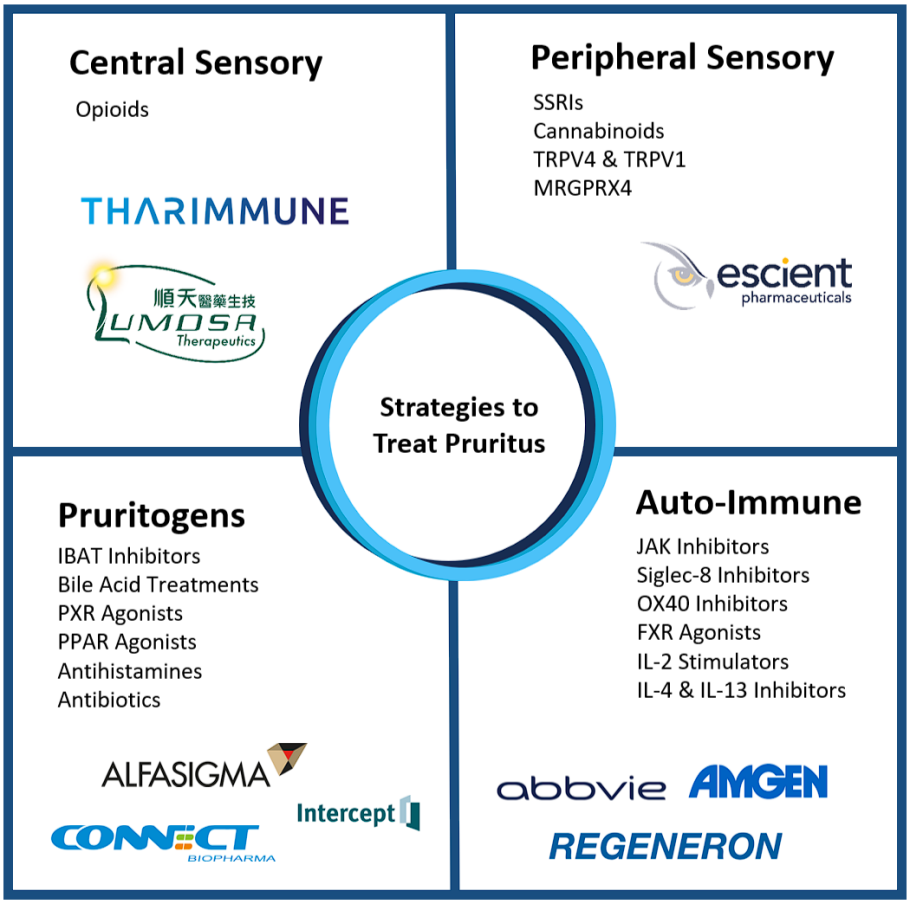


Figure 3: Strategies to treat pruritus.
Source: Stonegate Healthcare Research

Transformative Therapies to Treat Pruritus in PBC

Our research focused on 164 companies in the pruritus space, identifying 23 companies with significant potential to address the specific needs of PBC patients (see Appendix A & B). Through an evaluation of their regulatory approaches, differentiated mechanisms of action, and potential for nocturnal use, we have identified the most promising programs to address this unmet medical need. We believe that these innovative therapies will revolutionize the treatment of pruritus, consequently reshaping the landscape of PBC management.

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Company	Escient Pharma	Ironwood Pharma	Mirum Pharma	Tharimmune

Table 1: Leading programs to treat pruritus in PBC.
Source: Stonegate Healthcare Research

Escient Pharma

Escient Pharmaceuticals is a biotechnology specializing in the development of novel therapeutics for neurosensory-inflammatory disorders. The company is notable for its focus on targeting Mas-Related G Protein-Coupled Receptors (MRGPRS) to create small molecule antagonists. The company's pruritus PBC drug, EP547 stands out as a small molecule oral therapy. EP547 selectively targets MRGPRX4, a receptor found on sensory itch neurons in the skin.

Phase 1 study of EP547 demonstrated that the drug was well-tolerated and safe at all tested doses and determined potential for once-daily oral administration. A phase 2 proof of concept study for the program is underway and in the recruiting stage. The study is estimated to be completed in 2H 2024. We believe that Escient Pharma's treatment strategy is differentiated and can potentially address the unmet need in PBC. Studies will show whether this new MOA in CNS can provide efficacy and if the drug's profile allows for nocturnal use.

Ironwood Pharma

Ironwood Pharmaceuticals is a healthcare company focused on advancing the treatment of GI diseases and redefining the standard of care for GI patients. The company developed the leading commercial drug for adults with irritable bowel syndrome with constipation (IBS-C) or chronic idiopathic constipation (CIC), LINZESS® (linaclotide). Ironwood is actively engaged in advancing its drug programs, including a next-generation long-acting synthetic GLP-2 analog being developed for rare gastrointestinal diseases and notably, CNP-104, a potential disease-modifying therapy for PBC with an interesting mechanism of action.

CNP-104 is a nanoparticle encapsulating PDC-E2, a key auto immune modulator. CNP-104's action on the immune system can potentially prevent bile duct destruction and halt disease progression. The company's preliminary assessment from its phase 2 trial showed evidence of favorable T-cell responses in patients treated with CNP-104, supporting the mechanistic rationale for the asset. The Phase II study is ongoing, and the company expects topline results in the third quarter of 2024, which include safety and change in ALP levels as the primary endpoints. We believe the PDC-E2 pathway makes CNP-104 highly differentiated. We look forward to seeing how effective this drug can be at addressing pruritus.

Mirum Pharma

Mirum Pharmaceuticals is a biopharmaceutical company dedicated to addressing rare and orphan diseases by developing and commercializing novel therapies. The company is actively advancing Volixibat, an investigational oral therapy designed to address PSC and PBC in adults. Volixibat's is a selective inhibitor of ileal bile acid transporters (IBAT), a key protein responsible for recycling bile acids from the intestine to the liver.

The design of Volixibat minimizes its absorption into the bloodstream, which enhances its safety profile. Mirum Pharmaceuticals is actively engaged in clinical research, with Phase 2b interim analyses for Volixibat anticipated in the first half of 2024. We believe Mirum might have the potential to meet the severe unmet need in PBC. It remains to be seen whether an IBAT inhibitor can show efficacy in pruritus, and if Volixibat's minimally absorbing profile can allow for nocturnal use.

Tharimmune

Tharimmune is a clinical-stage biotechnology company dedicated to advancing therapeutic candidates for rare, inflammatory, and oncologic diseases. Their lead product candidate for Pruritus in PBC, TH104, is a transmucosal film nalmefene treatment that can modulate the mu and kappa opioid receptors for approximately 8 hours.

Activating both receptors allows for strong potential relief. Additionally, action on the kappa receptor can have anti-addictive effects. The company recently (November 2023) announced that it has entered into an exclusive global licensing agreement with Avior Bio to develop and commercialize TH104 for treating chronic pruritus. Tharimmune plans to conduct phase 1 and phase 2 trials, with completion expected in about 12 months post-FDA alignment on trial design. We believe their CNS approach with established opioid efficacy and a drug profile enabling nocturnal use can be highly effective in meeting patient need in PBC. The company's CNS approach can potentially translate well across indications causing pruritus.

Appendix A: Pruritus Programs Commercial & In-Development Matrix

Company	Drug	MOA	Stage
AbbVie	RINVOQ	JAK inhibitor	Commercial
Aclaris Therapeutics	ATI-1777	JAK inhibitor	Phase 2b
Alfasigma (acq. Intercept Pharmaceuticals)	Obeticholic acid + bezafibrate	Obeticholic acid + bezafibrate	Phase 2
Allakos	Lirentelimab	Siglec-8 inhibitor	Phase 2b
Amgen	Rocatinlimab	OX40 inhibitor	Phase 3
Apogee Therapeutics	APG777	Extended half-life IL-13 inhibitor	Phase 1
Arcutis Biotherapeutics	Roflumilast	PDE4 inhibitor	Phase 3
Calliditas	Setanaxib	NOX enzyme inhibitor	Phase 2b/3
Cara Therapeutics	Difelikefalin (Korsuva)	Kappa opioid agonist	Phase 3
Connect Biopharma	CBP-174	Antihistamine	Phase 1
CymaBay	Seladelpar	PPAR agonist	Phase 3
Escient Pharmaceuticals	EP547	Mas-related G receptor agonist	Phase 1/2a
Gannex	ASC42	FXR agonist	Phase 2
Ipsen (acq. Albireo)	ELAFIBRANOR	PPAR agonist	Phase 3
Ironwood Pharmaceuticals	CNP-104	PDC-E2	Phase 2
Kymera Therapeutics	KT-474	IRAK4 degrader	Phase 2
Lumosa Therapeutics	LT5001	Kappa and mu opioid agonist	Phase 1
Mirum Pharmaceuticals	Volixibat	IBAT inhibitor	Phase 2b/3
Nektar Therapeutics	REZPEG (NKTR-358)	IL-2 stimulator	Phase 2
Regeneron	DUPIXENT	IL-4 & IL-13 Inhibitor	Commercial
Roivant Sciences	VTAMA (Tapinarof)	Aryl hydrocarbon receptor agonist	Phase 3

Table 2: Pruritus Programs Commercial & In-Development Matrix
Source: Stonegate Healthcare Research

Appendix B: Pruritus Programs Commercial & In-Development Descriptions

1. Abbvie

AbbVie is a global pharmaceutical company known for its diverse portfolio of innovative drugs. One of the prominent programs, RINVOQ (upadacitinib), is used to treat various immune-mediated inflammatory diseases. The drug is FDA approved for the treatment of moderate to severe atopic dermatitis (AD) in adults and children aged 12 and older who have not responded to previous treatments or other pills and injections. RINVOQ is administered as an oral pill, offering a convenient daily treatment option. Its mechanism of action involves inhibiting JAK enzymes, preventing the activation of STATs, hematopoiesis, and immune cell functions.

The FDA approval for RINVOQ in AD was supported by one of the largest Phase 3 programs in the field, involving over 2,500 patients across three studies. The program found that RINVOQ was effective, even in patients with prior exposure to systemic AD treatments. Notably, the drug showed early itch reduction as early as week one and significant improvements in skin clearance at 16 weeks compared to a placebo. AbbVie's RINVOQ, although facing scrutiny, holds promise in the treatment of pruritus. Sales figures of RINVOQ are estimated to reach between 5 – 7 billion by 2025.

2. Aclaris Therapeutics

Aclaris Therapeutics, Inc. is a clinical-stage biopharmaceutical company specializing i n the development of novel drug candidates for immuno-inflammatory diseases. Operating in the United States, the company is actively engaged in two segments: Therapeutics and Contract Research. The Therapeutics segment focuses on identifying and developing innovative therapies to address significant unmet needs in immuno-inflammatory diseases.

A key candidate is ATI-1777, a soft JAK 1/3 inhibitor designed for the treatment of moderate to severe AD. The innovative aspect of ATI-1777 lies in its topical application to the skin, aiming to minimize systemic exposure by rapid metabolism and inactivation upon entering the bloodstream. Aclaris anticipates releasing phase 2b top-line efficacy, safety, and other preliminary data for ATI-1777 by the end of 2023. The company recently completed enrollment in the Phase 2b trial of ATI-1777 for mild to severe atopic dermatitis, with top-line data expected around year-end 2023.

3. Alfasigma (acq. Intercept Pharma)

Intercept Pharma, recently acquired by Italian pharma Alfasigma, is a biopharmaceutica l company focused on the development and commercialization of therapeutics to treat progressive non-viral liver diseases. Their portfolio includes OCALIVA (obeticholic acid), which has received conditional approval pending data from an ongoing phase 4 study.

The company is investigating a combination of OCA and bezafibrate for PBC treatment, currently in phase 2 studies. Bezafibrate is a pan-peroxisome proliferator activated receptor (pan-PPAR) agonist that is not approved in the U.S. for any indication. Data released in June 2023 from an interim analysis of its Phase 2 study showed that the combination treatment normalized several biomarkers associated with PBC-induced liver damage in 58% of patients after 12 weeks of treatment.

4. Allakos

Allakos is a pioneering clinical stage biopharmaceutic al company based in San Carlos, California, specializing in the development of immunomodulatory therapeutics for allergy, inflammatory, and proliferative diseases. Their pruritus drug program is the monoclonal antibody, lirentelimab (AK002), currently in Phase II clinical studies for AD and chronic spontaneous urticaria. Lirentelimab's mechanism of action involves activating the inhibitory receptor Siglec-8, selectively targeting mature mast cells and eosinophils, and depleting them through antibody-dependent cellular cytotoxicity in the blood.

The ongoing Phase 2b trials for AD are expected to yield data in the second half of 2023. Lirentelimab, administered subcutaneously, has demonstrated extended eosinophil suppression and favorable safety profiles in Phase 1 studies. Mild to moderate infusion-related reactions were the most commonly reported adverse events, occurring predominantly during the initial infusion.

5. Amgen

Amgen's inflammation company's portfolio encompasses treatments for conditions such as plaque ps oriasis, rheumatoid arthritis, and osteoporosis. In a strategic collaboration with Kyowa Kirin Co., Ltd., Amgen is advancing KHK4083 (rocatinlimab), a potential first-in-class anti-OX40 fully human monoclonal antibody designed for the treatment of AD and other autoimmune diseases.

KHK4083, discovered by Kyowa Kirin and engineered with innovative technology, selectively depletes activated T cells crucial in AD development. Under the collaboration agreement, Amgen will lead global development, manufacturing, and commercialization, excluding Japan, where Kyowa Kirin retains rights. The partnership includes a significant financial commitment, reflecting Amgen's confidence in the therapeutic potential of rocatinlimab. The program began phase 3 trials in June 2023.

6. Apogee Therapeutics

Apogee Therapeutics is a biotechnology company developing innovative b iologics for various inflammatory and immunology indications, with a specific focus on AD (AD) and chronic obstructive pulmonary disease (COPD). Their lead candidate, APG777, Apogee is pioneering a subcutaneous extended half-life monoclonal antibody designed to target IL-13, a critical cytokine in inflammation and a primary driver of AD.

APG777 aims to prevent the onset of an exaggerated immune response, often associated with overproduced IL-13 in AD patients, leading to weakened skin barriers and exacerbated inflammatory responses. The novel antibody is anticipated to offer significantly improved dosing regimens, potentially requiring administration once every two to three months. As of August 2023, Apogee has initiated dosing of healthy volunteers in the Phase 1 trial for APG777. The trial is expected to provide initial subcutaneous pharmacokinetic and safety data in mid-2024. We believe their extended-release design aligns with the pruritus need in PBC.

7. Arcutis Biotherapeutics

Arcutis Biotherapeutics, headquartered in Westlake Village, California, is a biopharmaceutical company focused on developing and commercializing innovative treatments for dermatological diseases. Th e company's lead product candidate, ARQ-151, is a topical roflumilast cream that has successfully completed Phase III clinical trials for both plaque psoriasis and AD. The drug functions as a small molecule inhibitor of phosphodiesterase-4 (PDE4), a crucial enzyme in inflammatory diseases.

A new drug application for ARQ-151 for the treatment of seborrheic dermatitis in individuals aged 9 years and older was accepted by the FDA in April 2023. The agency set a target action date of December 16, 2023, for the application. The foam formulation is designed to provide a steroid-free, once-daily treatment option. Arcutis Biotherapeutics is anticipating FDA approval and preparing for the commercial launch of roflumilast foam. The efficacy of a topical PDE4 inhibitor in PBC remains unclear however a once daily application would address the chronic pruritus patients suffer from.

8. Calliditas

Calliditas Therapeutics, a Swedish commercial-stage specialty pharmaceutical company, specializes i n identifying, developing, and commercializing pharmaceutical products for orphan indications, with a primary focus on renal and hepatic diseases. One of their lead candidates, Setanaxib, is a NOX inhibitor currently in a Phase 2b/3 clinical trial for PBC and Phase 2 for squamous cell carcinoma of the head and neck cancer, idiopathic pulmonary fibrosis, and type 1 diabetic kidney disease. Setanaxib targets NOX enzymes, known for producing reactive oxygen species.

In a phase 2 trial, the drug did not meet its primary endpoint, however it did demonstrate a reduction in ALP levels, an improvement in liver stiffness scores, and alleviated PBC-related fatigue. Currently in a pivotal 52-week, randomized, placebo-controlled Phase 2b/3 TRANSFORM TRIAL, Setanaxib aims to be an add-on therapy for PBC patients with an elevated liver stiffness score and intolerance or inadequate response to UDCA.

9. Cara Therapeutics

Cara Therapeutics is a biopharmaceutical company focused on treating pruritus in the United States. Their FDA-approved KORSUVA® injection is the first treatment for severe itching in adults with chronic kidney disease undergoing hemodialysis. The company is developing an oral version of the drug with Phase 3 programs for pruritus in advanced chronic kidney disease and atopic dermatitis. They also have a Phase 2/3 program for pruritus in patients with notalgia paresthetica. The company plans to report data from Phase 3 programs in December 2023 and expects results for other programs in 2024 and 2026.

In Novemeber 2023 Cara deprioritized its PBC program, sighting slow enrollment due to COVID-19 for its Phase 2 clinical. The unblinded data showed no unexpected AEs. However, the low number of patients (N=14) limits the ability to draw a meaningful conclusion regarding the efficacy (worst itch NRS change from baseline at 16 weeks: -3.8 difelikefalin vs. -3.0 placebo) of difelikefalin in this patient population. The company will direct all available resources towards our nephrology and dermatology franchises.

10. Connect BioPharma

Connect Biopharma Holdings Limited is a clinical-stage biopharmaceutical company with a primary focus on developing therapies for T cell-driven inflammatory diseases. The company employs functional T cell assays to screen and discover small molecules and antibodies against validated immune targets. Among its product candidates is CBP-174, a peripherally acting antagonist of histamine receptor 3 (H3R) designed to treat pruritus associated with allergic and inflammatory skin conditions, including AD.

An important milestone for CBP-174 was the successful completion of its Phase 1 single ascending dose study, demonstrating safety and tolerability in healthy adults. The study showed CBP-174 to be well-tolerated, with no serious adverse events reported. The drug's mechanism, acting peripherally on the H3 receptor without penetrating the blood-brain barrier, minimizes the risk of central nervous system side effects associated with common antihistamines. CBP-174's promising safety profile and observed efficacy in pre-clinical models support its potential as a treatment for chronic pruritus.

11. CymaBay

CymaBay Therapeutics is a clinical-stage biopharmaceutical company dedicated to developing innovative therapies for liver and other chronic diseases. The company's lead product candidate , seladelpar (MBX-8025), is a selective agonist of peroxisome proliferator-activated receptor delta (PPAR-δ) designed for the treatment of PBC. The drug's mechanism involves the modulation of PPAR-δ, a ligand-activated transcription factor that regulates gene expression in various liver cell types, decreases bile acid synthesis, and exhibits anti-inflammatory activity by inhibiting the activation of macrophages.

In clinical studies for PBC, seladelpar demonstrated a reduction in biomarkers associated with adverse clinical outcomes, including liver-related complications, transplantation, and death. Notably, seladelpar has shown efficacy in improving pruritus. The company plans to file an NDA for seladelpar early next year. This regulatory filing follows positive topline data from the Phase 3 RESPONSE trial, where seladelpar demonstrated a significant improvement compared to the placebo group.

12. Gannex Pharma

Gannex Pharma, a wholly owned subsidiary of Ascletis Pharma, is developing ASC42, a novel Farnesoid X receptor (FXR) agonist for PBC. Ascletis, the parent company of Gannex, is an R&D-driven biotech listed on the Hong Kong Stock Exchange. With a focus on viral diseases, NASH, and oncology. The drug's mechanism of action involves engaging the FXR target, as evidenced by a substantial increase in Fibroblast Growth Factor 19 (FGF19) biomarker levels during the U.S. Phase I trial.

Gannex recently announced the completion of patient enrollment for the Phase II clinical trial, totaling 98 patients with inadequate responses to UDCA. The 12-week study aims to assess the safety and efficacy of ASC42, with topline data expected by the end of 2023.

13. Ipsen

Albireo Pharma, now a subsidiary of Ipsen Biopharmaceuticals, Inc. since March 1, 2023, is a commercial-stage biopharmaceutical company headquartered in Boston, Massachusetts. The company is dedicated to developing and commercializing novel bile acid modulators for the treatment of orphan pediatric liver diseases, as well as other liver and gastrointestinal disorders. Under the Ipsen and Genfit partnership, Albireo's drug program, elafibranor, has shown promise in the Phase III ELATIVE trial for PBC.

Elafibranor is a dual peroxisome activated receptor agonist that demonstrated positive results in meeting its primary composite endpoint. The trial also demonstrated statistically significant improvements in secondary endpoints, including normalization of ALP and a trend for pruritus improvement. Ipsen intends to submit regulatory applications for elafibranor after discussions with the FDA and the EMA. The drug's safety profile, consistent with previous studies, and its efficacy in reducing cholestatic injury indicate its potential as a long-term therapeutic option for PBC patients, preventing disease progression.

14. Kymera Therapeutics

Kymera Therapeutics, a biopharmaceutical company headquartered in Watertown, Massachusetts, specializes in the discovery and development of innovative small molecule therapeutics that selectively degrade disease-causing proteins by leveraging the body's natural protein degradation system. The company's lead candidate, KT-474, is a selective orally bioavailable IRAK4 degrader. In Phase I clinical trials, KT-474 demonstrated IRAK4 degradation in both blood and active skin lesions of patients with hidradenitis suppurativa (HS) and AD.

The treatment has shown a systemic anti-inflammatory response and improvement in skin lesions and symptoms for both conditions, with internal consistency between the effect on biomarkers and clinical endpoints. Phase 1 results published in Nature Medicine. Sanofi, Kymera's collaboration partner, has initiated two Phase 2 trials for KT-474, targeting HS and AD. The first patient was dosed in the HS trial in October 2023, generating a significant $40 million milestone payment.

15. Lumosa Therapeutics

Lumosa Therapeutics, a clinical-stage pharmaceutical company based in Taipei, Taiwan, focuses on developing innovative therapies for neurological and oncological diseases. Among its notable programs is LT5001, a novel drug designed to address uremic pruritus, a complication commonly seen in patients with chronic kidney disease and end-stage renal disease. LT5001 contains dinalbuphine sebacate (DNS), with the active ingredient nalbuphine acting as a kappa agonist and mu antagonist, specifically formulated as a topical ointment to provide a localized effect, minimizing systemic exposure and the associated risks.

The company last provided an update on the program in 2019, announcing that LT5001 received IND approval from the Taiwan FDA for a phase Ib/II study. The phase Ib trial is set to commence in Taiwan, Lumosa is anticipating completion within a year after initiation. The preparatory works for the clinical trial, including IRB reviews, are underway, and the phase II study will follow adjustments based on phase Ib results. We believe the CNS approach to addressing pruritus can be promising. It will be interesting to see efficacy data of a topical drug exploring an opioid strategy.

16. Nektar Therapeutics

Nektar Therapeutics, a biopharmaceutical company based in San Francisco, is focused on discovering and developing medicines in the field of immunotherapy. One of its key drug programs is centered around rezpegaldesleukin (REZPEG/NKTR-358), a first-in-class IL-2 regulatory T-cell stimulator designed to address immune system imbalances underlying autoimmune disorders.

REZPEG preferentially stimulates the proliferation of regulatory T cells without activating cytotoxic CD8+ T and CD4+ T cells. The drug is currently in phase 2 clinical trials for systemic lupus erythematosus, ulcerative colitis, atopic dermatitis, and psoriasis. In an April 2023 press release, Nektar announced regaining of rights to REZPEG from Eli Lilly. The company plans to move forward with a Phase 2b study for moderate-to-severe AD and explore other autoimmune indications for REZPEG. Phase 1b durability of response suggests the potential for a quarterly maintenance dosing regimen.

17. Regeneron Pharmaceuticals

Regeneron Pharmaceuticals has a diverse portfolio of medicines aimed at treating autoimmune diseases worldwide. Among its products is Dupixent, an injectable medication designed to treat atopic dermatitis and asthma in both adults and pediatrics. Dupixent, approved by the FDA in 2017, is a human monoclonal antibody inhibiting IL-4 and IL-13 signaling by binding to the IL-4 receptor alpha subunit, shared by both IL-4 and IL-13 receptor complexes. By blocking this subunit, Dupixent aims to inhibit cytokine-induced responses, including the release of proinflammatory cytokines, chemokines, and immunoglobulin E.

In a March 2023 press release, Regeneron announced the European Commission's approval of Dupixent to treat severe atopic dermatitis in children aged 6 months to 5 years old who are candidates for systemic therapy. The approval is based on data from a Phase 3 trial, demonstrating the efficacy of Dupixent in improving skin clearance, reducing overall disease severity and itch in this age group. Dupixent is a valuable asset in Regeneron's efforts to address a range of chronic diseases driven by type 2 inflammation.

18. Roivant Sciences

Roivant Sciences, through its subsidiary Dermavant, is a biopharmaceutical company dedicated to developin g and commercializing therapies in the field of immuno-dermatology. One of the key programs under development is the VTAMA (tapinarof) cream, designed for the treatment of AD. VTAMA is an aryl hydrocarbon receptor agonist, offering a once-daily, steroid-free topical treatment.

The ADORING program, including ADORING 1 and ADORING 2, represents Dermavant's pivotal Phase 3 clinical trials for VTAMA cream in AD. Notably, VTAMA demonstrated significant improvements in multiple endpoints, including a reduction in itch, making it a promising treatment option. A supplemental New Drug Application for VTAMA in AD is expected to be filed with the FDA in Q1 2024.

Sources

Lindor, Keith D., et al. “Primary Biliary Cholangitis: 2018 Practice Guidance from the American Association for the Study of Liver Diseases.” Hepatology, vol. 69, no. 1, 6 Nov. 2018, https://doi.org/10.1002/hep.30145.

Mayo, Marlyn J, et al. “Impact of Pruritus on Quality of Life and Current Treatment Patterns in Patients with Primary Biliary Cholangitis.” Digestive Diseases and Sciences (2022) 68:995–1005 , vol. 68, no. 3, 15 June 2022, pp. 995–1005, https://doi.org/10.1007/s10620-022-07581-x. Accessed 28 July 2023.

Patel, Tejesh, and Gil Yosipovitch. “Therapy of Pruritus.” Expert Opinion on Pharmacotherapy, vol. 11, no. 10, 29 Apr. 2010, pp. 1673–1682, https://doi.org/10.1517/14656566.2010.484420. Accessed 24 Nov. 2019.

Smith, Helen, et al. “Cholestatic Pruritus Treatments in Primary Biliary Cholangitis and Primary Sclerosing Cholangitis: A Systematic Literature Review.” Digestive Diseases and Sciences, vol. 68, no. 6, 18 Mar. 2023, pp. 2710–2730, https://doi.org/10.1007/s10620-023-07862-z. Accessed 14 Nov. 2023.

Trivella, Juan, et al. “Primary Biliary Cholangitis: Epidemiology, Prognosis, and Treatment.” Hepatology Communications, vol. 7, no. 6, 1 June 2023,www.ncbi.nlm.nih.gov/pmc/articles/PMC10241503/, https://doi.org/10.1097/hc9.0000000000000179.

Weisshaar, Elke, and Uwe Matterne. “Epidemiology of Itch.” PubMed, CRC Press/Taylor & Francis, 2014, www.ncbi.nlm.nih.gov/books/NBK200924/. Accessed 14 Nov. 2023.

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