Key Potential Drug Launches in 2025

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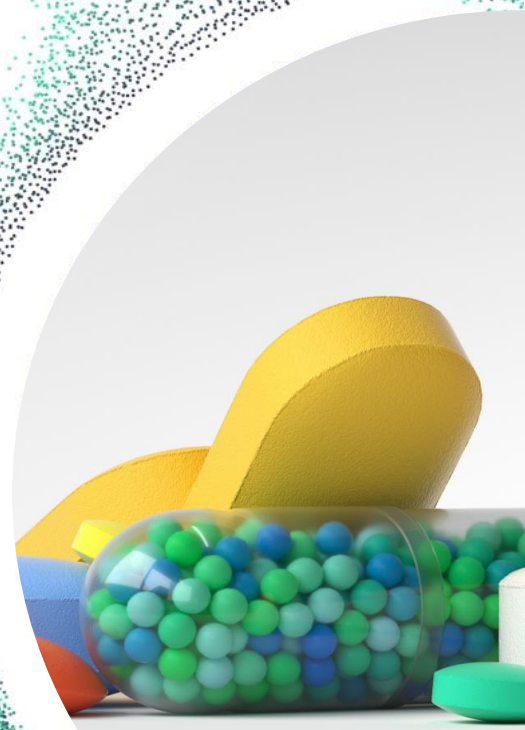
As a supplement to our well-known quarterly outlook report, Biomedtracker is pleased to present a longer-term look at some key late-stage drugs projected to hit the market in 2025. These drugs represent new drug classes, major changes to standards of care, and/or large market opportunities across the wide range of indications covered by Biomedtracker and Datamonitor Healthcare.

The information in this presentation, including likelihood of approval (LOA) ratings and upcoming catalysts, is up to date as of July 2024.

More details about each drug can be viewed instantly on Biomedtracker by clicking the ↗ icon.



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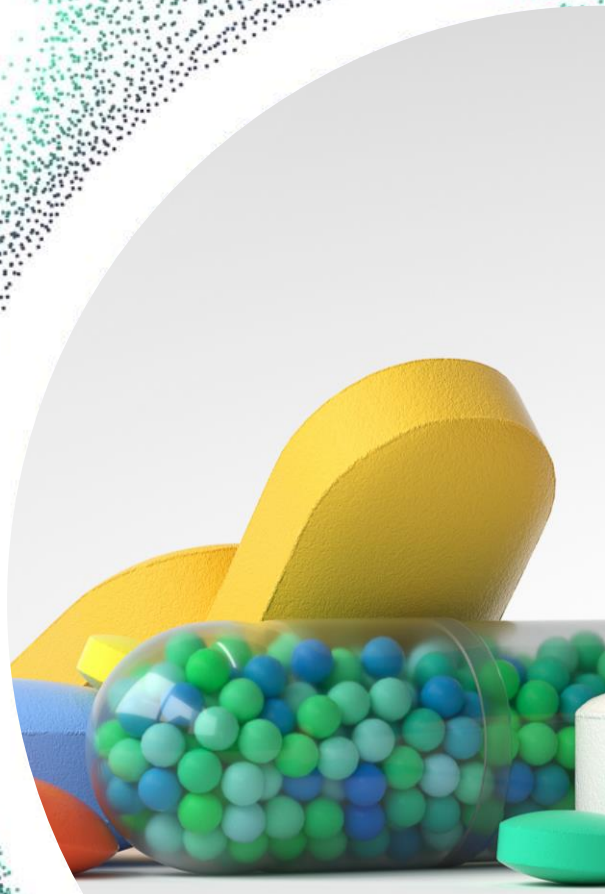
Allergy



VTAMA | DRMT | LOA: SAME AS AVERAGE | ↗

Atopic Dermatitis (Eczema)

Dermavant's Vtama (tapinarof) is a non-steroidal topical agent that targets the aryl hydrocarbon receptor. Approved for the treatment of psoriasis in the US in May 2022, Vtama has shown comparable efficacy to Zoryve, although it has been linked to side effects such as folliculitis and contact dermatitis. In February 2024, Dermavant submitted a supplemental NDA to the FDA for Vtama cream, aiming to treat atopic dermatitis in adults and children aged two years and older, supported by promising data from the ADORING studies.

The pivotal ADORING 1 study demonstrated that once-daily application of 1% Vtama cream resulted in 56% of patients in the treatment group achieving significant improvement in EASI-75 scores, versus 23% in the vehicle group. Furthermore, 45% of patients treated with Vtama achieved complete disease clearance as measured by vIGA-AD scores, compared to 14% of those receiving the vehicle treatment. These positive findings were corroborated by data from the ADORING 2 study. Upon approval, Vtama will enter an increasingly competitive eczema topical market, which includes the PDE4 inhibitor Eucrisa, known for its low efficacy, and the JAK inhibitor Opzelura, which, while potent, carries a black box warning. Compared to the newly approved Zoryve topical cream, Vtama remains a strong competitor due to its superior efficacy.

Tags: New Drug Class, Label Expansion (New Indication)

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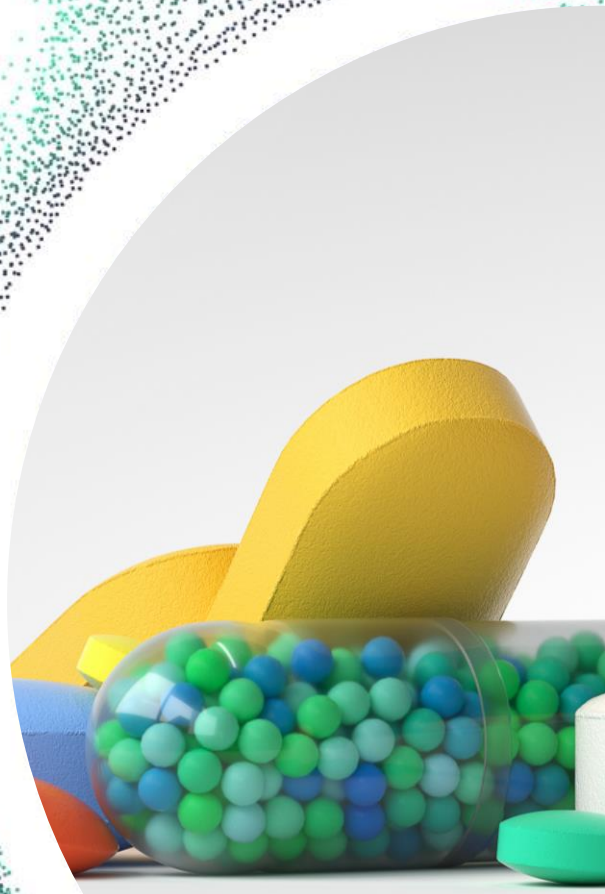
Autoimmune/ Immunology



Autoimmune/Immunology

TREMFYA| JNJ | LOA: ABOVE AVERAGE | ↗

Crohn's Disease (CD)

Johnson & Johnson's Tremfya has produced strong efficacy data in inadequate responders from its GALAXI Phase II/III trial and is positioned as a clinically attractive pipeline agent alongside other selective IL-23s. The GALAXI study also included a Stelara reference arm, revealing that Tremfya's remission rates were numerically better than this comparator's. Johnson & Johnson released topline results from the GALAXI 2 and 3 Phase III trials earlier in 2024, where both subcutaneous doses of 200mg every four weeks and 100mg every eight weeks showed superiority versus both placebo and Stelara, sparking anticipation for Tremfya's potential impact on the market. Although Tremfya could not demonstrate superiority on clinical remission endpoints, the 200mg monthly dose produced a statistically significant superior response over ustekinumab on a combined endpoint of clinical remission and endoscopic response.

Tremfya has already been launched for plaque psoriasis and is positioned to become the fourth-to-market drug in its class for treating CD. Johnson & Johnson has extensive experience in the IBD field through Stelara and will be confident in its strategy to promote Tremfya. However, these are big shoes to fill, as Stelara generated revenue of over $11bn in 2023. With biosimilar erosion around the corner, Johnson & Johnson will lean heavily on Tremfya to recover lost revenue.

Tags: Potential Blockbuster

Autoimmune/Immunology

HIZENTRA| CSL | LOA: SAME AS AVERAGE | ↗

Dermatomyositis

Subcutaneous infusion of immunoglobulin is not new in the autoimmune disease treatment landscape. However, it has not been an option for dermatomyositis patients, who typically require cumbersome intravenous immunoglobulin alongside immunosuppressants to manage their symptoms. Hizentra, a medication of human immunoglobulins administered via subcutaneous infusion, is approved for treating primary immunodeficiency (PI) and chronic inflammatory demyelinating polyneuropathy (CIDP). The drug is currently in late-stage clinical development for dermatomyositis, with initial data readout expected in the third quarter of 2024. Hizentra will offer a more convenient at-home treatment option in the long run.

Tags: Potential Blockbuster, Label Expansion (New Indication)

Autoimmune/Immunology

JAKAFI | INCY | LOA: AVERAGE | ↗

Graft vs. Host Disease (GVHD) - Treatment

Jakafi is a JAK1/JAK2 inhibitor developed by Incyte, currently seeking approval by the FDA as a ruxolitinib extended-release (XR) tablet for the treatment of chronic GVHD and acute GVHD. The FDA issued a Complete Response Letter (CRL) in March 2023, stating that the FDA cannot approve the application in its present form. While the study that was submitted with the New Drug Application (NDA) met the objective of bioequivalence based on area under the curve (AUC) parameter, the FDA identified additional requirements for approval.

The drug demonstrated a strong efficacy profile, supported by two studies designed to determine the relative bioavailability of ruxolitinib XR tablets to Jakafi tablets and to demonstrate that ruxolitinib XR tablets are dosage strength proportional to Jakafi tablets. The trials also demonstrated a well tolerated safety profile with no unexpected toxicities.

The Company has since met with the FDA in December 2023 to discuss the CRL. As Jakafi is already approved in other indications such as polycythemia vera and essential myelofibrosis, we anticipate that Incyte will address the additional requirements by the FDA, supporting a formal response to the CRL as well as potential launch in 2025.

Tags: New Drug Class

Autoimmune/Immunology

UPLIZNA | AMGN | LOA: ABOVE AVERAGE | ↗

Immunoglobulin G4-related disease (IgG4-RD)

Amgen's Uplizna (inebilizumab), an anti-CD19 antibody previously approved for neuromyelitis optica spectrum disorder (NMOSD), has achieved a significant milestone by demonstrating efficacy in treating IgG4-related disease (IgG4-RD), for which no approved therapies exist. In its Phase III trial, Uplizna demonstrated a statistically significant 87% reduction in the risk of IgG4-RD flare compared to placebo over one year, while also meeting all key secondary endpoints, including annualized flare rate, flare-free, treatment-free complete remission, and flare-free, corticosteroid-free complete remission.

Uplizna's success builds on the use of Rituxan, an anti-CD20 antibody that is currently the only non-steroidal, off-label option with long-term potential for treating IgG4-RD patients. Rituxan is administered once every six weeks and has shown effectiveness in reducing relapse risk and reversing organ enlargement, highlighting the role of B cells in pathogenesis of IgG4-RD. Although direct comparisons are limited, Uplizna may provide deeper and more sustained efficacy by targeting a broader range of B cell lineages.

Tags: New Drug Class, Label Expansion (New Indication)

Autoimmune/Immunology

UPLIZNA | AMGN | LOA: SAME AS AVERAGE | ↗

Myasthenia Gravis

The myasthenia gravis (MG) market, while becoming increasingly crowded, is primarily dominated by complement inhibitors that target overactive immune responses and FcRn inhibitors that decrease circulating autoantibodies responsible for triggering these responses. In contrast, Uplizna offers a novel mechanism of action by depleting B cells that produce all antibodies, thereby reducing the stimulation of abnormal immune responses. Uplizna is currently undergoing evaluation in the Phase III MINT study, with data readout expected in the second half of 2024.

Tags: New Drug Class, Label Expansion (New Indication)

Autoimmune/Immunology

ZORYVE TOPICAL FOAM| ARQT | LOA: ABOVE AVERAGE | ↗

Psoriasis

While topical corticosteroids are effective in treating psoriasis, their long-term use is constrained by safety concerns. Consequently, there is a demand for safe and effective non-steroidal alternatives. Arcutis has successfully introduced the topical PDE4 inhibitor roflumilast as a first-line treatment for dermatological diseases, aiming to replace generic topical corticosteroids. This initiative has resulted in the approval of Zoryve topical cream 0.3% for plaque psoriasis, 0.15% cream for eczema, and 0.3% foam for seborrheic dermatitis. Arcutis anticipates approval for Zoryve topical foam 0.3% for adults and adolescents with scalp and body psoriasis following a supplemental new drug application filed in July 2024.

Building on the clinical success of its topical cream for psoriasis, Zoryve topical foam demonstrated a 33% vehicle-adjusted PASI 75 response after eight weeks of treatment in the Phase III ARRECTOR study, comparable to that of Zoryve topical cream. In comparison to vehicle treatment, 39% of patients treated with Zoryve foam achieved skin clearance on the scalp, while 25% achieved clearance on the body. The efficacy of Zoryve topical foam for both scalp and body psoriasis provides a convenient option for patients who wish to streamline their treatment regimen.

Tags: Label Expansion (New Indication)

Autoimmune/Immunology

SOTYKTU| BMY | LOA: ABOVE AVERAGE | ↗

Psoriatic Arthritis

While most drugs for treating psoriatic arthritis were derived from psoriasis treatments, Bristol Myers Squibb's Sotyktu is no exception. As a potential blockbuster oral tyrosine kinase 2 (TYK2) inhibitor, Sotyktu (deucravacitinib) has shown efficacy comparable to TNFα inhibitors in improving psoriasis, which should enhance uptake among patients who prefer to avoid injectables. Approved in 2022 for moderate-to-severe plaque psoriasis, Sotyktu notably lacks the black box warning associated with other JAK inhibitors. It is currently being tested in psoriatic arthritis patients who are biologic-naïve in a Phase III study that began in July 2021, with topline results expected in the second half of 2024.

Tags: New Drug Class, Potential Blockbuster, Label Expansion (New Indication)

Autoimmune/Immunology

TREMFYA| JNJ | LOA: ABOVE AVERAGE | ↗

Ulcerative Colitis (UC)

Johnson & Johnson's Tremfya is a fully human IgG1 monoclonal antibody targeting the p19 subunit of IL-23. By contrast, Stelara binds to the p40 subunit of IL-23 as well as IL12. Thus, guselkumab may offer more specific inhibition for IL-23 and join the likes of Omvoh and Skyrizi. The drug has shown promise in Phase IIb/III trials, where Johnson & Johnson reported potentially best-in-class data with a first efficacy readout for the QUASAR clinical program, where Tremfya was evaluated in adults with moderate-to-severe active UC with an inadequate response or intolerance to conventional therapies.

Although a late entry to the market, after Stelara biosimilars and Omvoh, which is bound to affect sales negatively, Tremfya will have better commercial reach compared to Omvoh, as Johnson & Johnson has tremendous marketing experience in inflammatory bowel diseases and will lean on Tremfya to replace revenue lost due to biosimilar erosion of Stelara and Simponi.

Tags: Potential Blockbuster

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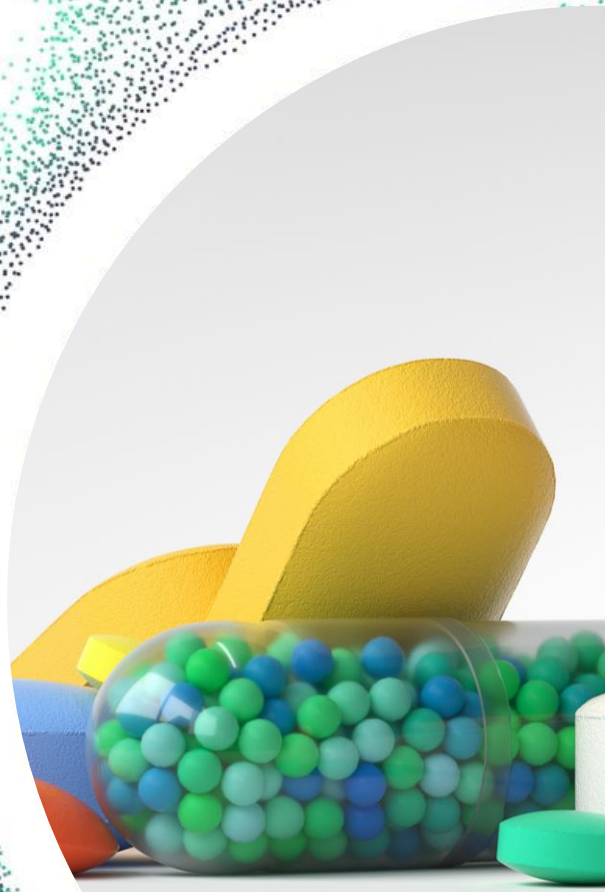
Cardiovascular



Cardiovascular

ELAMIPRETIDE | MITO | LOA: BELOW AVERAGE | ↗

Cardiomyopathy - Dilated

Barth Syndromes is an X-linked genetic disorder, primarily affecting males caused by a mutation in the gene encoding the tafazzin protein, vital for cardiolipin, a component of the mitochondrial membrane necessary for maintaining mitochondrial structure and functioning. It is a multi-system disorder in which patients can develop dilated cardiomyopathy, neutropenia, muscle wasting, growth delay, exercise intolerance, and feeding problems. There are no approved drug treatments for Barth Syndrome and management involves interventions to improve the signs and symptoms associated with the disease.

Stealth Biotherapeutics' elamipretide is a short peptide that selectively concentrates in the inner mitochondrial membrane and reduces the production of reactive oxygen species during ischemia/reperfusion. This activity protects the mitochondria and improves electron transport efficiency, maintains mitochondrial respiration and adenosine triphosphate levels, and prevents mitochondrial swelling and depolarization.

A new drug application was submitted to the FDA for elamipretide as a treatment for Barth Syndrome based on positive data from the SPIBA-001 Phase III Natural History Control Study and the TAZPOWER trial. Although data were mixed, elamipretide was shown to increase 6-min walk test by more than 90 meters after 76 weeks, increase hand muscle strength, and improve exercise tolerance. Left ventricular stroke volume also improved with elamipretide.

The FDA awarded elamipretide Fast Track Designation in 2017, Orphan Drug Designation in 2018, and Rare Pediatric Disease Designation in 2020. Stealth Biotherapeutics has submitted a new drug applications for elamipretide for the treatment of Barth syndrome to the FDA and was granted priority review; the Prescription Drug User Fee Act (PDUFA) action date is January 29, 2025.

Tags: First Approval, Practice Changing

KERENDIA | BAYN | LOA: ABOVE AVERAGE | ↗

Chronic Heart Failure – Preserved Ejection Fraction (Chronic HFpEF)

Chronic HFpEF, characterized by the heart muscle's inability to pump blood to meet the needs of the body despite normal or near-normal ejection fraction, has historically represented the most significant unmet need in heart failure (HF) treatment. Despite substantial improvements in care with the first approvals of drugs for HFpEF occurring in the early 2020s, there remains an unmet need as currently available drugs primarily address symptoms as opposed to the underlying disease mechanism. Non-steroidal mineralocorticoid receptor antagonist (MRA) Kerendia (finerenone) hopes to reduce cardiac fibrosis and improve heart function by targeting the primary processes of heart failure while overcoming the issues of hyperkalemia observed with steroidal MRAs.

First approved for the treatment of diabetic nephropathy, Kerendia is being evaluated across the heart failure spectrum in the MOONRAKER program that is expected to enroll over 15,000 patients. The program's first success came from the Phase III FINEHEARTS-HF trial, which showed Kerendia achieved a statistically significant and clinically meaningful reduction of the composite of cardiovascular death and total (first and recurrent) HF events in patients with HFpEF (New York Heart Association class II-IV) with a left ventricular ejection fraction (LVEF) of ≥40%). Although the primary endpoint was met and Kerendia demonstrated a safety and tolerability profile consistent with previous trials, numerical data were not provided, and it will be important to see the magnitude of the benefit and if the trial demonstrated a lower risk of hyperkalemia to steroidal MRAs. With MRAs recommended by guidelines across the HF spectrum, strong results would position Kerendia to likely be favored, positioning as a new approach to advance the management of HFpEF. A label expansion for HFpEF could be granted in 2025 based on the FINEARTS-HF trial data and could drive increased sales for Kerendia.

Tags: New Drug Class

LERODALCIBEP | LIBT | LOA: ABOVE AVERAGE | ↗

Dyslipidemia / Hypercholesterolemia

LIB Therapeutics' lerodalcibep is an injectable, recombinant fusion protein targeting PCSK9, which uses albumin to extend its half-life, such that low-volume injections can be given every four weeks in hypercholesterolemia patients. In comparison, PCSK9 inhibitor monoclonal antibodies (mAbs) such as Amgen's Repatha and Sanofi/Regeneron's Praluent, must be given every two weeks if a single injection is used, and monthly dosing requires multiple injections or an infusor. Additionally, mAbs also cannot be kept at room temperature for longer than 30 days, whereas lerodalcibep is stable at room temperature for up to nine months. If approved, lerodalcibep could potentially be preferred over mAbs given its convenience advantage and could compete on price, as manufacturing costs are reportedly lower.

Positive results from the Phase III LIBerate-HR trial showed that lerodalcibep has therapeutic potential in patients who are at high risk for CV disease and on lipid-lowering treatment but are not meeting LDL-C targets, which is a patient population with a high unmet need for therapeutic options. The long-term efficacy results showed that lerodalcibep substantially reduced LDL-C levels by a mean of more than 50% on top of existing oral agents, with ≥90% of lerodalcibep patients achieving ≥50% reductions in LDL-C, meeting new target recommendations set by the European Society of Cardiology.

The company had reported plans to file for both FDA and EMA approval for the treatment of dyslipidemia/hypercholesterolemia during H1 2024 but has not provided an additional timeline update. Lerodaclibep is also under development for both heterozygous (HeFH) and homozygous familial hypercholesterolemia (HoFH).

Tags: Practice Changing

Cardiovascular

CARDAMYST | MIST | LOA: ABOVE AVERAGE | ↗

Supraventricular Tachycardia

Cardamyst is a novel, short-acting calcium channel antagonist delivered nasally, developed by Milestone Pharmaceuticals. Recent ad hoc analysis from the NODE-303 study, which primarily focused on paroxysmal supraventricular tachycardia (PSVT), revealed promising data for its use in managing atrial fibrillation with rapid ventricular rate (AFib-RVR). The findings were presented at the Heart Rhythm 2023 Annual Meeting on May 19, 2023.

The NODE-303 study, involved patients self-administering Cardamyst. The analysis of 1024 treated episodes identified 21 episodes of AFib-RVR. Of these, 17 episodes had a baseline ventricular rate (VR) of 110 bpm or higher. Post-administration of Cardamyst, the average reduction in VR was significant, with a maximum decrease of 27.4 bpm at 22 minutes and a sustained reduction of 16.2 bpm at 60 minutes. Six episodes converted to sinus rhythm during the 60-minute window. Safety data indicated that Cardamyst was well-tolerated, with adverse events mainly related to the nasal administration site and reported as mild to moderate. Milestone Pharmaceuticals is also progressing with the ReVeRA trial, a Phase II double-blind, placebo-controlled study evaluating Cardamyst in emergency-department patients with AFib-RVR. Initial results suggest that Cardamyst could provide significant benefits in managing AFib-RVR outside of acute care settings, potentially reducing the need for emergency department visits.

Following guidance from the FDA, Milestone resubmitted its New Drug Application (NDA) for Cardamyst on May 26, 2024, addressing feedback from a previous Refusal to File (RTF) letter. The resubmission included restructured data sets and reformatted files to facilitate FDA analysis. The FDA has accepted the NDA, and the Prescription Drug User Fee Act (PDUFA) target date for a decision is set for ten months from the acceptance date.

Tags: New Drug Class, Potential Blockbuster

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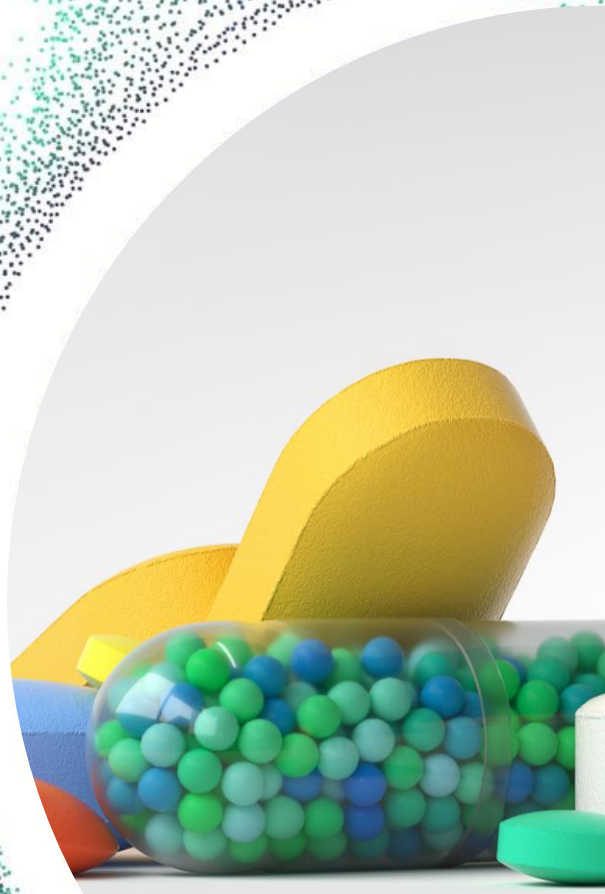
Dermatology



Dermatology

QRX-003 | ALM | LOA: SAME AS AVERAGE | ↗

Congenital Ichthyosis

QRX003, developed by Quoin Pharmaceuticals, is a broad-spectrum serine protease inhibitor designed to mimic the function of the LEKTI protein, showing promise as a potential treatment for Netherton Syndrome (NS). The ongoing Phase I open-label clinical trial is assessing the safety and efficacy of QRX003 in ten NS patients over a twelve-week period. All participants are continuing their off-label systemic therapies alongside QRX003.

Preliminary data from six evaluable subjects show encouraging results. Five out of six subjects reported significant improvement in pruritus (itching), with the pruritus either absent or negligible by the end of the dosing period. The sixth patient's pruritus remained unchanged. In terms of skin appearance, all six patients exhibited improvement, with three showing consistent progress throughout the study, while the remaining three displayed improvements at various points during treatment. Additionally, all subjects expressed a positive impression of QRX003 across several key metrics.

Safety data from the study has been favorable, with no treatment-related adverse events impacting the trial, supporting the further development of QRX003. Based on these promising results, Quoin Pharmaceuticals is targeting approval for QRX003 in both the U.S. and EU by late 2024.

Tags: New Drug Class, First Approval

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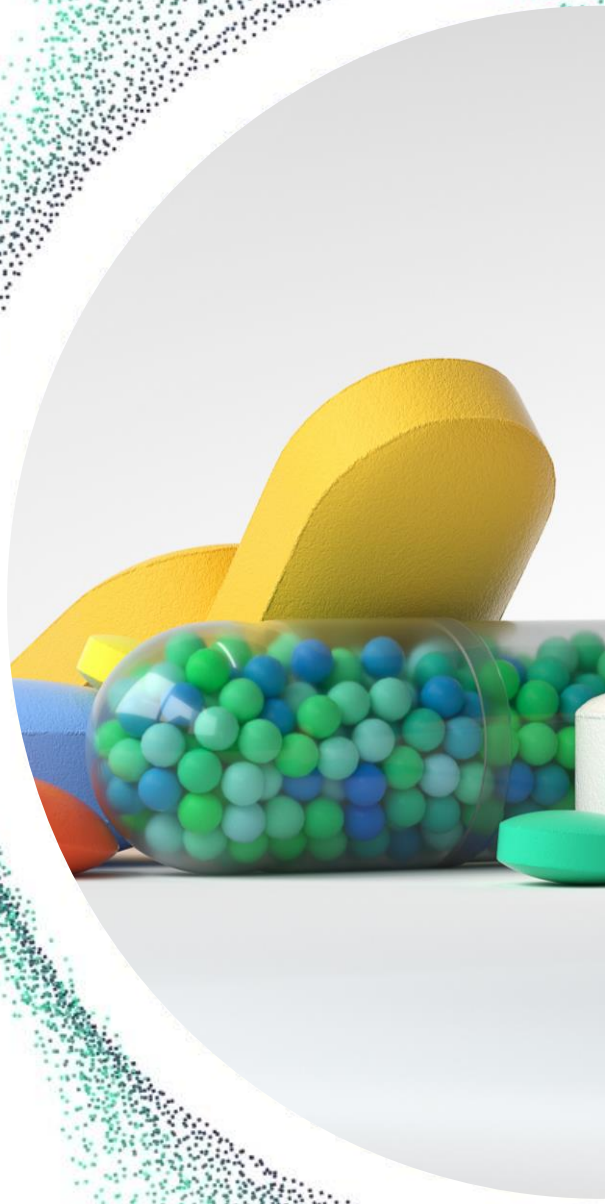
Endocrine



OCLAIZ | CAMX | LOA: ABOVE AVERAGE | ↗

Acromegaly

Acromegaly is a rare and severe chronic disease caused by a benign pituitary tumor resulting in overproduction of growth hormone (GH) and excess insulin-like growth factor (IGF-1). Together, this leads to abnormal growth of tissue and bone, causing enlargement of hands, feet and facial features, and a range of disease symptoms such as fatigue, joint pain, muscle weakness, weight gain, sleep apnea, headache, and excessive sweating and paresthesia. Patients with acromegaly have reduced quality of life and often report high treatment burden. First-line medical treatment of acromegaly is represented by first-generation injectable somatostatin receptor ligands (SRL), Novartis' Sandostatin (octreotide LAR) and Ipsen's Somatuline (lanreotide ATG).

Oclaiz is a ready-to-use octreotide for subcutaneous administration under development by Camurus. It is designed for convenient, once-monthly self-administration. Phase III trials met both primary and key secondary endpoints with high statistical significance. In the ACCROINNOVA 1 study, 72.2% of patients in the Oclaiz group showed IGF-1 response below 1x upper limit of normal (ULN) versus 37.5% in the placebo group (p=0.0018). One of the key secondary endpoints, the proportion of patients with mean IGF-1 $\leq$ ULN at week 22 and week 24 and mean GH cycle <2.5 ug/L at week 24, was met with a 70% response rate for both IGF-1 and GH in the Oclaiz group versus 37.5% in the placebo (p=0.0035). Significant unmet need in acromegaly comes from patients often suffering poor or limited biochemical control and data from ACROINNOVA 2 show Oclaiz is effective in achieving biochemical control across patient populations with differing treatment histories. These data combined with the convenience of administering Oclaiz may offer the potential for improved efficacy, convenience, and quality of life compared to current first-line medical treatments of acromegaly. The U.S. FDA has assigned a PDUFA date of October 17, 2024 for the New Drug Application. If approved, Oclaiz will be the first monthly somatastatin peptide analog that can be subcutaneously injected at home.

Tags: First Approval, New Drug Class

CRINECERFONT | NBIX | LOA: ABOVE AVERAGE | ↗

Congenital Adrenal Hyperplasia (CAH)

Congenital adrenal hyperplasia (CAH) typically results from a mutation affecting the 21-hydroxylase (21-OH) enzyme, leading to deficient production of adrenal hormones including cortisol and often aldosterone. Untreated CAH can lead to salt wasting, dehydration, and even death. Patients require steroid therapy to correct cortisol deficiency and reduce the high levels of adrenocorticotropic hormone (ACTH) that are stimulated as a result; high ACTH levels can cause excess levels of androgens that can affect female development as well as stature and fertility. However, high doses of glucocorticoid (GC) treatment can be required, but these agents have potentially serious side effects including increased cardiovascular risk, bone loss, fractures, growth impairment, muscle weakness, and increased infection risk. As such, steroid-free treatment options are highly desirable.

Crinecerfont is an oral, selective corticotropin-releasing factor type 1 receptor (CRF1) antagonist being developed by Neurocrine Biosciences for the treatment of classic CAH due to 21-OH deficiency. This steroid-independent agent blocks the CRF1 receptors in the pituitary gland, leading to a reduction in ACTH levels and lower adrenal androgen levels, with the hope of physiologic dosing of glucocorticoids reducing the risk of the complications of long-term steroid treatment. Phase III data in adults showed that crinecerfont treatment led to a significantly greater GC dose reduction at Week 24 while maintaining androstenedione control compared to placebo (least squares mean [LSM] change from baseline of -27.3% versus -10.3%, with LS mean difference [LSMD] of -17.0%, $p<0.001$). In children ages 2 to 17 years, crinecerfont treatment led to a significantly greater reduction in androstenedione compared to an increase with placebo at Week 4 (LSM change from baseline of -196.8 ng/dL versus +71.0 ng/dL, with LSMD of -268 ng/dL, $p<0.001$). Importantly, 30% of crinecerfont-treated participants achieved a physiologic GC dose ($\leq$ 11 mg/m2/day hydrocortisone equivalents) at Week 28 while maintaining androstenedione control, compared to zero participants in the placebo group ($p=0.0009$). Neurocrine Biosciences has filed two New Drug Applications (NDAs) for the capsule formulation and oral formulation of crinecerfont for the treatment of children, adolescents and adults with CAH. The U.S. FDA granted both NDAs Priority Review designation, setting PDUFA targets of December 29, 2024, and December 30, 2024, respectively. Currently, there are no non-glucocorticoid treatments FDA approved for use in CAH. If approved, crinecerfont could become the first new treatment for CAH in 70 years.

Tags: First Approval, Practice Changing, New Drug Class

ZEGALOGUE | NVO| LOA: BELOW AVERAGE | ↗

Congenital Hyperinsulinism (CHI)

Zealand Pharma's dasiglucagon, a glucagon analog already approved as Zegalogue to treat severe hypoglycemia in patients with diabetes aged 6 years and above, hopes to be the first subcutaneous glucagon infusion for CHI and could see a US launch in 2025. CHI is a rare genetic disorder that causes the body to produce too much insulin, which causes hypoglycemia in infants and children; endogenous glucagon counterbalances the action of insulin. Currently first line treatment of CHI consists of diazoxide, which acts by increasing cellular permeability to potassium ions, leading to polarization of pancreatic beta cells, followed by the inhibition of insulin secretion. However, diazoxide is burdened by side effects such as hypertrichosis and fluid retention, a particular problem for newborns receiving large intravenous (IV) glucose doses to maintain glycemic control. If patients are unresponsive to diazoxide, surgery is pursued to see if there is a focal lesion to resect. Should there not be a lesion to be treated surgically, intensive medical treatments such as octreotide, which inhibits insulin release from beta cells, are attempted, but carry suboptimal risk-benefit profiles. Given this significant unmet need, Zealand hopes to carry on dasiglucagon's success in severe hypoglycemia, for which it received approval from the FDA back in 2021, to CHI.

Regulatory filing for dasiglucagon for the prevention and treatment of low blood sugar (hypoglycemia) in pediatric patients 7 days of age or older with congenital hyperinsulinism were submitted to the FDA in June 2023. Notably, the NDA was split into two parts, with Part 1 relates to dosing of up to 3 weeks, whereas Part 2 relates to the use beyond 3 weeks. The submission was supported by the data from two pivotal Phase III trials and interim results from an ongoing Phase III long-term extension trial. Despite receiving a Complete Response Letter (CRL) in December 2023, the CRL only cited deficiencies related to a third-party contract manufacturing facility and not specific to dasiglucagon's clinical data package or safety. Following this CRL, Zealand resubmitted part 1 of its NDA in early 2024, which the FDA accepted with a Prescription Drug User Fee Act (PDUFA) of October 8, 2024. If approved, Zealand plans to make dasiglucagon available immediately for commercialization ahead of the part 2 submission for full approval.

Tags: Practice Changing

INPEFA | LXRX | LOA: BELOW AVERAGE | ↗

Type 1 Diabetes

Despite their success in type 2 diabetes, sodium-glucose cotransporter-2 (SGLT-2) inhibitors have not had the same impact for type 1 diabetes, owing to safety concerns over the increased class risk of diabetic ketoacidosis. Beyond their oral administration, SGLT-2 inhibitors have demonstrated clinical benefits in lowering HbA1c levels more than insulin alone, as well as benefits in blood pressure and weight loss, which are attractive as patients on insulin tend to gain weight.

Lexicon Pharmaceutical's sotagliflozin, approved as Zynquista for type 1 diabetes in the EU and as Inpefa for heart failure in the US, has been resubmitted for approval as an adjunct to insulin therapy for glycemic control in patients with type 1 diabetes and chronic kidney disease (CKD), which was considered a response to the complete response letter issued in 2019. Lexicon claims to have a trove of Phase III data in patients with diabetes and CKD for Inpefa when paired with insulin. The inTandem3 study in this population showed treatment with sotagliflozin led to similar significant reductions in HbA1c, body weight, and systolic blood pressure in the CKD and total cohorts. If the FDA's advisory committee can be convinced that the risk of diabetic ketoacidosis can be mitigated properly, sotagliflozin could become the first SGLT-2 inhibitors approved in the US for type 1 diabetes, a considerable achievement given the class struggles to date. With a meeting of the FDA's Endocrinologic and Metabolic Drugs Advisory Committee set for October 2024, sotagliflozin could see its label expansion approved by the end of year with an action date of December 20th, 2024.

Tags: New Drug Class, Label Expansion (New Indication)

OZEMPIC | NVO | LOA: ABOVE AVERAGE | ↗

Diabetic Nephropathy

Diabetic nephropathy, also known as diabetic kidney disease, is a common co-morbidity of type 2 diabetes involving structural and functional damage to the kidney filtering apparatus. Diabetic nephropathy is a leading cause of end-stage renal disease and imparts a higher risk of cardiovascular (CV) disease than that for diabetes alone. Novo Nordisk's glucagon-like peptide-1 (GLP-1) receptor agonist semaglutide, approved as Ozempic for type 2 diabetes and Wegovy for obesity, quickly reached global blockbuster status, touting exceptional glycemic control and weight loss, and is the first GLP-1 agonist with a dedicated type 2 DN outcomes trial.

Now, in the Phase III FLOW trial, the first dedicated type 2 DN outcomes trial, Ozempic has shown clear benefits ~~for Ozempic~~ on kidney, cardiovascular, and survival outcomes. Specifically, Ozempic demonstrated a superior reduction of 24% compared to placebo on the composite primary endpoint consisting of five measures of CKD progression and risk of kidney and CV mortality. Though cross-trial comparisons are unsubstantiated, the SGLT-2 inhibitors Jardiance and Farxiga demonstrated better reductions on the primary endpoints of renal progression/CV death in their renal outcome trials (28% and 39%, respectively). For CV outcomes, Ozempic reduced the risk of major adverse cardiovascular events and all-cause mortality by 18% and 20%, respectively, compared to placebo. Furthermore, subgroup analysis found no consistent evidence of heterogeneity of Ozempic's benefits with or without baseline SGLT-2 inhibitor use, which suggests there may be value in concurrent use of both treatment in these patients. There is potential for synergistic effects with these classes, and also with Bayer's non-steroidal mineralocorticoid receptor antagonist Kerendia (finerenone), owing to these drugs exerting benefits on different aspects of the disease's pathophysiology. Though further evidence is needed, this could represent a promising treatment paradigm shift to improve patient outcomes and slow the progression of diabetic kidney disease.

Novo Nordisk submitted the supplemental New Drug Application for Ozempic in the first quarter of 2024 and an approval decision is anticipated in January 2025.

Tags: New Drug Class, Label Expansion (New Indication), Potential Blockbuster, Practice Changing

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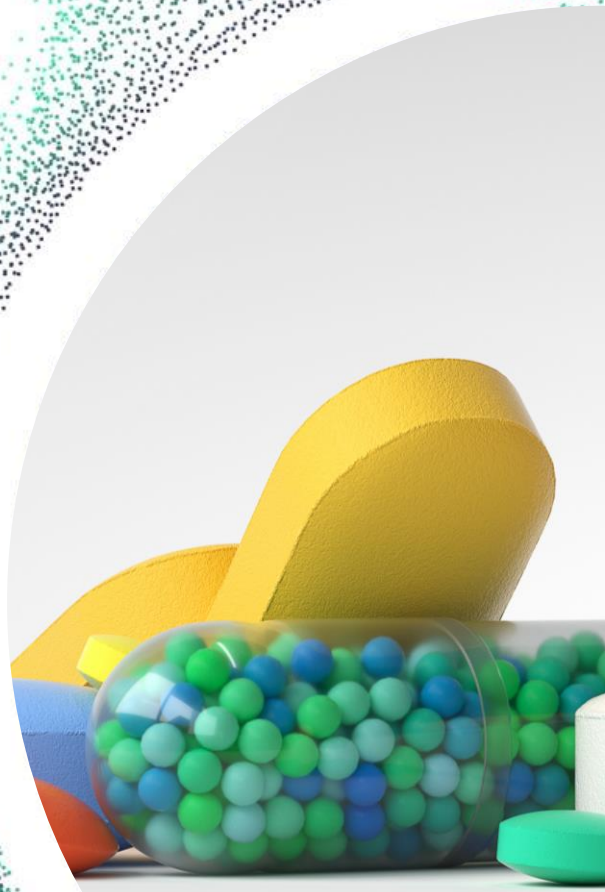
Hematology



Hematology

RP-L102 | RCKT | LOA: SAME AS AVERAGE | ↗

Fanconi Anemia

RP-L102, Rocket Pharmaceuticals' investigational gene therapy for Fanconi Anemia (FA) complementation group A, has yielded promising results in its global Phase I/II clinical trial, leading to the European Medicines Agency (EMA) accepting its Marketing Authorization Application (MAA). This therapy, which uses a lentiviral vector to deliver the FANC-A gene, has shown significant genetic correction in patients, with sustained increases in vector copy numbers (VCNs) in both bone marrow and peripheral blood. Among the 12 patients with over 12 months of follow-up, eight demonstrated sustained genetic correction, phenotypic improvement, and stable blood counts.

Importantly, RP-L102 was well tolerated without the need for cytotoxic conditioning, and no significant safety concerns, such as bone marrow dysplasia, clonal dominance, or insertional mutagenesis, were observed.

Building on these positive results, Rocket Pharmaceuticals is moving forward with regulatory filings, with a Biologics License Application (BLA) for RP-L102 expected to be submitted to the U.S. Food and Drug Administration (FDA) in the first half of 2024. This submission represents a significant step toward making this potentially curative therapy available to patients with FA.

Tags: First Approval, Practice Changing

MIM8 | NVO | LOA: ABOVE AVERAGE | ↗

Hemophilia A

Novo Nordisk's bispecific antibody Mim8 "mimics" the action of the missing clotting fVIII in hemophilia A patients by providing an assembly with fIXa and fX in the clotting cascade. The bispecific antibody class has already proved to be very successful in the treatment of hemophilia A, with Roche's Hemlibra (emicizumab) dominating the market. Part of Hemlibra's success is due to its convenient subcutaneous dosing schedule (weekly, every two weeks, or monthly versus intravenous factor VIII replacement weekly at best) and its availability for patients both with and without inhibitors (a common complication of factor therapy affecting approximately 30% of patients). This large patient population is expected to be the same for Mim8, with the additional advantage that Novo Nordisk has improved on the convenience of the bispecific antibody class with pre-filled injection pens for the delivery of Mim8.

Mim8 has achieved very positive data from its Phase III FRONTIER-2 trial, achieving zero treated bleeds in 86% (weekly) and 95% (monthly) of patients who had not been on prior prophylaxis with factor VIII replacement. Mim8's efficacy at weekly and monthly dosing in patients on prior factor prophylaxis is similar for reduction of bleeds (48% and 43%, respectively) and for those experiencing zero treated bleeds (66% and 65%, respectively). This might suggest that, from an efficacy standpoint, Mim8 has a smoother pharmacokinetic profile, which truly supports monthly dosing, compared to Hemlibra, which is reportedly primarily dosed every two weeks.

If approved, Mim8 will have to contend with the popularity of Hemlibra with both patients and physicians, and the launches of novel alternative coagulation products such as Sanofi's fitusiran, which benefits from its availability as an offering to hemophilia A and B populations with or without inhibitors as a monthly or two-monthly subcutaneous injectable option.

Novo Nordisk has announced plans to file with the FDA in the first half of 2025, if successful Mim8 could achieve its first approval at the end of 2025.

Tags: First Approval, Potential Blockbuster

FITUSIRAN | SNY | LOA: BELOW AVERAGE | ↗

Hemophilia A and B

Fitusiran is an RNA interference (RNAi) therapeutic that targets antithrombin in the liver with the aim of providing greater hemostatic control and more convenient administration than many of the currently available marketed products for hemophilia. This RNAi drug candidate is being investigated for the treatment of all hemophilia A and B patients, irrespective of the patients' status regarding inhibitors to factor therapy. As well as this broad target population, fitusiran offers a much longer dosing interval (administered every 2 months) compared with factor replacement.

The Phase III ATLAS clinical trials have shown that the drug is efficacious, with a median annual bleed rate (ABR) of 1.08 which is in line with other drugs in the space. Unfortunately, fitusiran has been plagued with safety concerns which will likely limit its uptake upon its potential approval in early 2025. There have been two amendments to trial safety protocols as a result of adverse thrombotic events, with the most notable being a fatality in its Phase II trial from an intercranial blood clot. As a result, fitusiran is now being investigated at a lower dosing regimen of 50mg every 2 months. With the available data from the ATLAS-OLE trial, this reduction does not seem to have hampered its efficacy results, reporting consistent protection with a minimum of 6 injections per annum, and has encouragingly bolstered its safety profile as no more thrombotic events were observed following the latest protocol. Sanofi has filed for the approval of fitusiran with several regulatory authorities including the FDA, with an expected PDUFA date of 28 March 2025.

Fitusiran will be hard pressed to capture market share in the hemophilia A space due to competition from Roche's bispecific factor IXa- and factor X-directed antibody Hemlibra (emicizumab), which is widely regarded as a safe, convenient, and efficacious therapy. However, in the hemophilia B market, there is an unmet need for a convenient therapeutic option for those not eligible for gene therapies. Fitusiran meets this unmet need with a subcutaneous extended dosing schedule (every two months versus once every 7–10 days for replacement factor therapy); however, the therapy will have to overcome physician and patient uncertainty over its safety profile and may initially be relegated to the inhibitor population, which is a minority share of the market (estimated at 1-5%).

Tags: First Approval, New Drug Class, Potential Blockbuster

PYRUKYND | AGIO | LOA: ABOVE AVERAGE | ↗

Thalassemia

Beyond transfusions and allogeneic hematopoietic transplantation, treatment of beta-thalassemia is currently limited to Bristol Myers Squibb's subcutaneous injectable Reblozyl (luspatercept), an erythroid maturation agent, and gene therapies such as bluebird bio's Zynteglo (betibeglogene autotemcel) and Vertex Pharmaceuticals' Casgevy (exagamglogene autotemcel). While gene therapies are overall an effective treatment option that restores patients to a partially disease-free state for a length of time, not all patients are physically and financially eligible. Agios Pharmaceuticals' Pyrukynd (mitapivat) is a first-in-class pyruvate kinase inhibitor, which works by increasing the activity of erythrocyte pyruvate kinase, a key enzyme involved in the survival of red blood cells. Pyrukynd has already been approved in the US and EU for the treatment of hemolytic anemia in adults with pyruvate kinase (PK) deficiency and has demonstrated efficacy for non-transfusion-dependent thalassemia in the global Phase III ENERGIZE study. Furthermore, this treatment is a more convenient oral product for use in a broader target population.

Agios Pharmaceuticals are planning on submitting a marketing application for Pyrukynd as a treatment for thalassemia to the FDA by the end of 2024 for a potential approval and launch in 2025.

Tags: Label Expansion (New Indication), Practice Changing, New Drug Class

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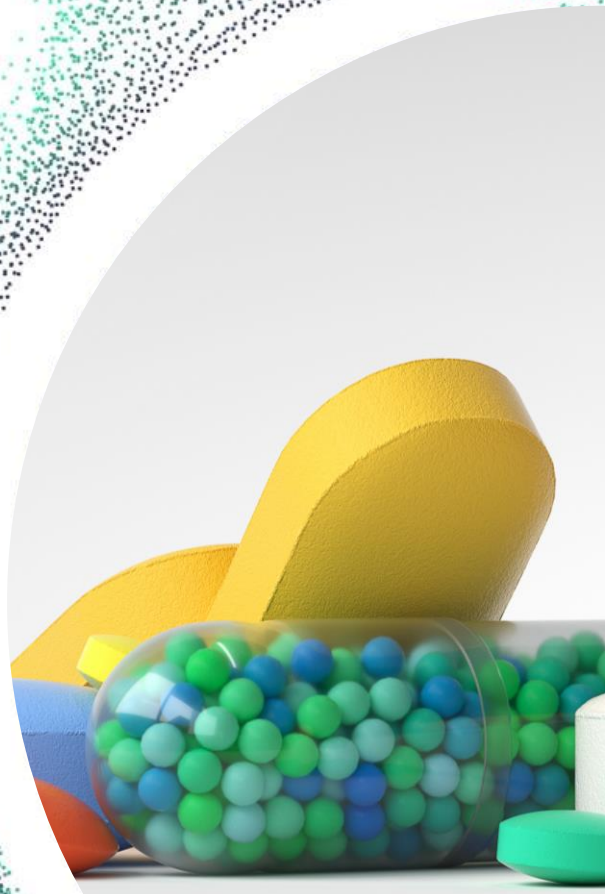
Infectious Disease



Infectious Disease

BREXAFEMME | GSK | LOA: BELOW AVERAGE | ↗

Fungal Infections - Systemic

In October 2022, the World Health Organization (WHO) released a list of the 19 fungi that represent the greatest threat to public health in an effort to stimulate new research and policy interventions. New mechanisms of action targeting fungal infections are key to addressing this issue and Brexafemme (ibrexafungerp; SCY-078) from GSK and SCYNEXIS fits the bill. Brexafemme is a novel, oral, semi-synthetic derivative of the natural product enfumafungin, a structurally distinct class of glucan synthase inhibitors that disrupt synthesis of the fungal cell wall polymer ß-(1,3) D-glucan. The US Food and Drug Administration (FDA) granted Fast Track, Qualified Infectious Disease Product (QIDP) and orphan drug designations (ODD) for the oral and IV formulations of the drug for the indications of invasive Candida infections (including candidemia) and invasive Aspergillus infections. The FDA approved Brexafemme for vulvovaginal candidiasis in 2021.

Considering the broader unmet need for novel antifungals, the Phase III FURI study investigated oral ibrexafungerp in patients with severe fungal infections who either could not tolerate or did not respond to standard antifungal therapy. The Phase III CARES study evaluated oral ibrexafungerp in patients with systemic Candida auris infections, which are often multi-drug resistant. Combined data from these trial showed that more than 60% of patients achieved complete or partial responses or had clinical improvements. Brexafemme has also been investigated as a stepdown therapy in the Phase III MARIO study involving patients with invasive candidiasis treated with intravenous echinocandin, one of the current standard of care therapeutic options. Although a manufacturing issue has led to a pause in the study (and a temporary market withdrawal of the product), the company expects the MARIO study to resume in the near future as new batches of Brexafemme are being produced, which will see marketing resume and could lead to a label expansion in late 2025.

Tags: New Drug Class, Label expansion (New Indication), Practice changing

SUNLENCA | GILD | LOA: ABOVE AVERAGE | ↗

HIV Prevention

Sunlenca [lenacapavir] is Gilead's first long-acting asset in HIV, a first-in-class HIV capsid inhibitor. This long-acting subcutaneous injectable works by selectively inhibiting HIV-1 capsid function and, thus, HIV-1 replication. Sunlenca has already achieved regulatory success in 2022 in HIV treatment in combination with other antiretrovirals, supported by results from the Phase II/III CAPELLA and CALIBRATE trials.

This product has achieved further clinical success in the first of its PURPOSE suite of Phase III trials in HIV pre-exposure prophylaxis (PrEP), reporting 100% efficacy in stopping HIV acquisition in June 2024 (PURPOSE-1: cisgender women and adolescent girls). Furthermore, Sunlenca was able to demonstrate statistical superiority to Gilead's current daily oral offerings, Descovy and Truvada, in this setting. This superiority is somewhat attributable to greater adherence conferred from its twice-yearly dosing schedule. Indeed, ~93% of participants received on-time injections of Sunlenca; by comparison, 80–90% were considered to have low adherence for the oral daily options (low adherence defined as low or no detection of comparator drugs). The drug was initially being investigated in two pivotal Phase III trials: PURPOSE-1 (as previously discussed) and PURPOSE 2, which initiated in June 2021, investigating Sunlenca in men at risk of HIV infection. In addition, Gilead initiated three more trials (PURPOSE 3–5) in late 2023, to investigate further geographic and demographic HIV groups. The PURPOSE 2 trial in men at risk of HIV infection is expected to provide the first interim data in late 2024 or early 2025, for a potential approval in HIV PrEP in late 2025 when combined with data from PURPOSE-1.

If successful in regulatory filings, Sunlenca will be competing with GSK's rival injectable Apretude (Vocabria), a once-every-two-months, physician-administered intramuscular integrase strand transfer inhibitor. Despite Sunlenca being the second-to-market injectable offering, it may have the advantage in not only dosing schedule and administration method but also in clinical efficacy thus far.

Tags: Label Expansion (New Indication), Practice Changing, New Drug Class, Potential Blockbuster

GSK3536819A | GSK| LOA: ABOVE AVERAGE | ↗

Meningococcal Vaccines

GSK's GSK3536819A is a pentavalent meningococcal vaccine combining the antigenic components of GSK's licensed meningococcal vaccines, Bexsero (Meningococcal group B; MenB) and Menveo (Meningococcal group A, C, W-135, and Y; MenACWY) into one vaccine candidate. It is intended to be administered intramuscularly in two doses, six months apart. Meningococcal disease is a serious infection that is caused by the Gram-negative Neisseria meningitidis bacteria. There are multiple serogroups of N.meningitidis, but typically serogroups A, B, C, W and Y cause the majority of disease worldwide with serogroups B, C and Y account for the most incidence in the United States. However, there were no singular meningococcal vaccine that address all five serogroups until October 2023, when Pfizer's Penbraya became the first US approved pentavalent meningococcal vaccine attempting to address the unmet need for a simplified meningococcal vaccine schedule and broader serogroup coverage. With the approval of Pfizer's Penbraya, the CDC revised its guidance and allowing the use of Penbraya when both MenACWY and MenB are indicated at the same visit. However, the CDC indicated that the MenB vaccines from GSK and Pfizer are not interchangeable. This requirement could be an advantage to GSK3536819A given the dominance of Bexsero within the US market, which has a shorter dosing interval than Pfizer's MenB vaccine Trumenba (1 month versus 6 months) and comparable immunogenicity. The prospect of increased convenience of pentavalent meningococcal vaccine could boost overall meningitis vaccine coverage and improve uptake.

Topline results from the pivotal Phase III in March 2023 demonstrated statistical non-inferiority for GSK3536819A compared to Bexsero and Menveo in individuals 10-25 years old. Following these results, GSK submitted a Biologics License Application (BLA) for GSK3536819A to the US FDA. The Prescription Drug User Fee Act (PDUFA) action date for a regulatory decision by the US FDA on this application is February 14, 2025.

Tags: Practice Changing

mRNA-1010 | MRNA| LOA: ABOVE AVERAGE | ↗

Seasonal Influenza Vaccines

Moderna's mRNA-1010 is a quadrivalent mRNA influenza vaccine that encodes four hemagglutinin (HA) glycoprotein antigens (A/H1N1, H3N2, influenza B/Yamagata, and Victoria lineages) and has a similar design to its debut COVID-19 vaccine mRNA-1273 (Spikevax). mRNA vaccine success during the COVID-19 pandemic has led to the technology being leveraged by developers and such vaccines are becoming increasingly common in the influenza vaccines pipeline. mRNA-1010 could gain significant uptake owing to positive public opinion with regards to mRNA vaccines following the COVID-19 pandemic, which may allow it to capture a significant portion of market share in the elderly segment, if priced competitively.

Moderna now plans to file with regulators following positive results from the P303 Phase III trial which was conducted in 8,400 adults aged >18 years. Results showed that across all four strains (A/H1N1, A/H3N2, influenza B/Yamagata, B/Victoria) mRNA-1010 met all co-primary endpoints and showed higher hemagglutination inhibition (HAI) geometric mean titers and seroconversion rates compared to GSK's Fluarix, a key competitor in the influenza space.

mRNA-1010 is also a key component of multiple influenza combination vaccines that Moderna has in its current pipeline. These include mRNA-1083, which comprises mRNA-1010 and its next-generation, refrigerator-stable COVID-19 vaccine mRNA-1283, alongside mRNA-1045, which combines mRNA-1010 with RSV vaccine candidate mRNA-1345, as well as mRNA-1230, a triple-combination influenza/COVID-19/RSV vaccine strategy combining mRNA-1010/Spikevax/mRNA-1345.

Tags: Practice Changing

Infectious Disease

GSK2140944 | GSK | LOA: ABOVE AVERAGE | ↗

Urinary Tract and Reproductive Tract Infections (Antibacterial)

GSK2140944 is first-in-class triazaacenaphthylene antibiotic with a unique dual mechanism of action targeting bacterial DNA replication via two different Type II topoisomerase enzymes. The two-target approach limits antibiotic development in key pathogens such as Neisseria gonorrhoeae.

The ongoing pivotal Phase III EAGLE-1 trial met its primary efficacy endpoint, demonstrating non-inferiority of GSK2140944 to the current standard of care, ceftriaxone and azithromycin combination. Antimicrobial resistance in N. gonorrhoeae has established itself as a priority pathogen by the WHO, as in many countries ciprofloxacin resistance is exceedingly high, azithromycin resistance is increasing, and resistance or decreased susceptibility to cefixime and ceftriaxone continue to emerge. It is currently estimated that there are approximately 80 million new cases of gonorrhoea worldwide every year, with drug-resistant strains being found in more than 50 countries.

Success in the EAGLE-1 trial follows GSK2140944 proving efficacy against other drug-resistant strains found in uncomplicated UTIs (uUTIs), tested in the EAGLE-2 and EAGLE-3 trials. Both trials have had non-inferior results to the standard of care, and in further updated analyses, GSK2140944 has shown statistical superiority to nitrofurantonin in EAGLE-3.Based on results from the EAGLE-1 clinical trial, GSK plans to submit a new drug application (NDA) to the U.S. FDA in the second half of 2024.

Tags: New Drug Class

CITELINE
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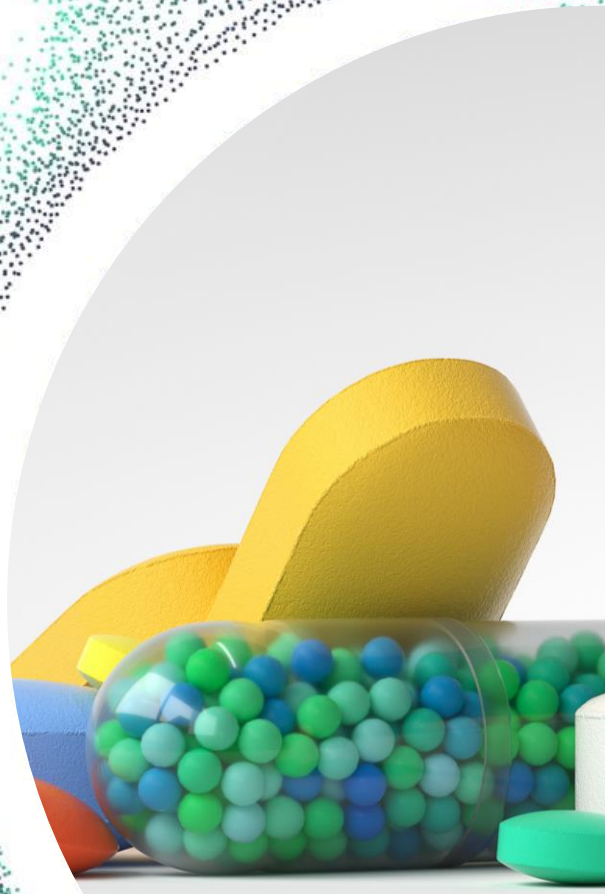
Metabolic



DERAMIOCEL | CAPR | LOA: ABOVE AVERAGE | ↗

Duchenne Muscular Dystrophy (DMD)

Capricor's deramiocel is an allogenic cardiosphere-derived cell therapy in Phase III development for Duchenne muscular dystrophy (DMD), which is differentiated from other pipeline and marketed therapies for DMD by its mechanism of action. The safety profile of deramiocel has been consistently strong throughout its development, indicating potential advantages of regenerative cell therapies over gene therapy approaches. Deramiocel is designed to treat late-stage DMD patients and does not appear to have any direct competition at the advanced stage of the disease.

Promising efficacy data have been released thus far. In the Phase II HOPE-2 trial, deramiocel demonstrated a statistically significant 2.4-point improvement in PUL 2.0 score (preservation of skeletal muscle function; the primary endpoint), as well as statistically significant improvements in cardiac function. Data from the three-year open-label extension study suggested continued benefit, with deramiocel demonstrating a statistically significant 3.7-point improvement in PUL 2.0 score and stabilization of left ventricular ejection fraction (a measure of cardiac function) compared to the external comparator. The continued positive effects on cardiac function are particularly important as cardiomyopathy is the leading cause of death in DMD patients and there are no approved treatments, demonstrating an unmet need in this space. Phase III data are expected from the pivotal HOPE-3 trial in Q4 2024. Capricor recently announced that it conducted a positive pre-BLA meeting with the FDA and is moving closer to filing a BLA.

Tags: New Drug Class, Practice Changing, First Approval

OLEZARSEN | IONS | LOA: ABOVE AVERAGE | ↗

Familial Chylomicronemia Syndrome (FCS)

Ionis Pharmaceutical's olezarsen works by inhibiting production of apolipoprotein C-III (APOC3) but uses Ionis's next-generation ligand-conjugated antisense (LICA) technology to increase its potency. The APOC3 protein is a key component of triglyceride-rich very-low-density lipoproteins (VLDL).

As of June 2024, olezarsen has been filed for approval in the US following positive results in the Phase III BALANCE trial. The trial included a monthly 80mg dose that showed a statistically significant reduction in triglyceride levels of 73.7% at six months and 81.3% at 12 months, as well as a 100% drop in acute pancreatitis events, all compared to placebo.

FCS is a rare genetic disorder which causes extremely elevated levels of triglycerides, which can lead to a sufferer developing type 2 diabetes and can also cause acute pancreatitis, which can be potentially fatal. There is a high unmet need for treatments, and there are currently no FDA-approved drugs for FCS. Currently, Ionis Pharmaceuticals' Waylivra is the only approved drug therapy for FCS, but it is only available in the EU, Canada and Brazil. In the US, olezarsen has orphan drug status and the FDA has granted fast track designation and breakthrough therapy designation for the treatment of FCS.

Tags: First Approval, Practice Changing

PLOZASIRAN | ARWR | LOA: ABOVE AVERAGE | ↗

Familial Chylomicronemia Syndrome (FCS)

Arrowhead's plozasiran (ARO-APOC3) is also an APOC3 inhibitor which works through RNA interference (RNAi), which is a mechanism of action that silences gene expression, leading to the inhibition of APOC3.

Plozasiran has shown positive results in the Phase III PALISADE trial which met the primary endpoint of lowering triglycerides at month 10 with quarterly doses of 25mg and 50mg achieving median triglyceride reductions of -80% and -78%, respectively. It now has the potential to become the second FDA-approved drug for FCS, launching behind olezarsen, with an NDA filing in the US expected before the end of 2024.

One potential advantage for plozasiran is that it has a more convenient dosing than olezarsen, quarterly versus monthly, although there is potential for physicians to have concerns over such prolonged dosing in case of safety issues, so long-term safety data will be needed. In the US and EU, plozasiran has orphan drug status and the FDA has granted fast track designation and breakthrough therapy designation for the treatment of FCS.

Tags: First Approval, Practice Changing

Metabolic

CAGRISEMA | NVO | LOA: AVERAGE | ↗

Obesity

Novo Nordisk's CagriSema is a combination of its own semaglutide, the active ingredient in blockbuster weight loss product Wegovy, with an amylin agonist, cagrilintide. Data from a Phase Ib trial evaluating CagriSema's safety and pharmacokinetic profile, found that the addition of cagrilintide increased mean percentage body weight reductions by up to 7.4% more than semaglutide alone after 20 weeks, with an acceptable safety and tolerability profile. Furthermore, cagrilintide monotherapy was associated with a body weight reduction of almost 11% in a 26-week Phase II trial and Wegovy achieved weight loss of almost 15% after 68 weeks in a Phase 3 trial. While results from the REDEFINE Phase III trial program obesity are awaited, there is a great degree of expectation around this combination for which there is the potential for ≥20% body weight loss, greater than that seen with Wegovy, Rybelsus (an oral formulation of semaglutide), and Eli Lilly's Zepbound (tirzepatide). Current consensus forecasts estimates its future sales potential at $20.5bn in 2030, ahead of both Wegovy and Zepbound, although this includes sales in type 2 diabetes, for which approval is anticipated in 2026, and subsequent label expansions for CV disease prevention.

Tags: First Approval, Practice Changing, Potential Blockbuster

ZOLGENSMA | NVS | LOA: APPROVED|

Spinal Muscular Atrophy (SMA)

Zolgensma, administered intravenously, remains the only gene therapy available for spinal muscular atrophy (SMA) following its FDA approval in 2019 for patients less than two years old with mutations in the survival motor neuron 1 (SMN1) gene. These patients primarily have type 1 SMA (the most severe form). To increase the number of patients eligible for treatment, Novartis plans to submit an sNDA to the FDA in 2025 focusing on an intrathecal formulation of Zolgensma that targets patients up to 18 years old, including those with type 2 SMA (less severe than type 1). Revenue generated from Zolgesma is currently limited by the birth rate of eligible SMA patients. Approval of the sNDA would provide a one-time therapy option for older patients who currently rely on the only other options for SMA, Biogen's Spinraza and Roche's Evrysdi, both chronic treatments which modulate the SMN2 gene to increase production of the SMN protein.

Topline data from the Phase III STEER trial assessing Zolgensma in type 2 SMA patients who are 2 – 18 years old, treatment naïve, sitting, and never ambulatory are expected in 2024. Data are also expected from the Phase III STRENGTH trial evaluating patients aged 2 – 18 years old who discontinued treatment with Spinraza or Evrysdi.

Tags: Label Expansion (Existing Indication), Practice Changing

APITEGROMAB | SRRK | LOA: ABOVE AVERAGE| ↗

Spinal Muscular Atrophy (SMA)

Scholar Rock is developing apitegromab, a monoclonal antibody, which aims to improve motor function in SMA by addressing muscle atrophy and associated weakness. Current treatments for SMA target motor neurons to slow motor neuron degeneration, but treatments for muscle atrophy and associated weakness remains an unmet need. Apitegromab inhibits the activation of a protein called myostatin which regulates the breakdown of muscle. Preventing the activation of myostatin reduces this breakdown and could lead to an increase in muscle mass in patients with SMA.

Six-month interim analysis results from the Phase II TOPAZ trial suggested apitegromab has the potential to be used as a monotherapy or in combination with Spinraza. Whilst it should be noted that there was no placebo or active control group in any of the three patient cohorts, there were consistent improvements in motor function scores across all three cohorts, including a substantial minority of patients (34.5%) with ≥3-point increases in motor scores, which is supportive of a positive treatment effect. The most promising results derived from cohort 3 (non-ambulatory type 2 SMA patients already receiving Spinraza for ~2 years), where combination therapy led to large mean increases in Hammersmith Functional Motor Scale Expanded (HFMSE) scores (+2.4 to +5.6), with a clear dose-response relationship. Long-term data showed that motor function gains achieved at earlier endpoints were sustained (if not improved) at 48 months.

A Phase III trial assessing apitegromab in patients with non-ambulatory SMA receiving background Spinraza or Evrysdi treatment is underway, with data expected in Q4 2024. Scholar Rock expects to initiate a commercial product launch of apitegromab for the treatment of SMA in 2025 assuming positive results.

Tags: New Drug Class, Practice Changing, First Approval

CITELINE
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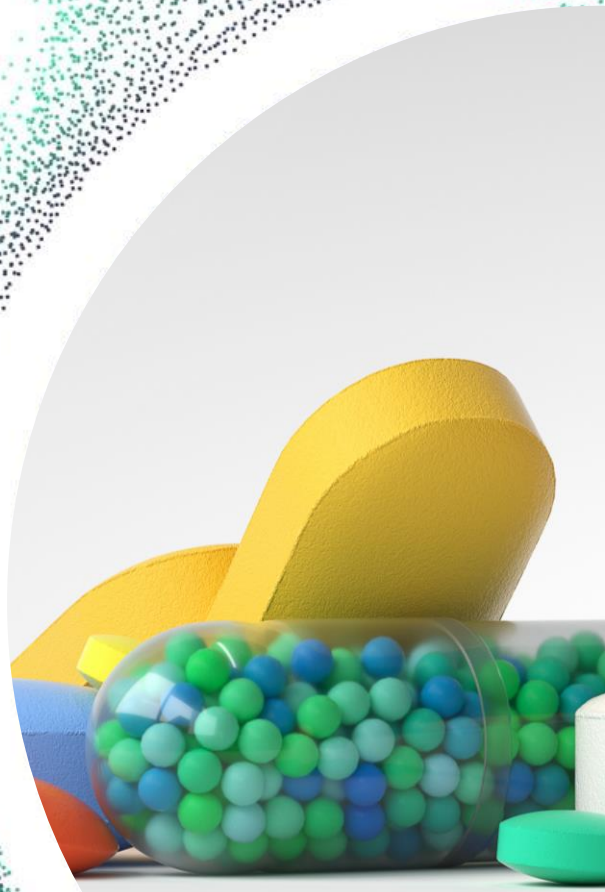
Neurology



TONMYA | TNXP | LOA: BELOW AVERAGE | ↗

Fibromyalgia

Tonmya is a sublingual tablet formulation of cyclobenzaprine hydrochloride, which is already FDA-approved as an adjunctive therapy for acute, painful musculoskeletal conditions, but is commonly used off-label in fibromyalgia, particularly for those also suffering from insomnia. The drug has a decade-long record of mixed results across Phase II and Phase III development for fibromyalgia, resulting in the current below-average LOA.

On the positive side, in 2020, the Phase III RELIEF trial showed that Tonmya reduced the weekly average of daily diary pain severity scores by 1.9 units compared to 1.5 in the placebo group, representing a statistically significant improvement. More recently, similarly positive results for another Phase III trial, RESILIENT, read out at the end of 2023, producing a 1.8-unit improvement at the same endpoint compared to 1.2 units for placebo. It should be noted that only about 20% of fibromyalgia patients report satisfactory pain management, leaving substantial room for improvement in the treatment of this indication. Tonmya has also consistently shown statistically significant improvements on measures of sleep quality across all late-phase trials and, although pain is the primary concern in fibromyalgia, sleep disturbances are also quite common.

While the molecule itself is widely available as a generic oral tablet, Tonmya's unique sublingual administration bypasses first-pass hepatic metabolism, reducing the production of a metabolite thought to build up with long-term usage and contribute to the eventual loss of effectiveness often seen with the oral formulation. However, all Tonmya studies thus far have been 14 weeks or shorter, so no data are available on whether this drug produces the same tolerance issues.

Tonix is expected to submit an sNDA for Tonmya in the second half of 2024.

Tags: New Drug Class, Label Expansion (New Indication)

AXS-12 | AXSM | LOA: ABOVE AVERAGE | ↗

Narcolepsy

Axsome's AXS-12, a highly selective and potent norepinephrine reuptake inhibitor, is in development for cataplexy in narcolepsy, with positive Phase II and Phase III efficacy and safety data released thus far. If approved, AXS-12 will compete with several off-label and marketed therapies but should be differentiated by its efficacy against co-morbidities (such as cognitive symptoms, depression, and anxiety), its rapid onset of action, and its likely lack of DEA scheduling. An NDA submission is planned following completion of the Phase III open-label extension trial, with data expected in this year.

The FDA's breakthrough therapy designation for AXS-12 in the treatment of cataplexy was supported by results from the Phase II CONCERT study, whereby the drug met cataplexy and Epworth Sleepiness Scale (ESS) endpoints with statistical significance. In the Phase III SYMPHONY trial, AXS-12 comparably met the primary endpoint by significantly reducing weekly cataplexy attacks at week five (83% for AXS-12 and 66% for placebo) and met several secondary endpoints including a significant reduction on the ESS, significantly improved cognition, and a significant increase in remission of cataplexy. Improvement from baseline in the anxiety/depression domain of the EuroQol 5 Dimension 5 Level (EQ-5D-5L) was achieved by 55% of patients treated with AXS-12, compared to 32% of placebo patients.

If approved, AXS-12 will compete with Jazz Pharmaceuticals' Xyrem, which is FDA-approved for cataplexy and excessive daytime sleepiness in narcolepsy. AXS-12 could take the edge regarding onset of action, with significant reductions in weekly cataplexy attacks demonstrated from week one, whilst Xyrem showed significant benefit at primary endpoints of prior studies at two weeks. AXS-12 could also prevail in terms of market access and safety compared to Xyrem, and other competitors in this space, Lumryz and Xywav, which are all DEA scheduled. Harmony Biosciences' Wakix is the only non-scheduled drug approved for cataplexy and excessive daytime sleepiness in narcolepsy and will potentially pose the biggest threat to AXS-12, although the two differ in terms of mechanism of action.

Tags: Practice Changing, First Approval

UPSTAZA | PTCT | LOA: AVERAGE | ↗

Neurology – Other

PTC's Upstaza, an investigative gene therapy with adeno-associated virus (AAV) delivering the human aromatic L-amino acid decarboxylase (AADC) gene, hopes to be the first approved therapy in the U.S. for Aromatic L-amino acid decarboxylase deficiency (AADC Deficiency), and could see approval as early as the end of 2024. AADC deficiency is an ultra-rare, inherited genetic disease which typically manifests within the first year of life. It is caused by changes in the gene that produces the AADC enzyme, which is needed to produce substances that are vital for the normal functioning of the brain and nerves, including dopamine and serotonin. These substances are crucial for signaling in the brain and the development of motor functions.

When administering Upstaza to the patient by infusion into the brain, it is expected that the virus will carry the AADC gene into nerve cells, enabling them to produce the missing enzyme. As a result, this is expected to enable the cells to produce the substances needed to function properly, thus improving symptoms of the condition. This therapy was first approved in Europe in 2022 for the treatment of AADC deficiency and has since been submitted to the FDA for review in March 2024. The regulatory filings are supported by the clinical studies conducted in Taiwan. The FDA granted the application priority review in May 2024, if approved, this would be the first disease-modifying treatment for L-amino acid decarboxylase (AADC) deficiency for patients 18 months and older directly infused into the brain in the US.

Tags: Practice Changing

AT-007 | APLT | LOA: ABOVE AVERAGE | ↗

Neurology – Other

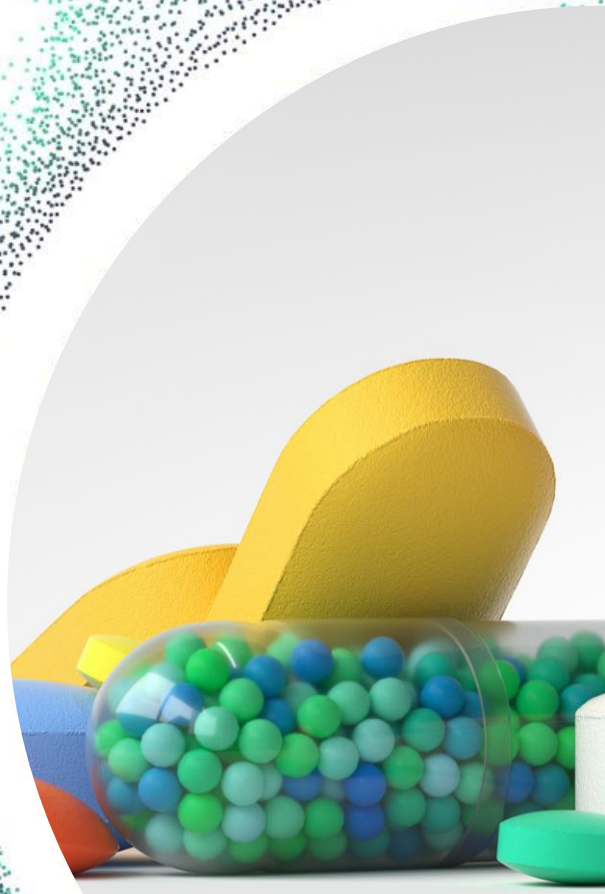
Applied Therapeutics' AT-007, a novel, potent, investigational CNS penetrant aldose reductase inhibitor, hopes to be the first approved therapy for Sorbitol dehydrogenase (SORD) deficiency. SORD deficiency is a hereditary condition that is caused by a mutation that prevents the body from producing or properly functioning the SORD enzyme, which is responsible for metabolizing sortibol. When the body lacks this enzyme, sorbitol accumulates to toxic levels, and can result in progressive neuropathy. There are currently no FDA-approved treatments specifically for SORD deficiency. The current standard of care is management, with a focus on palliative care utilizing physical and occupational therapy and pain management strategies.

Applied plans to submit a regulatory filing to the FDA for AT-007 for the treatment of SORD deficiency early in the first quarter of 2025. The filing will be supported by data from the Phase II/III INSPIRE study which evaluated the pharmacodynamic efficacy and clinical benefit of AT-007 in patients with SORD deficiency. The initial results from this study demonstrated a statistically significant reduction in sorbitol levels, and the pre-specified interim analysis of the Phase III INSPIRE trial showed that AT-007 reduced sorbitol levels by a mean of approximately 52% compared to placebo over 90 days of treatment. These results show strong evidence that this therapy can address the underlying cause of this inherited disorder. If this therapy is approved,

Tags: Practice Changing

CITELINE
a norstella company

Oncology



Oncology

REVUMENIB | SNDX | LOA: AVERAGE | ↗

Acute Myeloid Leukemia (AML)

The first-in-class menin inhibitor revumenib is being developed by Syndax Pharmaceuticals to target adult and pediatric relapsed/refractory AML with KMT2A rearrangements and NPM1 mutations, with Phase I/II AUGMENT-101 trial data supporting its NDA submission in the first quarter of 2024. The trial met its primary endpoint at the time of interim analysis with a CR/CRh rate of 23% (n=57) in the heavily pretreated KMT2Ar study population. Its efficacy is also supported by an ORR of 63% (6.1-month median follow up), and MRD-negativity achieved in 70% of AML patients who achieved a CR/CRh. Of the patients who responded to treatment, 39% additionally underwent HSCT, and median OS at the time of data cutoff was 8.0 months. Following the NDA submission by Syndax, and Priority Review granted in March 2024, a PDUFA date was initially assigned for September 2024; however, the FDA notified the company of a need for additional time for a full review of the supplemental information provided by Syndax, without further trial or manufacturing data, resulting in a three-month PDUFA date extension to December 2024.

Data from early-phase trials of revumenib combinations with Venclexta and azacitidine (BEAT AML trial), Venclexta and Inqovi (SAVE AML trial), and fludarabine and cytarabine (AUGMENT-102 trial) in newly diagnosed as well as relapsed/refractory AML patients with altered NPM1, NUP98r, or KMT2Ar also showed revumenib's potential as part of combination regimens, supporting its advancement into future pivotal trials.

Tags: First Approval, New Drug Class, Practice Changing, Potential Blockbuster

VESIGEL | URGN | LOA: ABOVE AVERAGE | ↗

Bladder Cancer

UroGen has completed an NDA submission for VesiGel, an intravesical solution of mitomycin for the treatment of low-grade intermediate-risk non-muscle-invasive bladder cancer (LG-IR NMIBC). Disease management typically involves endoscopic surgical tumor resection or transurethral resection of the bladder tumor (TURBT), but recurrence is particularly common in patients with LG-IR NMIBC after TURBT. VesiGel's NDA submission is supported by impressive long-term data from ENVISION, a Phase III single-arm study evaluating VesiGel as chemoablative therapy in LG-IR NMIBC. VesiGel met its primary endpoint in ENVISION, demonstrating a CR rate of 79.6% at three months after first instillation, and an 82.3% duration of response at 12 months in patients who achieved CR at three months (n=108). An approval for VesiGel will make it the first non-surgical treatment option for LG-IR NMIBC approved by the FDA, highlighting both the unmet treatment needs of this patient population, and the vast market opportunity for VesiGel.

Should VesiGel's NDA filing be accepted, and priority review be granted by the FDA, UroGen expects approval for VesiGel in the first half of 2025.

Tags: First Approval

SCEMBLIX | NVS | **LOA: AVERAGE** | ↗

Chronic Myeloid Leukemia (CML)

Novartis' Scemblix is a third-generation tyrosine kinase inhibitor (TKI) which is currently approved for use in third-line and beyond CML patients, or CML patients with a T315I mutation. Though the drug has seen strong uptake in these settings, supported by its impressive efficacy and safety data, these patient populations are relatively small and Scemblix's market potential has been limited by this. Novartis are now seeking a label expansion for use in the front-line and second-line settings, and the FDA has granted this submission priority review based on data from the Phase III ASC4FIRST trial. Data from ASC4FIRST reveal Scemblix to prove superior to both first-generation and second-generation TKIs, including blockbuster and market leader Sprycel, on efficacy and safety endpoints, alike. In ASC4FIRST, Scemblix demonstrated just shy of a 20% improvement in 48-week major molecular response rate compared to investigator selected TKIs, marking an unprecedented benefit. The drug also reported fewer adverse events and treatment discontinuations compared to imatinib and second-generation TKIs. These data prime Scemblix to be in a strong position to receive both FDA and EMA approval, and uptake can be expected across all settings.

Though Scemblix is armored with superiority data, the looming genericization of the CML market will likely hinder uptake in the more lucrative first-line setting, with physicians likely to opt for cheaper, but still effective, generic TKIs. Nevertheless, Scemblix is still anticipated to see strong uptake in the relapsed/refractory settings and is anticipated to earn blockbuster status by 2028.

Tags: Label Expansion (Existing Indication), Potential Blockbuster

GRANITE| GRTS | LOA: ABOVE AVERAGE | ↗

Colorectal Cancer (CRC)

GRANITE is a personalized neoantigen-based vaccine being developed by Gritstone bio. It is engineered to elicit a significant T-cell response (particularly CD8+ cytotoxic T-cells) against mutation-derived tumor-specific neoantigens (TSNA) identified for each patient through the company's proprietary EDGE machine learning-based platform. .

A substantial gap exists in addressing the treatment needs of CRC patients with microsatellite stable (MSS) tumors, comprising over 80% of metastatic colorectal cancer (mCRC) cases. Our epidemiology estimates a potential patient pool exceeding 100,000 individuals in 2023 for GRANITE in the US and EU5 alone, representing a significant commercial opportunity. The standard of care for first-line CRC, including those patients with MSS tumors, typically combines cytotoxic chemotherapy, utilizing the fluoropyrimidine backbone (5-FU or capecitabine), with either oxaliplatin (FOLFOX or XELOX) or irinotecan (FOLFIRI or XELIRI), alongside the anti-VEGF agent Avastin. Encouraging results in terms of progression-free survival (PFS) and long-term circulating tumor DNA (ctDNA) responses from the Phase II segment of the Phase II/III GRANITE-CRC-1L trial have instilled hope for MSS CRC patients with few treatment alternatives. Although these results are preliminary and derived from a relatively small patient sample size, but the emerging trend suggesting potential benefits for patients treated with GRANITE, immune checkpoint inhibitor, and fluoropyrimidine/bevacizumab combination therapy is encouraging.

Therefore, given the favorable preliminary results, coupled with the substantial unmet need and the sizable addressable patient population, GRANITE has the potential to achieve significant success in this segment of CRC treatment.

Tags: First Approval, Practice Changing, Potential Blockbuster

VYLOY | ASTELLAS | LOA: ABOVE AVERAGE | ↗

Gastric Cancer

Vyloy is a first-in-class monoclonal antibody which targets the cell adhesion protein Claudin 18.2, which is overexpressed in approximately 40% of gastric cancers. The current gastric cancer treatment paradigm splits patients via the presence of one actionable biomarker; namely, human epidermal growth factor 2 (HER2). HER2-negative disease represents 80% of the market and hence is the most lucrative space for agents to enter. The Phase III SPOTLIGHT and GLOW trials investigated Vyloy in combination with chemotherapy as a front-line treatment for metastatic or locally advanced HER2-negative gastric cancer. Both of these trials met the primary endpoint of improving PFS compared to placebo plus chemotherapy. Subsequently, the company filed a BLA for use of Vyloy in July 2023, however, on January 4, 2024, the FDA issued a complete letter of response due to third-party manufacturing deficiencies identified during the pre-license inspection of the facility. There were no concerns raised related to the clinical data within the BLA. Astellas resubmitted the BLA on May 9, 2024, and a PDUFA date has been set for November 9, 2024. If the drug is to be approved it would require patients to be screened for Claudin 18.2 expression, diversifying the biomarker portfolio within gastric cancer. Vyloy has been estimated to reach blockbuster status by 2028.

Current treatment options are limited for patients with HER2-negtaive gastric cancer, with Bristol Myers Squibb's PD-1-targeted inhibitor Opdivo (nivolumab) standing as the only approved targeted therapy in this setting. While Opdivo reigns as the market leader of the gastric cancer space, Vyloy is anticipated to steal considerable share. The survival data for both agents look to be comparable; however, Vyloy looks set to offer a potentially improved safety profile compared to Opdivo, with SPOTLIGHT reporting a similar incidence of treatment-related adverse events in both the placebo and zolbetuximab arms. In the Phase III CheckMate 649 trial, on the other hand, the incidence of serious treatment-related adverse events was higher in the Opdivo arm compared to placebo. This positions Vyloy as an attractive alternative, especially for patients who are immunodeficient. Vyloy also has the potential to carve a niche for itself in patients who are poorly immunogenic. While Opdivo is approved regardless of PD-1 expression and is often prescribed in HER2-negative patients with combined positive score (CPS) <1, this is predominantly due to the lack of effective available therapies for these patients, as the survival benefit from CheckMate 649 was observed in patients with CPS ≥1. If Vyloy is afforded the approval, it can be expected that the drug will steal market share from Opdivo in these patients who are PD-1-negative/PD-1-low.

Tags: First Approval, Practice Changing, Potential Blockbuster

Oncology

PRGN-2012 | PGEN | LOA: ABOVE AVERAGE | ↗

INO-3107 | INO | LOA: AVERAGE | ↗

Head and Neck Cancer

Precigen's PRGN-2012 and Inovio's INO-3107 are being developed for recurrent respiratory papillomatosis (RRP), a disease with no approved systemic therapies. RRP is a rare, lifelong disease caused by infection with HPV6 or HPV11. Benign papillomas grow in the respiratory tract and can cause severe voice disturbance. The current standard of care is repeat surgical debulking of papilloma, which can lead to irreversible scarring of the trachea.

PRGN-2012 is a therapeutic vaccine that uses a replication incompetent gorilla adenoviral vector to express HPV6 and HPV11 antigens and elicit a T-cell immune response. A pivotal Phase II trial enrolled patients who had at least three surgeries in the prior 12 months and the primary endpoint was complete response (CR) rate defined as the percentage of patients who require no RRP surgeries in the 12-month period after PRGN-2012 treatment completion (four subcutaneous administrations of PRGN-2012 over a 12-week treatment period). At ASCO 2024, the trial reported a CR rate of 51% (n=35) and no grade ≥3 adverse events. The responses were durable, and with a median follow-up of 20 months, the median duration of response has not been reached; all patients with a CR remain in response and have not had surgery. In addition to the 51% of patients with a CR, an additional 35% of patients reported a partial response (fewer surgeries in the 12 months following treatment compared to the 12 months preceding treatment) for an ORR of 86%. Precigen plans to submit a BLA in H2 2024 under an accelerated approval pathway and if approved, marketing of PRGN-2012 may begin in 2025. A single arm, confirmatory Phase III trial was initiated in July 2024.

INO-3017 is DNA plasmid based therapeutic vaccine that targets both HPV6 and HPV11. A pivotal Phase I/II trial enrolled patients who had at least two surgeries in the prior 12 months and INO-3017 was administered by intramuscular injection followed by electroporation using Cellectra, a proprietary device. Four doses of INO-3107 were administered at Day 0 and weeks 3, 6 and 9 and the trial reported a CR rate of 28% (n=32) and a partial response rate of 53% for an ORR of 81%. INO-3017 is differentiated from PRGN-2012 in that it does not require a viral vector which reduces concern for neutralizing antibodies and may allow for retreatment. In August 2024 Inovio reported a manufacturing issue with the single use disposable administration component of the Cellectra device which they are currently addressing. The company plans to submit a BLA in mid-2025 once the manufacturing issue is fully addressed and request a priority review. Assuming a six-month priority review, INO-3017 may be approved in late 2025 or early 2026 and would be the first plasmid-based medicine approved in the US. A randomized, placebo controlled, Phase III confirmatory study is expected to initiate in mid-2025.

Tags: First Approval, Practice Changing, New Drug Class

ENHERTU | DSNKY| LOA: AVERAGE | ↗

Breast Cancer (HER2+)

Enhertu is Astra Zeneca and Daiichi Sankyo's blockbuster TROP-2 targeted antibody drug conjugate (ADC), which has experienced resounding success in the other subtypes of breast cancer. It earned its first US approval in the HER2+ breast cancer space in December 2019 in patients who had progressed on at least two lines or prior anti-HER2 therapies.

In a bid to confirm Enhertu's position in a more clinically relevant patient population, the Phase III DESTINY-Breast02 trial was initiated. This study evaluated Enhertu in metastatic HER2+ breast cancer patients who had been previously treated with Kadcyla, which is an established standard-of-care therapy in the second-line. Full data from the DESTINY-Breast02 trial were published in May 2023 highlighting that the trial had met its primary endpoint with highly promising results. mPFS in the Enhertu group was 17.8 months versus 6.9 months in the treatment of physician's choice group. Notably, in the additional analyses, Enhertu also demonstrated strong mPFS score (HR of 0.35) in patients with brain metastases, an area of huge unmet need. These data look competitive compared to Tukysa's Phase II HER2CLIMB results which solidified the drug as the optimal treatment for heavily pre-treated patients with brain metastases. The DESTINY-Breast02 trial also met its secondary endpoint through significantly increasing median OS by 12.7 months.

Based on the success of these results, in July 2023, AstraZeneca submitted an sNDA for full approval in the third-line setting in the US and EU. The PDUFA date was originally expected to be May 27th 2024 but regulatory approval is now expected in the second half of 2024. Given the clinically meaningful improvement in PFS and OS and comparable safety profile to prior trials, is anticipated that approval will be highly likely. Although Enhertu shows huge clinical benefit in the third-line, its cemented standard-of-care reputation in the second-line will limit its uptake later in the treatment algorithm due to the lack of re-treatment efficacy when prescribing ADCs.

Tags: Label Expansion (Existing Indication), Potential Blockbuster

DATOPOTAMAB DERUXTECAN | DSNKY| LOA: AVERAGE | ↗

Breast Cancer (HR+/HER2-)

Astra Zeneca and Daiichi Sankyo announced positive topline results for its potent TROP2-directed antibody drug conjugate (ADC), datopotamab deruxtecan (Dato-Dxd) in September 2023. The drug was being investigated in HR+/HER2- metastatic breast cancer patients who had progressed on endocrine therapy and had also received 1-2 prior lines of systemic chemotherapy in the Phase III TROPION-Breast01 trial. Dato-DXd demonstrated a significantly improved mPFS of 6.9 months versus 4.9 months in the chemotherapy arm. OS data were not mature but a trend for improvement favoring Dato-DXd was observed. Subsequently, a Biologics License Application (BLA) for Dato-Dxd was approved in the US in April 2024 and the PDUFA data has been set for January 29th 2025.

The TROPION-Breast01 data are comparable to the TROP2-targeted ADC Trodelvy's Phase III TROPICS-02 trial results, which already has an approval in second-line and beyond metastatic patients, but came up short when compared with ADC market leader Enhertu. Furthermore, according to the TROPION-Breast01 committee, there was one treatment-related death in the trial and given that pre-treated metastatic patients are not without options, the potential long-term safety risks could cast Dato-Dxd lower on a physicians list of available therapies. Therefore, while Dato-Dxd is clearly clinically active and the OS data are expected to trend in the drugs favor, the results are unlikely to mark out Dato-Dxd as a clear leader in this setting, and, if approved, the drug is expected to garner only a small market share as a result.

Tags: First Approval

INAVOLISIB | ROG | LOA: ABOVE AVERAGE | ↗

Breast Cancer (HR+/HER2-)

Inavolisib is an orally available potent and selective PI3Kα inhibitor that also promotes the degradation of mutant p110α. It is set to be the third PI3K/AKT inhibitor approved in the HR+/HER2- breast cancer space following the approval of Truqap this year. Inavolisib is being investigated in the Phase III INAVO120 trial in combination with Ibrance (a CDK4/6 inhibitor) and fulvestrant (an ET) versus placebo with Ibrance and fulvestrant as a first-line therapy for patients with *PIK3CA*-mutant HR+/HER2- locally advanced or metastatic breast cancer. It is hypothesised that a PI3K inhibitor in combination with the current standard-of-care ET and CDK4/6 inhibitor combination will show a synergistic anti-tumor effect. *PIK3CA* is one of the most frequently mutated oncogenes in breast cancer with up to 40% of HR+HER2- patients having the mutation and contributes to both chemotherapy and endocrine therapy resistance. Therefore, the patient population studied in the INAVO120 trial has multiple elements of unmet need.

The primary analysis of INAVO120, which was presented at SABCS 2023, was highly promising. The inavolisib/Ibrance/fulvestrant combination showed a statistically significant mPFS of 15.0 months versus 7.3 months in the placebo/Ibrance/fulvestrant control arm. Data presented at ASCO 2024 highlighted the next stage of analysis with a PFS2 of 24.0 v 15.1 months, which is described as time from randomization to end of next-line treatment. At this time OS data remained immature but a clear positive trend had been observed.

PI3K inhibitors have had limited success in the past due to poor efficacy and tolerability, and low combinability with CDK4/6 inhibitors. The high rates of toxicity and discontinuation rates, specifically associated with Piqray, leave room for inavolisib to be a more well-tolerated and selective PI3K inhibitor in the first-line setting, which could distinguish it as a new standard-of-care for *PIK3CA*-mutant patients. Given the robust efficacy and therapeutic index of inavolisib, which is partially attributed to its mutant-selective mechanism of action, it is likely it will gain approval following its PDUFA date on November 27th 2024.

Tags: First Approval, Potential Blockbuster, Practice Changing

BLENREP | GSK | LOA: AVERAGE | ↗

Multiple Myeloma (MM)

An anti-BCMA antibody-drug conjugate, Blenrep has had a rocky history. Although it received separate conditional approvals from the FDA and EMA in August 2020 for relapsed/refractory MM patients who have received at least four prior therapies, these approvals were withdrawn in 2022/2023 after a confirmatory trial, DREAMM-3, failed to meet its primary endpoint of PFS. DREAMM-3 was a head-to-head superiority trial comparing Blenrep monotherapy to Pomalyst combined with dex (Pd) in third-line or later MM. In a surprising turn of events, Blenrep reported positive results in two additional Phase III trials, DREAMM-7 and DREAMM-8, both of which enrolled second-line or later patients. DREAMM-7 compared Blenrep combined with bortezomib and dexamethasone (Vd) to Darzalex combined with Vd. Numerical results were presented in February 2024 and included a statistically significant increase in the primary endpoint of PFS (37 months vs. 13 months; HR 0.41) and a trend for improved OS (HR 0.57; p=0.00049), which may reach the criteria for statistical significance ($p \leq 0.00037$) with longer follow-up. DREAMM-7 also reported induction of deep responses as measured by complete response or better (≥CR) rate (35% vs. 17%) and by the MRD negativity rate in patients with a very good partial response or better (≥VGPR) (39% vs. 17%). DREAMM-8 compared Blenrep combined with Pd versus bortezomib combined with Pd and at ASCO 2024 impressed with a statistically significant improvement in median PFS (not reached vs. 12.7 months with a median follow-up of 21.8 months) and improvements in the ≥CR rate (40% vs. 16%) and in the MRD negativity rate in patients with a ≥VGPR (32% vs. 5%). DREAMM-8 also showed a trend for improvement in OS that will be re-examined after a longer follow-up. Following regulatory fillings in the EU in July 2024, we expect additional filings in the US and Japan in H2 2024 and approval of Blenrep for second-line or later MM in 2025.

Unlike the other approved BCMA-targeting agents which include bispecific antibodies and CAR-T therapies, Blenrep does not require any hospitalizations and its efficacy is independent of T-cell activity, which may make it attractive for patients with T-cell exhaustion. As such, Blenrep is well suited for older patients, including those who are transplant-ineligible and those whose immune systems have been degraded by previous treatments. Given the positive efficacy, we expect that Blenrep will be approved and will become an option for relapsed/refractory multiple myeloma. The DREAMM-7 and DREAMM-8 regimens would be useful for lenalidomide-refractory patients (common as early as second line given that many patients are receiving lenalidomide maintenance), and patients previously treated with an anti-CD38 antibody (increasingly more common at second line with the rising popularity of Darzalex-based regimens for first-line patients). The main drawback for Blenrep is that it is associated with keratopathy, an ocular toxicity that can lead to decreases in visual acuity which are managed primarily by dose interruptions. Consensus forecasts have Blenrep sales reaching $966m by 2030.

Tags: Practice Changing, Potential Blockbuster

PATRITUMAB DERUXTECAN | MRK | LOA: ABOVE AVERAGE | ↗

Non-Small Cell Lung Cancer (NSCLC)

Patritumab deruxtecan is a first-in-class HER3 directed antibody drug conjugate (ADC) developed by Merck and Daiichi Sankyo for the treatment of NSCLC. In December 2023, the FDA granted priority review to the BLA for patritumab deruxtecan for the treatment of adult patients with locally advanced or metastatic EGFR-mutated NSCLC previously treated with two or more systemic therapies, based on positive results from the HERTHENA-Lung01 pivotal Phase II trial. However, on June 26, 2024, the FDA issued a complete response letter (CRL) due to concerns discovered during an inspection of a third-party manufacturing facility. It should be noted that the CRL did not raise any issues regarding the trial or clinical data. Thus, there is a strong possibility of a prompt decision, especially considering the encouraging trial results in a patient population with significant unmet medical needs. With EGFR gene mutations occurring in approximately 15% of NSCLC patients in the West and in about 40% of patients in Asia, this is a large and commercially lucrative patient population. HER3 is a member of the EGFR family of receptor tyrosine kinases, and around 90% of advanced EGFR-mutated tumors express HER3 after prior EGFR tyrosine kinase inhibitors treatment.

Patritumab deruxtecan is currently under assessment as a monotherapy and in combination with other treatments as part of a global development program in NSCLC. This includes HERTHENA-Lung02, a Phase III study comparing it to platinum-based chemotherapy in patients with EGFR-mutated locally advanced or metastatic NSCLC after disease progression on or after treatment with a third-generation EGFR TKI; a Phase I study in combination with osimertinib in EGFR-mutated locally advanced or metastatic NSCLC; and a Phase I study in previously treated patients with advanced NSCLC..

Tags: First Approval

IVONESCIMAB | SMMT | LOA: ABOVE AVERAGE | ↗

Non-Small Cell Lung Cancer (NSCLC)

Ivonescimab (SMT112) is a first-in-class tetravalent bispecific antibody targeting VEGF and PD-1. Ivonescimab's tetravalent structure is designed to form large complexes with dimeric VEGF, resulting in high avidity to PD-1, enhanced function, and potent antitumor activity in preclinical studies.

Encouraging results in terms of progression-free survival (PFS) from the HARMONi-A study evaluating Ivonescimab combined with chemotherapy indicate its potential application in non-squamous EGFR-mutated NSCLC patients who have progressed after treatment with a third-generation EGFR tyrosine kinase inhibitor (TKI). Data indicates that this regimen could be an alternative treatment option for patients failing the FLAURA (Tagrisso) and MARIPOSA (Rybrevant + Lazertinib) regimens. The Ivonescimab + chemotherapy combination was approved in China in May 2024 for EGFR-mutated NSCLC patients who progress after EGFR-TKI treatment. The primary analysis of the Phase III HARMONi-2 trial evaluating Ivonescimab against monotherapy Keytruda in patients with locally advanced or metastatic NSCLC whose tumors have positive PD-L1 expression (PD-L1 TPS >1%) and Phase II study of perioperative Ivonescimab alone or combined with chemotherapy in resectable NSCLC will be presented at World Conference on Lung Cancer (WCLC) 2024. Thus, if the mentioned trial's outcome turns out to be positive, the market potential of Ivonescimab could be substantial.

Tags: First Approval, Potential Blockbuster

Oncology

AVUTOMETINIB | VSTM | LOA: AVERAGE | ↗

DEFACTINIB | VSTM | LOA: ABOVE AVERAGE | ↗

Ovarian Cancer

Verastem Oncology is developing its lead assets avutometinib, a Raf/MEK inhibitor, and defactinib, a selective FAK inhibitor for the treatment of recurrent KRAS-mutated low-grade serous ovarian cancer (LGSOC) patients who have received at least one prior systemic therapy. LGSOC is a rare ovarian cancer subtype and accounts for roughly 10% of epithelial ovarian cancer cases. These malignancies are known to respond poorly to chemotherapy, highlighting the need for effective new therapies targeting this disease subtype. The FDA granted orphan drug and breakthrough therapy designations to the avutometinib/defactinib combination for the treatment of patients with recurrent LGSOC in March 2024. Interim data from RAMP-201, a registration-directed Phase II trial, reported a 45% ORR in all patients, a 60% ORR in patients with KRAS mutations, and a 29% ORR in KRAS wild-type patients. Additionally, tumor regression was observed in 80% of patients following treatment with the combination. Based on these preliminary data, Verastem initiated a rolling NDA submission of avutometinib and defactinib for accelerated approval anticipated in the first half of 2025. Trial investigators expect mature data from RAMP 201 to be available by the end of 2024.

A confirmatory trial, the Phase III RAMP 301 study, is currently underway, evaluating the combination versus investigator's choice of chemotherapy or hormone therapy for the treatment of recurrent LGSOC. Favorable safety and efficacy results from the trial will place the combination in a position to compete with hormone therapies and platinum-based chemotherapy, the current standard treatments in recurrent LGSOC.

Tags: First Approval, Practice Changing

PLUVICTO | NVS | LOA: AVERAGE | ↗

Prostate Cancer

The first-in-class PSMA-targeting radioconjugate, Pluvicto, was approved in 2022 for patients with metastatic castration-resistant prostate cancer (mCRPC) who had received prior treatment with an androgen receptor pathway inhibitor (ARPI) and a taxane. This approval was practice changing and offered an alternative therapy for heavily pre-treated patients with limited options. Although the uptake of Pluvicto was initially hindered by manufacturing and access issues, Novartis is working to iron out these supply chain issues with four sites actively manufacturing Pluvicto and two further sites under construction.

In a continued effort to expand Pluvicto's label into earlier lines of the prostate cancer treatment algorithm, Novartis initiated the Phase III PSMAfore trial, investigating the drug in taxane-naïve mCRPC patients. In 2022, Novartis announced that the PSMAfore trial had met its primary endpoint of radiographic progression free survival (rPFS) with Pluvicto significantly increasing rPFS by 6.4 months over the ARPI control arm. Following this, submission to the FDA was delayed due to the lack of mature OS analysis and interim analysis was extended to 75% of OS events needed prior to filing. In April 2024, at the pre-planned analysis, Pluvicto demonstrated an OS hazard ratio of less than 1.0 in the intent-to-treat population unadjusted for cross-over, highlighting durable clinical benefit. Following these delays in regulatory submission, Novartis announced that it plans to file in the second half of 2024.

While entry into this larger and healthier patient population could garner significant profit for Pluvicto, the approval will not come without competition from standard-of-care market leaders Xtandi and Zyitga, as well as pipeline radiotherapies. Eli Lilly's pipeline radioconjugate PNT2002 is also looking to enter the mCRPC space with a more practical dosing schedule albeit less promising rPFS data (9.5 versus 6.0 months in the ARPI control group). Nonetheless, approval of Pluvicto in this earlier setting would further bolster the development of the radiotherapy drug class in the prostate cancer space.

Tags: Label Expansion (Existing Indication), Potential Blockbuster

XPOVIO | KPTI | LOA: APPROVED |

Uterine (Endometrial) Cancer

First-in-class XPO1 inhibitor Xpovio is in development for endometrial cancer in the Phase III SIENDO and XPORT-EC-042 trials, in a bid to expand the drug's outreach beyond multiple myeloma, for which it received an FDA label in 2020. Both trials are assessing Xpovio as maintenance after therapy with platinum and a taxane (SIENDO) or a platinum agent (XPORT-EC-042), both targeting advanced/recurrent endometrial cancer patients who respond to systemic therapy. Primary results from SIENDO showed improvements in median PFS for the intent-to-treat population, but these were not clinically meaningful. Data from a prespecified subgroup of patients with *TP53* wild-type disease, which were presented at ASCO 2024, however, showed that Xpovio maintenance after first-line platinum-based chemotherapy led to a median PFS of 28.4 months (compared to 5.2 months in the placebo arm). Even more notably, Xpovio-treated patients with *TP53* wild-type/pMMR endometrial cancer showed a median PFS of 39.5 months (compared to 4.9 months in the placebo arm). These data bode well for the XPORT-EC-042 trial, which focuses on *TP53* wild-type patients only. Xpovio was not, however, without safety signals, and of the *TP53* wild-type patients treated with the drug, 90% experienced nausea, 60% experienced vomiting, and 45% diarrhea, with most cases being grades 1-2. Adverse events led to treatment discontinuation in 17% of patients, which is not insignificant, and may prove to be problematic for Xpovio, should the drug pass any regulatory hurdles.

Advanced/recurrent endometrial cancer has a poor prognosis, with the current standard of care in the first-line setting (carboplatin plus paclitaxel) yielding a median PFS of 13 months and a median OS of 37 months. The data from SIENDO, therefore, are sending a positive signal that Xpovio maintenance can improve these outcomes. Half of advanced/recurrent cases are associated with a *TP53* wild-type phenotype, which in turn is found in both pMMR and dMMR/MSI-H tumors, with the latter subgroup mostly targeted by immune checkpoint inhibitors. With a clear unmet need remaining for pMMR tumors (comprising approximately 70% of *TP53* wild-type endometrial cancer cases), Xpovio maintenance treatment has the potential to prolong systemic therapy response, provide a much-needed therapeutic option for these patients, and boost the drug's commercial outlook. The data from the XPORT-EC-042 trial are now much awaited.

Tags: Label Expansion (New Indication)

LYNPARZA | AZN | LOA: ABOVE AVERAGE | ↗

Uterine (Endometrial) Cancer

The Phase III DUO-E trial assessed Imfinzi in combination with platinum-based chemotherapy followed by Imfinzi and Lynparza or Imfinzi alone maintenance therapy, in newly diagnosed or recurrent Stage III or IV endometrial cancer patients. While both arms of the trial demonstrated a reduction in the risk of disease progression or death, with the Imfinzi + Lynparza arm showing better clinical results than the Imfinzi arm, the much-awaited data on progression or risk of death from the DUO-E trial did not manage to strengthen Imfinzi's position as a contender for the first-line setting. Its competitors in this space—GSK's Jemperli and Merck & Co.s' Keytruda—showed significantly higher rates of the same metric, particularly in the dMMR/MSI-H population, in the RUBY and NRG-GY018 trials, respectively. Nevertheless, the data from the DUO-E trial formed the basis of Imfinzi's FDA approval in June 2024, for use in primary advanced or recurrent endometrial cancer that is dMMR. The drug's label indicates the drug will be used in combination with carboplatin and paclitaxel, followed by Imfinzi monotherapy maintenance.

The trial design of the DUO-E trial may allow Imfinzi to differentiate itself from Jemperli and Keytruda, with the addition of PARP inhibitor Lynparza potentially providing a much-needed clinical boost. Maintenance with either Imfinzi alone or Imfinzi + Lynparza led to impressive median PFS values, particularly in the dMMR population, where an astounding median PFS of 31.8 months was achieved in the Imfinzi + Lynparza arm. Indeed, regulatory applications for both Imfinzi and Imfinzi + Lynparza are currently under review in the EU and Japan, with EU's CHMP recommending the combination for approval for pMMR advanced or recurrent endometrial cancer in July 2024. Imfinzi was also recommended for patients with dMMR disease.

Median OS data are not yet available for DUO-E, RUBY, or NRG-GY018, but all are showing favorable trends for their respective immune checkpoint inhibitors, especially in the dMMR/MSI-H population. Different follow-up times, as well as differences in histologies included in these trials do not allow a complete picture of how they compare, but nevertheless, mature OS data are now needed to get a complete picture for not just Imfinzi, but also for Jemperli and Keytruda. With 25-30% of endometrial cancers dMMR/MSI-H, this is a substantial commercial opportunity for all three immune checkpoint inhibitors.

Tags: Label Expansion (New Indication)

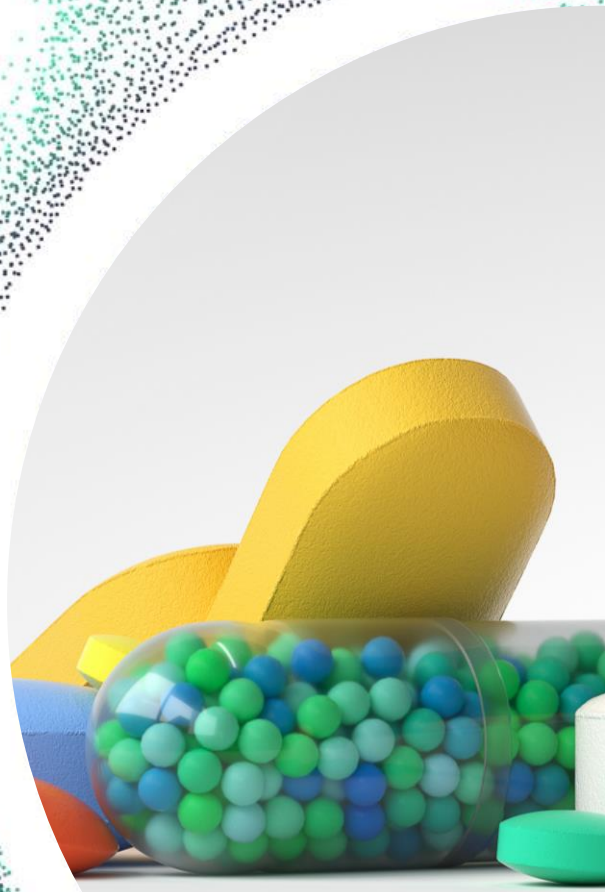
CLR 131 | CLRB | LOA: AVERAGE | ↗

Waldenstrom's Macroglobulinemia (WM)

Cellectar Biosciences CLR 131 (iopofosine I-131) is a radiopharmaceutical conjugated to a phospholipid that targets lipid rafts present on cancerous cells. A pivotal Phase II trial, CLOVER-WaM, is evaluating a four-dose, fixed course of treatment of CLR 131 in third-line or later WM including patients who failed or had a suboptimal response to a BTK inhibitor. Updated data from the trial (n=55) were presented in July 2024 and the trial met its primary endpoint with a major response rate (MRR) of 56.4% (95% CI, 42%-67%) which exceeded the null hypothesis of 20%. The trial also reported an ORR of 80% and a complete response / very good partial response rate of 7.3%. The responses were durable with 72% of responding patients still in response at 18 months. An NDA submission to the US FDA is expected in Q4 2024 and with a Fast Track designation in hand, the company will seek a priority review with a six-month review process. Third-line WM patients, especially those resistant to a BTK inhibitor, represent an unmet medical need and so CLR 131 may offer a much-needed option for these patients. CLR 131 is also being evaluated in Phase II trials for additional indications including primary central nervous system lymphoma and multiple myeloma.

Tags: First Approval, New Drug Class, Practice Changing

Ophthalmology



Ophthalmology

SUSVIMO | ROG | LOA: ABOVE AVERAGE |↗

Diabetic Macular Edema

Having been approved in wet AMD in 2021, Roche's Susvimo was later recalled in 2022 owing to issues with the implant's septum, or seal, which could fail after repeated use. With these issues resolved and Susvimo relaunched in the wet AMD market, Roche will be poised to return to the broader ophthalmology field, with approval expected in DME in 2025. In the Phase III Pagoda trial, people with DME receiving Susvimo refilled every six months through approximately two years (112 weeks) continued to maintain improvements in vision gains seen at one year (9.8 eye chart letters). A gain of 9.8 eye chart letters is similar to gaining two more lines on an eye chart. Approximately 95% of individuals did not need additional treatment with supplemental injections.

With no cases of endophthalmitis reported up to one year and the rate of endophthalmitis through week 112 being 0.7%, compared to 0.8% in the control arm, the safety profile looks promising. As with other ophthalmic indications, Roche's Susvimo will address patients' preference for longer dosing intervals and safety and will compete with Eylea HD and Vabysmo, both of which offer shorter dosing intervals.

Tags: Label Expansion (New Indication), Practice Changing

Ophthalmology

SUSVIMO | ROG | LOA: ABOVE AVERAGE | ↗

Diabetic Retinopathy

With positive results from the Phase III PAVILION trial, Roche is looking for another potential approval in the ophthalmology market with Susvimo in diabetic retinopathy. The trial, designed to evaluate the efficacy, safety, and pharmacokinetics of the Port Delivery System (PDS) every 36 weeks in patients with diabetic retinopathy, showcased impressive results, with over 80% of patients achieving a ≥2-step improvement in the Early Treatment of Diabetic Retinopathy Scale - Diabetic Retinopathy Severity Scale (ETDRS-DRSS), as compared to only 9% in the control group.

Success in the ophthalmology market is often associated with reasonable safety and longer dosing intervals, and Roche will try to capitalize on both these areas with Susvimo. Susvimo is expected to contend against the market leader Eylea HD, for which Regeneron has gained approval for a high-dose version, which increased the dosing interval to 16 weeks. Susvimo offers a longer dosing interval to its main competitor, Eylea HD, with 100mg/ml ranibizumab PDS offered every 32 weeks as a refill-exchange procedure. The balance could shift towards the novel route of administration as studies conducted using the PDS indicate that patients prefer it over traditional intravitreal injections, with over 93% favouring the former.

Tags: Label Expansion (New Indication), Practice Changing

Ophthalmology

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LNZ-100 | LENZ | LOA: ABOVE AVERAGE | ↗

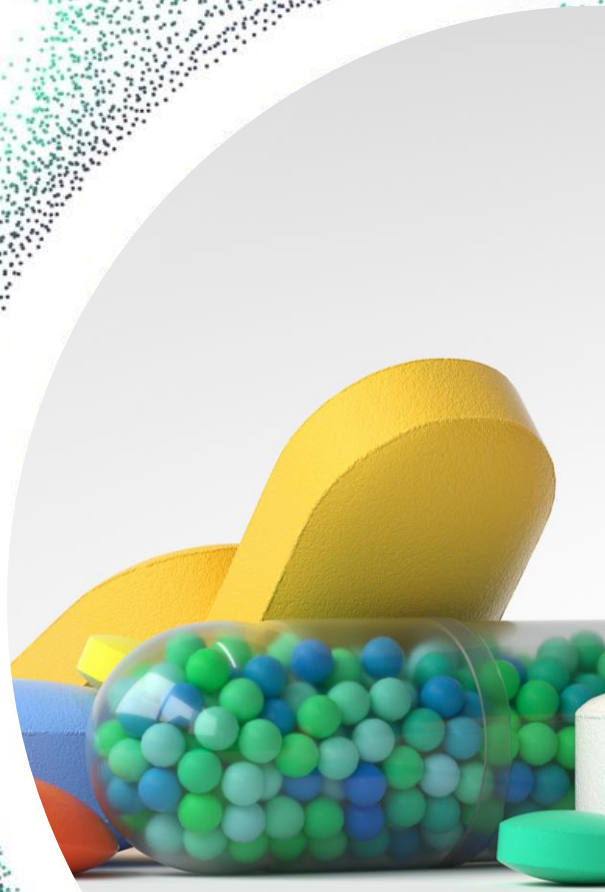
Presbyopia

LENZ Therapeutics is developing LNZ-100, an aceclidine-based ophthalmic solution to be administered as an eye-drop, for the treatment of presbyopia. The Company submitted a New Drug Application (NDA) for LNZ-100 in August 2024, which was supported by the pivotal Phase III CLARITY study of LNZ100 for the treatment of presbyopia. In the Phase III CLARITY study LNZ100 achieved all primary and secondary near vision improvement endpoints with statistically significant three-lines or greater improvement in Best Corrected Distance Visual Acuity (BCDVA) at near, without losing one line or more in distance visual acuity, demonstrating LNZ100 was well tolerated with no serious treatment-related adverse events observed in the over 30,000 treatment days monitored in the CLARITY study.

Presbyopia is a condition that affects approximately 1.8 billion people globally, and 128 million people in the United States. Though this condition has been counteracted with treatments such as corrective lenses and refractive surgery, having an unintrusive treatment option in the form of eyedrops to remedy near vision would provide immense benefit to this large patient population.

Tags: Blockbuster Potential, First Approval

Psychiatry



NRX-101 | NRXP | LOA: ABOVE AVERAGE | ↗

Bipolar Disorder (BD)

NRX-101 is a proprietary formulation of D-cycloserine and lurasidone under development by NeuroRx for the maintenance, and potentially acute, treatment of bipolar disorder (BD) depression in patients with suicidality. If successful, this would be the first drug approved to treat this specific patient population. The current standard of care for suicidal ideation, electroconvulsive therapy, is often stigmatized due to its controversial history. The intended treatment regimen is an initial stabilization dose of NeuroRx's NRX-100 (ketamine), followed by daily oral outpatient administration of NRX-101 for maintenance of remission. While intravenous and intranasal ketamine have previously demonstrated rapid and potent effects in achieving remission from both depression and suicidal ideation in BD and unipolar depression, its use is associated with hallucinations and dissociative side effects, as well as abuse potential, and it must be administered in a monitored hospital or clinic setting. NRX-101 will potentially provide an alternative, safe, non-hallucinogenic, non-addictive, oral medication to maintain the effects of ketamine in BD depression patients with acute suicidal ideation.

NeuroRx plans to file two NDAs in 2024: one for the accelerated approval of NRX-101 to treat BD depression in patients with akathisia (based on data from Phase II and Phase IIb/III trials) and one for the approval of NRX-100 for the treatment of suicidal depression. In the Phase IIb/III trial, treatment with NRX-101 demonstrated a 33% reduction in suicidality compared to lurasidone, as well as a 76% reduction in akathisia. Another Phase III trial, due for completion in December 2024, is assessing NRX-101 for maintenance of remission from severe BD depression in patients with suicidal ideation following a successful response to ketamine treatment. NRX-101 has been granted fast track and breakthrough therapy designations by the FDA.

Tags: Practice Changing, First Approval

CAPLYTA | ITCI | LOA: ABOVE AVERAGE | ↗

Major Depressive Disorder

Caplyta was first approved for schizophrenia in December 2019 and the label was expanded to include bipolar disorder, specifically bipolar depression, two years later in December 2021. There is a long history of using antipsychotics to treat Major Depressive Disorder (MDD) and, like other atypical antipsychotics, Caplyta modulates both serotonin and other monoamines, particularly dopamine, although the exact mechanism of action is unknown. Intra-Cellular Therapies' decision to pursue a further label expansion into MDD will give this drug a wide potential patient population, although it will likely be relegated to refractory patients.

In the Phase III Study 403 trial, Caplyta was explored as a monotherapy in MDD with mixed features, as well as bipolar I and II. For the combined patient population, Caplyta demonstrated a statistically significant reduction of 5.7 points on the MADRS total score compared to placebo at week six and an even higher 5.9-point reduction over placebo in the MDD subpopulation. These results are unsurprising given the drug's prior success and ultimate approval in bipolar depression, but notable nonetheless.

Data from two Phase III studies of Caplyta as an adjunctive were released in April and June of 2024. Caplyta passed with flying colors, reducing MADRS total score by 4.9 points compared to placebo at week six in study 501 and 4.5 points in study 502. Notably, both trials reported a 14.7-point total improvement in the Caplyta cohort, so the variation in reported efficacy was due to placebo group scores, demonstrating reassuring consistency across almost 1,000 patients in the Phase III adjunctive program. Two other adjunctive Phase III trials, 503 and 505, are ongoing.

Intra-Cellular plans to file an sNDA in the second half of 2024, setting the drug up to be launched in 2025.

Tags: Label Expansion (New Indication)

REXULTI | OTSUKA | LOA: ABOVE AVERAGE | ↗

Post-Traumatic Stress Disorder

Rexulti is an atypical antipsychotic already approved as an adjunctive for major depressive disorder and as a monotherapy in schizophrenia and agitation due to Alzheimer's. In Phase III trials, Rexulti as an adjunctive to sertraline demonstrated a statistically significant improvement in Clinician-Administered PTSD Scale (CAPS-5) score of 19.2 points in the flexible dose setting but did not reach significance in the fixed dose setting. In these trials, Rexulti plus placebo did not produce statistically significant results, nor did sertraline plus placebo, reiterating the sentiment echoed by patients and providers alike that currently available PTSD treatments remain inadequate.

Only sertraline and paroxetine are FDA-approved for PTSD and no new therapies have been approved in over two decades. These two drugs are sometimes combined with psychotherapy, but the . Given the recent rejection of midomafetamine for PTSD and the controversy surrounding the application, Rexulti represents a more familiar option with a robustly characterized safety profile that physicians may welcome. The FDA is expected to make a decision on Rexulti sNDA in February 2025.

Tags: Label Expansion (New Indication), New Drug Class

SEP-363856 | SUMITOMO | LOA: ABOVE AVERAGE | ↗

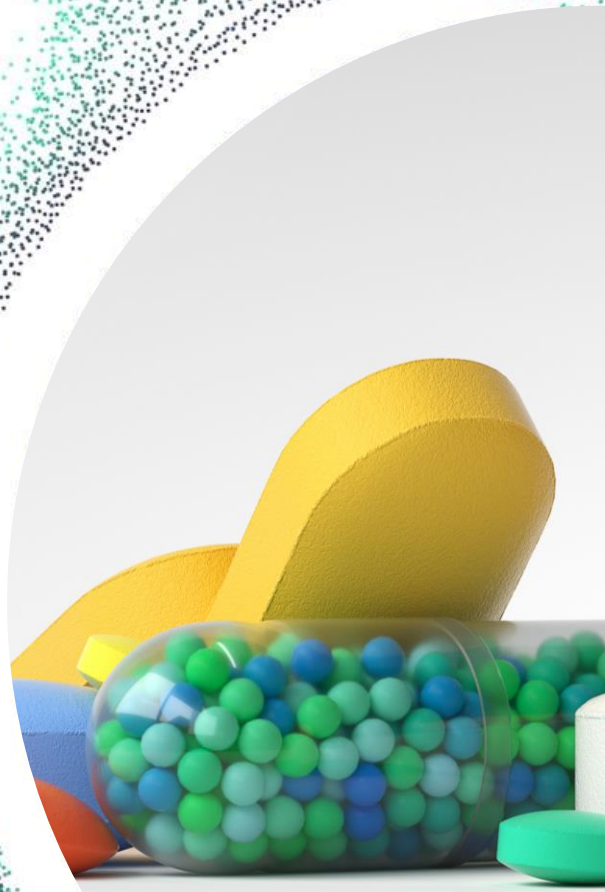
Schizophrenia

SEP-363856 (ulotaront) is a novel schizophrenia pipeline candidate with the potential to be a first-in-class TAAR1 agonist, although trial results thus far have been mixed. The drug was discovered by Sunovion, but exclusive rights to develop, manufacture, and commercialize now belong to Otsuka. Compared to existing schizophrenia drugs, SEP-363856 has serotonin 1A (5-HT1A) agonist activity but does not bind dopamine D2 or 5-HT2A receptors, which are associated with unwanted adverse metabolic side effects and weight gain. Due to this novel mechanism of action, the FDA granted the drug breakthrough therapy designation in May 2019. SEP-363856 has a broad commercial outlook, although the treatment of negative symptoms in schizophrenia appears to be a priority.

Phase II results (from patients with acute exacerbation of schizophrenia) were promising, demonstrating a statistically significant and clinically meaningful improvement in Positive and Negative Syndrome Scale (PANSS) total score compared to placebo at four weeks (-17.2 in the 50mg arm vs. -9.7 for placebo and -11.9 in the 75mg arm vs. -3.0 for placebo). Overall discontinuation rates were similar to placebo, and importantly the incidence of extrapyramidal symptoms was also similar to placebo, suggesting the drug can mitigate the tolerability problems associated with antipsychotics. Results from the DIAMOND 1 and DIAMOND 2 Phase III trials were markedly similar to the Phase II data; however, the trials did not meet their respective primary endpoints due to a high placebo response. Although the next steps are currently unclear, Otsuka is likely to continue pursuing an NDA for SEP-363856 given the positive Phase II data and the numerical decreases in PANSS scores in the Phase III trials.

Tags: New Drug Class, First Approval

Renal



FABHALTA | NVS | LOA: ABOVE AVERAGE | ↗

C3 Glomerulopathy (C3G)

Fabhalta (iptacopan) is an oral, Factor B inhibitor of the alternative complement pathway in development by Novartis, intended for the treatment of C3G.

The Phase III APPEAR-C3G study of Fabhalta vs. placebo demonstrated positive efficacy and favorable safety at the recent European Renal Association (ERA) Congress on May 25, 2024. Patients treated with Fabhalta in addition to supportive care achieved a 35.1% (p=0.0014) reduction in proteinuria (as measured by 24-hour urine protein to creatinine ratio [UPCR]) at 6 months when compared to placebo on top of supportive care. Additional data on the secondary endpoint of estimated glomerular filtration rate (eGFR), a measure of kidney function, showed a numerical improvement of +2.2 mL/min/1.73 m2 (p=0.1945) over 6 months with Fabhalta compared to placebo. Fabhalta also demonstrated no new safety signals.

C3G is a rare disease with poor prognosis, with half of the affected patients progressing to kidney failure requiring dialysis or transplant within 10 years of being diagnosed. There are currently no approved therapies for C3G, which adds to the blockbuster potential of Fabhalta should it get approved. Fabhalta was previously approved by the FDA in December 2023 and the EMA in May 2024 for the treatment of adults with the rare blood disorder paroxysmal nocturnal hemoglobinuria (PNH), which may add to the likelihood of the approval in C3G.

Tags: New Drug Class, Potential Blockbuster

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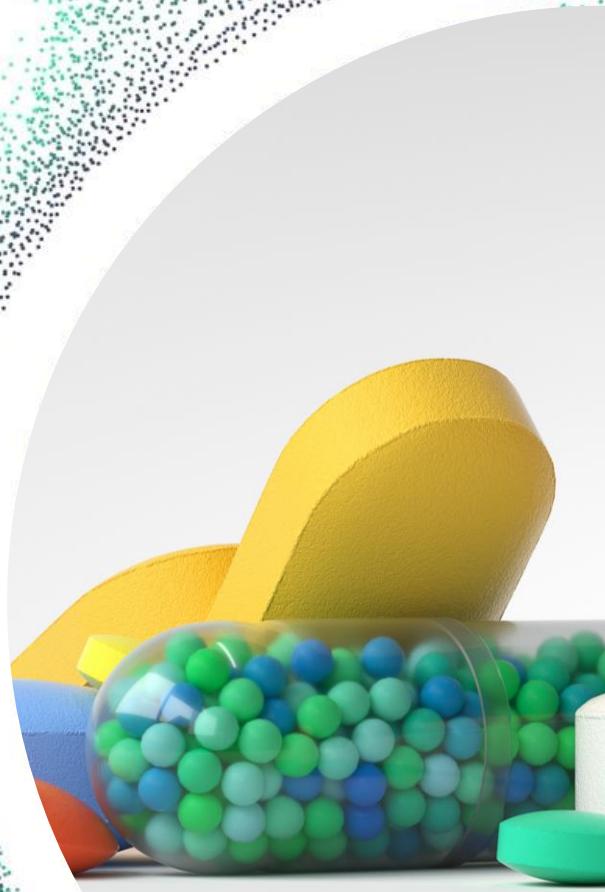
Respiratory



BREZTRI AEROSPHERE | AZN | LOA: AVERAGE | ↗

Asthma

Breztri Aerosphere is an ICS/LABA/LAMA combined inhaler approved for treating chronic obstructive pulmonary disease. It is currently being tested in Phase III studies (KALOS and LOGOS) for severe asthma patients, with topline data yet to be released.

Closed triple ICS/LABA/LAMA combination therapies are used for severe asthma patients with a history of exacerbations who are not adequately controlled with a high dose of an ICS and LABA. The added LAMA component may help further relax the airways in patients with more severe asthma, although some physicians may remain skeptical of the extent of the added benefit. Triple therapies delivered from a single inhaler may capture market share from patients currently using separate ICS/LABA and LAMA inhalers. The first ICS/LABA/LAMA triple inhaler, Trelegy Ellipta, has shown commercial success. Despite the pending release of Breztri Aerosphere's Phase III data and its potential second-to-market position, its large patient base and pulmonologists' familiarity suggest it is poised to become a blockbuster.

Tags: Potential Blockbuster, Label Expansion (New Indication)

DEPEMOKIMAB| GSK | LOA: ABOVE AVERAGE | ↗

Asthma

The success of Nucala and Fasenra has established interleukin-5 (IL-5) signaling as a key target for treating severe asthma patients with eosinophilic phenotypes. Depemokimab (GSK3511294), an anti-IL-5 antibody administered every six months, was developed to maintain GSK's market position established by Nucala, another anti-IL-5 antibody administered monthly, whose patent is set to expire in the next three to four years. In the eosinophilic asthma market, Nucala faces direct competition from Fasenra, a once-every-two-month injection preferred by pulmonologists according to our KOL interviews.

In May 2024, GSK released positive results from two pivotal trials, SWIFT-1 and SWIFT-2, of depemokimab. Though numerical data is yet to be disclosed, the drug met its primary endpoints of reducing the annualized rate of asthma attacks after one-year treatment, with balanced adverse events between the treatment and placebo groups. Following these positive outcomes, GSK is conducting an additional study, NIMBLE, to evaluate the effectiveness of depemokimab in patients who have switched from Nucala or Fasenra.

Tags: Potential Blockbuster

BRENSOCATIB | INSM | LOA: ABOVE AVERAGE | ↗

Bronchiectasis

Brensocatib is a once-daily oral medication developed to treat patients with non-cystic fibrosis bronchiectasis (NCFB), a condition with limited treatment options. NCFB patients experience symptoms such as shortness of breath, persistent cough, and excessive mucus production due to recurrent infections and airway inflammation. The condition can arise from genetic disorders, previous respiratory infections, airway injuries, immunodeficiency states, or unknown causes. NCFB not only imposes an economic burden but also increases the risk of all-cause mortality, primarily due to malignancy and respiratory-related deaths. Brensocatib works by inhibiting dipeptidyl peptidase 1, which activates neutrophil serine proteases (NSPs) involved in pathogen destruction and inflammatory mediation. Dysregulation of NSPs can lead to excessive secretion of active NSPs, resulting in damaging inflammation and neutrophil-mediated inflammatory diseases.

In its Phase III ASPEN study, brensocatib demonstrated promising results, including a 19% reduction in the annual rate of pulmonary exacerbations, a 26% reduction in severe pulmonary exacerbations, an 18% extension in the time between exacerbations, prevention of lung function decline, and a 3.8-point improvement in overall quality of life compared to placebo treatment at higher doses of 25 mg. Although the trial did not specifically address mortality or reduced respiratory infection rates, these topline results indicate brensocatib's potential in alleviating the disease. These findings, along with its favorable safety profile, suggest that brensocatib could significantly improve the lives of NCFB patients.

Tags: First Approval, New Drug Class, Practice Changing

ZEPBOUND | LLY | LOA: ABOVE AVERAGE | ↗

Sleep Apnea

Zepbound is a dual GIP (glucose-dependent insulinotropic polypeptide) and GLP-1 (glucagon-like peptide-1) receptor agonist that integrates the actions of the GIP and GLP-1 incretins into a single molecule. Patients with OSA are often obese and experience episodes of shallow breathing or they can also stop breathing for periods during sleep. These events occur due to the collapse of the upper airway. Patients can develop oxygen desaturation and many snore or briefly wake during the night. As a result of the interrupted sleep, patients may experience daytime symptoms including morning headaches, excessive daytime sleepiness, fatigue, cognitive impairment, and mood changes. Lifestyle changes, such as improving sleep hygiene and weight loss can be beneficial, but more severe OSA can require mechanical interventions like nasal continuous positive airway pressure (CPAP) or even surgery. A drug treatment that can improve OSA (such as zepbound) would be highly desirable considering how invasive these latter interventions can be.

In the Phase III SURMOUNT-OSA clinical trial, tirzepatide injection (10 mg or 15 mg) reduced the apnea-hypopnea index (AHI) compared to placebo, achieving the primary endpoints. Based on these results, Eli Lilly submitted tirzepatide for the treatment of moderate-to-severe OSA and obesity to the U.S. Food and Drug Administration (FDA) with an approval decision anticipated on December 21, 2024. Eli Lilly's asset is likely to be first to market with the added bonus of broader cardiometabolic benefits and the support of the large pharmaceutical company's sales and marketing power.

Tags: Potential Blockbuster, Practice Changing

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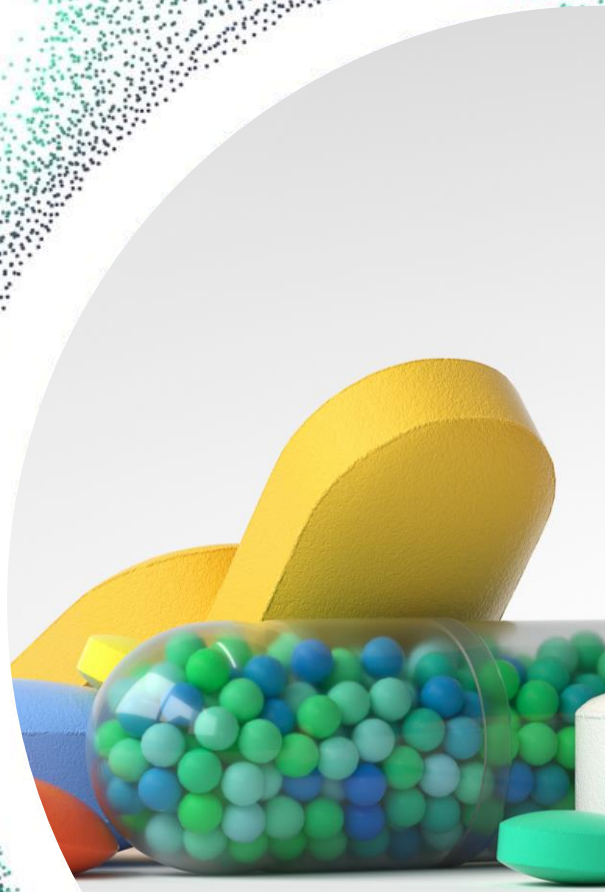
Appendix



Appendix

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Drugs covered (listed alphabetically):

APITEGROMAB |SRRK|
AT-007 |APLT|
AVUTOMETINIB |VSTM|
AXS-12 |AXSM|
BLENREP |GSK|
BRENSOCATIB |INSM|
BREXAFEMME |GSK|
BREZTRI AEROSPHERE |AZN|
CAGRISEMA |NVO |
CAPLYTA |ITCI|
CARDAMYST |MIST|
CLR 131 |CLRB|
CRINECERFONT |NBIX|
DATOPOTAMAB DERUXTECAN |DSNKY|
DEFACTINIB |VSTM|
DEPEMOKIMAB |GSK|
DERAMIOCEL |CAPR|
ELAMIPRETIDE |MITO|
ENHERTU |DSNKY|
FABHALTA |NVS|
FITUSIRAN |SNY|
GRANITE |GRTS|
GSK2140944 |GSK|
GSK3536819A |GSK|
HIZENTRA |CSL|
INAVOLISIB |ROG|
INO-3107 |INO|
INPEFA |LXRX|
IVONESCIMAB |SMMT|
JAKAFI |INCY|
KERENDIA |BAYN|
LERODALCIBEP |LIBT|
LNZ-100 |LENZ|
LYNPARZA |AZN|
MIM8 |NVO|
mRNA-1010 |MRNA|
NRX-101 |NRXP|
OCLAIZ |CAMX|
OLEZARSEN |IONS|
OZEMPIC |NVO|
PATRITUMAB DERUXTECAN |MRK|
PLOZASIRAN |ARWR|
PLUVICTO |NVS|
PRGN-2012 |PGEN|
PYRUKYND |AGIO|
QRX-003 |ALM|
REVUMENIB |SNDX|
REXULTI |OTSUKA|
RP-L102 |RCKT|
SCEMBLIX |NVS|
SEP-363856 |SUMITOMO|
SOTYKTU |BMY|
SUNLENCA |GILD|
SUSVIMO – DME |ROG|
SUSVIMO – DR |ROG|
TONMYA |TNXP|
TREMFYA – CD |JNJ|
TREMFYA – UC |JNJ|
UPLIZNA – IgG4-RD |AMGN|
UPLIZNA – MG |AMGN|
UPSTAZA |PTCT|
VESIGEL |URGN|
VTAMA |DRMT|
VYLOY |ASTELLAS|
XPOVIO |KPTI|
ZEGALOGUE |NVO|
CAGRISEMA |NVO|
ZOLGENSMA |NVS|
ZORYVE TOPICAL FOAM |ARQT|

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BIOMEDTRACKER
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Biomedtracker is an independent research service that offers proprietary clinical assessments of developmental drugs within a comprehensive and intuitive drug information database. Clients from the pharmaceutical, biotech, and investment industries rely on Biomedtracker for its insight on the likelihood of approval, commercial potential, and future data and regulatory catalysts for drugs within the competitive landscape of every important disease and indication. Over recent years, Biomedtracker has become the leader in providing objective information alongside evidence-based clinical assessments and investment research on pipeline drugs worldwide.

DATAMONITOR HEALTHCARE
CITELINE COMMERCIAL

Datamonitor Healthcare provides a total business information solution to the pharmaceutical and healthcare industries. Datamonitor Healthcare provides expertise in therapeutic, strategic, and company market analysis, and competitive intelligence to the global pharmaceutical and healthcare markets, enabling them to ultimately make valuable and profitable decisions.