EXPRESS SCRIPTS®

EMERGING THERAPEUTICS

Specialty Pipeline

September 2021

	Pipeline Drug	Current Status	Anticipated Approval	What is this drug being developed for?
1.	abrocitinib (Pfizer)	NDA Filed	2021 2021	Janus kinase 1 (JAK1) inhibitor for the treatment of patients with moderate-to-severe atopic dermatitis (AD); oral Breakthrough Therapy
2.	adagrasib (Mirati Therapeutics)	Phase 2	2022	KRAS G12C specific inhibitor for the treatment of KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC); oral Breakthrough Therapy PGx
3.	arimoclomol (Miplyffa - Orphazyme)	Complete Response	2022	Molecular chaperone activator that stimulates the normal cellular protein repair pathway for the treatment of Niemann-Pick Disease Type C (NPC); oral Breakthrough Therapy Orphan Drug
4.	bardoxolone methyl (Reata Pharmaceuticals)	NDA Filed	2022 02/25/2022	antioxidant inflammation inhibitor that acts on Nrf2 for the treatment of chronic kidney disease caused by Alport Syndrome; oral Orphan Drug
5.	betibeglogene autotemcel (Zynteglo – Bluebird Bio)	BLA Filed	2022	Gene therapy for the treatment of β-globin gene therapy for the treatment of transfusion-dependent β thalassemia; IV infusion Breakthrough Therapy Orphan Drug
6.	bimekizumab (UCB)	BLA Filed	2021 10/15/2021	Monoclonal antibody that blocks the effects of IL-17A and IL-17F for the treatment of moderate-to-severe plaque psoriasis; SC injection
7.	ciltacabtagene autoleucel (JNJ-4528 – Janssen)	BLA Filed	2021 11/29/2021	B-cell maturation antigen (BCMA)-directed chimeric antigen receptor T cell (CAR-T) therapy in previously treated patients with multiple myeloma; IV infusion Breakthrough Therapy Orphan Drug
8.	deucravacitinib (Bristol Myers Squibb)	Phase 3	2022	tyrosine kinase 2 (TYK2) inhibitor for use in patients with moderate to severe plaque psoriasis; oral therapy.
9.	efgartigimod (Argenx)	BLA Filed	2021 12/17/2021	FcRn-targeting antibody fragment designed to depleted pathogenic IgGs for the treatment of myasthenia gravis (MG); IV infusion Orphan Drug
10.	eladocagene exuparvovec (PTC Therapeutics)	Phase 3	2022	Recombinant, adeno-associated virus, containing the human cDNA encoding the AADC enzyme for the treatment of AADC deficiency; intracerebral infusion Orphan Drug

PGx = Pharmacogenetic test in development

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11.	futibatinib (Taiho Oncology)	Phase 3	2022	fibroblast growth factor (FGFR) 1-4 inhibitor for the treatment of patients with previously treated locally advanced or metastatic cholangiocarcinoma harboring FGFR2 gene rearrangements, including gene fusions; oral Breakthrough Therapy Orphan Drug PGx
12.	inclisiran (Leqvio - Novartis)	NDA Filed	2022 01/01/2022	small interfering RNA (siRNA) therapy that lowers low-density lipoprotein cholesterol (LDL-C) for the treatment of adults with atherosclerotic cardiovascular disease (ASCVD) or heterozygous familial hypercholesterolemia (HeFH) who have elevated LDL-C while being on a maximum tolerated dose of a lipid-lowering therapy (LLT); subcutaneous injection (administration by a healthcare professional)
13.	obeticholic acid (Intercept Pharmaceuticals)	Complete Response	2022	Farnesoid X receptor (FXR) agonist for the treatment of nonalcoholic steatohepatitis (NASH); oral Breakthrough Therapy Orphan Drug
14.	pegunigalsidase alfa (Protalix BioTherapeutics)	Complete Response	2022	Plant cell-expressed, recombinant alpha-galactosidase-A enzyme for the treatment of Fabry disease; IV infusion (monthly) Breakthrough Therapy Orphan Drug
15.	sutimlimab (Sanofi)	Complete Response	2022	anti-C1s antibody for the treatment of primary cold agglutinin disease (CAD); IV infusion Breakthrough Therapy Orphan Drug
16.	teplizumab (Provention Bio)	Complete Response	2021	Humanized monoclonal antibody engineered to alter the function of the T lymphocytes that mediate the destruction of the insulin-producing beta cells of the islets of the pancreas to delay or prevent the onset of type 1 diabetes in at-risk individuals; IV Breakthrough Therapy
17.	tezepelumab (Amgen/AstraZeneca)	BLA Filed	2022 01/10/2022	anti-thymic stromal lymphopoietin (anti-TSLP) monoclonal antibody for the treatment of severe, uncontrolled asthma; SC Breakthrough Therapy
18.	tralokinumab (LEO Pharma)	Complete Response	2021	Anti-IL-13 for the treatment of moderate to severe atopic dermatitis (AD); SC
19.	valoctocogene roxaparvovec (Roctavian – BioMarin Pharmaceuticals)	Complete Response	2022	Adenovirus-associated virus vector-mediated the transfer of Human Factor VIII gene in patients with severe hemophilia A; IV infusion Breakthrough Therapy Orphan Drug
20.	vosoritide (Voxzogo - BioMarin)	NDA Filed	2021 11/20/2021	Analog of C-type Natriuretic Peptide (CNP) for the treatment of children with achondroplasia; SC Orphan Drug

PGx = Pharmacogenetic test in development

Top 20 Specialty Pipeline Report: Drug Review

1. abrocitinib (Pfizer)

Current Status: NDA filed. Priority review granted. Breakthrough therapy for atopic dermatitis indication. July 2021: approval delayed.

Route of Administration/Dosing: oral tablet (100 mg or 200 mg orally once daily)

Proposed Indication(s): treatment for moderate to severe atopic dermatitis (AD) in adults and adolescents 12 years and older.

Mechanism of Action: Abrocitinib is a small molecule inhibitor of Janus kinase (JAK) 1. Selectively inhibiting JAK 1 is thought to modulate pro-inflammatory cytokines, including interleukin (IL)-4, IL-13, IL-31, and interferon gamma, which are key drivers in the pathophysiology of atopic dermatitis.

Patient Impact: Atopic dermatitis (AD) is a chronic skin disease characterized by inflammation of the skin and skin barrier defects. Children are often affected by AD during their first year of life and it will appear as dry, scaly patches on the scalp, arms and legs. The affected areas are often very itchy, which can range in severity, but is generally associated with inability to sleep and increased risk of skin infection. AD can be long-lasting and continue throughout adulthood. If left untreated, affected skin can become bumpy, discolored, and remain persistently itchy. The American Academy of Dermatology (AAD) estimates that between 10% and 20% of children and about 1% to 3% of adults are affected by AD. There are approximately 3 million children in the US with moderate AD and 800,000 children in the US with severe AD. There are approximately 1.5 million adults in the US with moderate AD and 500,000 adults in the US with severe AD. Most patients (90%) have disease onset before 5 years of age, as AD rarely begins in adulthood. Incidence of AD has increased 2- to 3-fold since the 1970s and is commonly associated with additional atopic manifestations, such as food allergies, allergic rhinitis, and asthma. About 20% of children who develop AD before 2 years of age will have persisting symptoms of disease and 17% will have intermittent symptoms by 7 years of age. In many cases, childhood AD resolves by the time a child reaches adulthood, but approximately 10% to 30% of patients will continue to have symptoms of disease throughout their lifetime.

Cost Estimates (per Patient): $55,000/yr

Current Therapies: Dupixent (dupilumab), a monoclonal antibody that antagonizes interleukin (IL)-4 and IL-13. Following a one-time loading dose of 600 mg (administered as two 300 mg subcutaneous injections), the recommended dose of Dupixent is 300 mg subcutaneously every other week. Other therapies to treat atopic dermatitis include topical steroids; phototherapy; topical immunomodulators (calcineurin inhibitors) such as Protopic (tacrolimus) and Elidel (pimecrolimus); Xolair (omalizumab), a monoclonal antibody that blocks IgG function that is sometimes used off label for AD. Methotrexate, cyclosporine, and mycophenylate mofetil are also sometimes used in patients with severe disease.

Pipeline Product(s): Lilly and Incyte's baricitinib is a once-daily oral JAK inhibitor that has greater inhibitory potency at JAK1, JAK2, and tyrosine kinase (TYK)-2 relative to JAK3. It received FDA approval for moderately-to-severely active rheumatoid arthritis (RA) in May 2018 and is currently in phase III development for moderate-to-severe AD with anticipated completion in August 2019. AbbVie's upadacitinib is a once-daily oral selective JAK1 inhibitor currently in phase III development for moderate-to-severe AD with probable completion in September 2020. AbbVie is also seeking approval of upadacitinib for Crohn's Disease, psoriatic arthritis, rheumatoid arthritis, ulcerative colitis, and axial spondyloarthritis. LEO Pharma's tralokinumab is a monoclonal antibody that selectively inhibits IL-13 and is given through subcutaneous injection every two weeks. It is currently in phase III development for moderate-to-severe AD and uncontrolled asthma. Xbiotech's bermekimab is a monoclonal antibody that selectively inhibits IL-1-alpha. Bermekimab is a novel agent in phase II development for atopic dermatitis and hidradenitis suppurativa. Lilly and Incyte's ruxolitinib is an oral JAK inhibitor with approved indications for myelofibrosis, polycythemia vera, and steroid-refractory acute graft-versus-host disease. Ruxolitinib topical cream is currently in phase II development for moderate-to-severe AD. Dermira's lebrikizumab is a monoclonal antibody that targets IL-13 and is currently in phase II development for AD.

Comments: In February 2018, Pfizer gained breakthrough designation for abrocitinib in moderate-to-severe atopic dermatitis. On Oct. 12, 2019 Pfizer announced complete results from a Phase 3, 12-week, pivotal study (JADE MONO-1). Abrocitinib, an investigational oral Janus kinase 1 (JAK1) inhibitor, met all the co-primary and key secondary endpoints, which were related to skin clearance and itch relief compared to placebo. Safety data showed that both evaluated doses of abrocitinib (200mg and 100mg) were well tolerated and were consistent with a companion study

(JADE MONO-2). The co-primary study endpoints in JADE MONO-1 were the proportion of patients who achieved an Investigator Global Assessment (IGA) score of clear (0) or almost clear (1) skin and two-point or greater improvement relative to baseline; and the proportion of patients who achieved at least a 75% or greater change from baseline in their Eczema Area and Severity Index (EASI) score. The key secondary endpoints were the proportion of patients achieving a four-point or larger reduction in itch severity measured with the pruritus numerical rating scale (NRS), and the magnitude of decrease in the Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD), a patient-reported measurement scale developed by Pfizer. Other secondary endpoints included the proportion of patients who achieved a 90% or greater change in EASI score, and the percentage change from baseline in their SCORing Atopic Dermatitis (SCORAD) response at all scheduled time points. After 12 weeks, 43.8% of subjects on high-dose abrocitinib had an Investigator Global Assessment (IGA) score of clear or almost clear skin, compared to 7.9% in the placebo group. That was one of two co-primary endpoints. The other showed 62.7% of patients on high-dose abrocitinib experienced a 75% or greater improvement on the EASI symptom score, compared to 11.8% in the placebo cohort. The most frequently reported treatment-emergent adverse events in abrocitinib-treated patients (200mg, 100mg) were short-lasting nausea (20.1%, 9.0%), headache (9.7%, 7.7%), and nasopharyngitis (11.7%, 14.7%), while for placebo, it was dermatitis (16.9%). On Mar. 18, 2020, Pfizer announced that its Phase 3 trial, JADE COMPARE, met its co-primary efficacy endpoints: the proportion of patients who achieved an IGA of clear (0) or almost clear (1) and a two-point or greater reduction from baseline at Week 12; and the proportion of patients who achieved at least a 75% or greater change from baseline in their EASI score at Week 12. Results showed that the percentage of patients achieving each co-primary efficacy endpoint at Week 12 was statistically superior with both doses of abrocitinib than with placebo. Superiority to placebo with both doses was maintained at Week 16. Dupilumab, the active control on these primary endpoints, demonstrated superiority to placebo at Week 12 and Week 16. A secondary endpoint, the percentage of patients who had a clinically significant reduction in itch by Week 2 of treatment was statistically superior for the 200mg abrocitinib dose compared to dupilumab and numerically higher, but not statistically significantly higher, for the 100mg abrocitinib dose compared to dupilumab. Safety results showed that 61.9% of patients receiving abrocitinib 200mg experienced adverse events compared to placebo (53.4%), abrocitinib 100mg (50.8%), and dupilumab (50%). The percentage of patients experiencing serious adverse events and adverse events leading to study discontinuation were similar across the placebo (3.8% each), abrocitinib 100mg (2.5% each), abrocitinib 200mg (0.9% and 4.4%, respectively), and dupilumab (0.8% and 3.3%, respectively) treatment arms. On June 3, 2020, Pfizer announced that JAMA Dermatology published complete results from the second Phase 3 monotherapy pivotal study (JADE MONO-2) in patients aged 12 and older with moderate to severe atopic dermatitis (AD). Both doses (100mg and 200mg once daily) of abrocitinib met all co-primary and key secondary endpoints and were generally well tolerated. JADE MONO-2 was a randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of two doses of abrocitinib monotherapy over 12 weeks. A total of 391 subjects with moderate to severe atopic dermatitis were randomized to abrocitinib 200mg, abrocitinib 100mg, and placebo in the trial. Efficacy endpoints evaluated measures of improvements in skin clearance, disease extent and severity, and itch. The co-primary study endpoints in JADE MONO-2 were the proportion of patients who achieved: an Investigator Global Assessment (IGA) score of clear (0) or almost clear (1) skin and two-point or greater improvement relative to baseline at Week 12 and at least a 75% or greater change from baseline in their Eczema Area and Severity Index (EASI) score at Week 12. The key secondary endpoint was the proportion of patients achieving a four-point or larger reduction in itch severity measured with the Peak Pruritus Numerical Rating Scale (PP-NRS) at Weeks 2, 4, and 12. The proportion of patients who achieved a 90% or greater change from baseline in EASI score at Week 12 was included as a secondary endpoint. By Week 12, a greater proportion of patients on either dose of abrocitinib achieved the IGA, EASI-75, PP-NRS, and EASI-90 responses compared to those on placebo. The following co-primary efficacy and secondary endpoint results were seen at Week 12: IGA: abrocitinib 200mg 38.1%, abrocitinib 100mg 28.4%, placebo 9.1%; EASI-75: abrocitinib 200mg 61%, abrocitinib 100mg 44.5%, placebo 10.4%; PP-NRS: abrocitinib 200mg 55.3%, abrocitinib 100mg 45.2%, placebo 11.5%; EASI-90: abrocitinib 200mg 37.7%, abrocitinib 100mg 23.9%, placebo 3.9%. The most frequently reported treatment-emergent adverse events were nausea, nasopharyngitis, and atopic dermatitis in the abrocitinib 200mg, abrocitinib 100mg, and placebo groups, respectively. Observed serious adverse events that were considered related to treatment were reported for two patients in the abrocitinib 100mg group (herpangina and pneumonia) and one patient with two events in the placebo group (eczema herpeticum and staphylococcal infection). Platelet counts had a median decrease of 26% in patients on abrocitinib 200mg, 19% in patients taking abrocitinib 100mg and less than 1% in the placebo group. There were no serious treatment-related adverse events in the 200mg group. Serious infections occurred in none of the patients taking abrocitinib 200mg, 1.9% of patients in the 100mg group and 1.3% in the placebo group. The rate of discontinuation due to an adverse event was abrocitinib 200mg 3.2%, abrocitinib 100mg 3.8%, placebo 12.8%. The most frequently reported Aes leading to treatment discontinuation were headache in the abrocitinib 200mg group

and atopic dermatitis in the abrocitinib 100mg and the placebo groups. On June 10, 2020, Pfizer announced positive top-line results from the Phase 3 JADE TEEN study of abrocitinib in patients 12 to <18 years of age with moderate to severe atopic dermatitis (AD) who were also on background topical therapy. Both doses of abrocitinib met the co-primary endpoints and were generally well tolerated. The safety profile seen with abrocitinib was consistent with previous studies. Safety results showed that a higher percentage of patients receiving either the 100mg or 200mg dose of abrocitinib experienced adverse events compared to placebo (56.8%, 62.8%, and 52.1%, respectively). The percentage of patients who experienced serious adverse events or adverse events leading to study discontinuation were similar across the placebo (2.1% each), abrocitinib 100mg (0% and 1.1%, respectively), and abrocitinib 200mg (1.1% and 2.1%, respectively) treatment arms. On Sept. 15, 2020, Pfizer announced that it submitted its application for approval of abrocitinib, an oral JAK inhibitor, for atopic dermatitis in Aug. If priority review is granted, approval is expected in April 2021. On Oct .27, 2020, Pfizer announced that FDA granted priority review, confirming expected approval in April 2021. On Mar. 25, 2021, the JADE COMPARE trial was published online in the New England Journal of Medicine. In the phase 3, double-blind trial, patients with atopic dermatitis that was unresponsive to topical agents or that warranted systemic therapy were randomly assigned (in a 2:2:2:1 ratio) to receive 200 mg or 100 mg of abrocitinib orally once daily, 300 mg of dupilumab subcutaneously every other week (after a loading dose of 600 mg), or placebo; all the patients received topical therapy. The primary end points were an Investigator's Global Assessment (IGA) response (defined as a score of 0 [clear] or 1 [almost clear] on the IGA [scores range from 0 to 4], with an improvement of ≥2 points from baseline) and an Eczema Area and Severity Index–75 (EASI-75) response (defined as ≥75% improvement from baseline in the score on the EASI [scores range from 0 to 72]) at week 12. The key secondary end points were itch response (defined as an improvement of ≥4 points in the score on the Peak Pruritus Numerical Rating Scale [scores range from 0 to 10]) at week 2 and IGA and EASI-75 responses at week 16. A total of 838 patients underwent randomization; 226 patients were assigned to the 200-mg abrocitinib group, 238 to the 100-mg abrocitinib group, 243 to the dupilumab group, and 131 to the placebo group. An IGA response at week 12 was observed in 48.4% of patients in the 200-mg abrocitinib group, 36.6% in the 100-mg abrocitinib group, 36.5% in the dupilumab group, and 14.0% in the placebo group (P<0.001 for both abrocitinib doses vs. placebo); an EASI-75 response at week 12 was observed in 70.3%, 58.7%, 58.1%, and 27.1%, respectively (P<0.001 for both abrocitinib doses vs. placebo). The 200-mg dose, but not the 100-mg dose, of abrocitinib was superior to dupilumab with respect to itch response at week 2. Neither abrocitinib dose differed significantly from dupilumab with respect to most other key secondary end-point comparisons at week 16. Nausea occurred in 11.1% of the patients in the 200-mg abrocitinib group and 4.2% of those in the 100-mg abrocitinib group, and acne occurred in 6.6% and 2.9%, respectively. On April 7, 2021, Pfizer announced that FDA extended its review of abrocitinib by three months to early in the third quarter of 2021. On July 21, 2021, Pfizer announced that approval has been delayed. FDA is continuing to review Xeljanz safety as part of the ORAL Surveillance study. It possible FDA will hold an ad board to review JAK inhibitor safety. Approval is likely delayed until late-2021 or early-2022. On Aug. 30, 2021, Pfizer announced that JADE DARE, a 26-week, randomized, double-blind, double-dummy, active-controlled, multi-center Phase 3 study, met its co-primary and key secondary efficacy endpoints. The study showed that abrocitinib was statistically superior compared to dupilumab in each evaluated efficacy measure and had a safety profile consistent with previous studies. The head-to-head study was designed to directly compare the efficacy of abrocitinib 200mg versus dupilumab 300mg, in adult participants on background topical therapy with moderate to severe atopic dermatitis (AD). Abrocitinib 200mg was administered by once-daily oral tablet and dupilumab was administered by subcutaneous injection every other week following a 600mg induction dose. The co-primary efficacy endpoints in JADE DARE were the proportion of patients achieving at least a 4-point improvement in the severity of Peak Pruritus Numerical Rating Scale (PP-NRS4) from baseline at Week 2 and the proportion of patients achieving Eczema Area and Severity Index (EASI)-90 (≥90% improvement from baseline) at Week 4. The key secondary endpoint was the proportion of patients achieving EASI-90 at Week 16. The study will allow assessment of any difference in efficacy that may persist at month 6 of treatment. A larger percentage of patients treated with abrocitinib 200mg experienced adverse events compared to dupilumab 300mg. The proportion of patients experiencing serious adverse events, severe adverse events, and adverse events leading to study discontinuation were similar in both treatment arms. Two deaths occurred in patients treated with abrocitinib 200mg, which were characterized by the investigator as unrelated to the study drug. One death was attributed to COVID-19 and the second was attributed to intracranial hemorrhage and cardiorespiratory arrest, and classified as a major adverse cardiovascular event (MACE). There were no cases of malignancies or venous thromboembolism (VTE) events confirmed through adjudication. The safety profile seen with abrocitinib was consistent with previous studies in the JADE program.

2. adagrasib (Mirati Therapeutics)

Current Status: Breakthrough therapy. Phase III. Approval expected in 2022.

Route of Administration/Dosing: Oral (600mg twice daily)

Proposed Indication(s): Treatment of patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), as determined by an FDA-approved test, following at least one prior systemic therapy.

Mechanism of Action: KRAS G12C inhibitor

Patient Impact: Around 14% of NSCLC patients carry KRAS G12C mutations, and the cancer-linked gene is implicated in up to a third of all human cancers. KRAS G12C mutations are frequently linked to negative outcomes. Each year in the US, approximately 25,000 patients with NSCLC with G12C mutations may be candidates for treatment with a KRAS inhibitor.

Cost Estimates (per Patient): $215,000/yr

Current Therapies: Amgen's Lumakras (sotorasib) is an oral KRAS G12C inhibitor that was approved for the treatment of adult patients who have advanced or metastatic non-small cell lung cancer (NSCLC) that tests positive for KRAS G12C mutations and that has been treated systemically one or more times with chemotherapy (chemo) and/or immunotherapy. Lumakras was approved on May 28, 2021.

Pipeline Product(s): Companies with earlier-stage KRAS programs include Boehringer Ingelheim, Johnson & Johnson/Wellspring, Merck/Moderna and AstraZeneca/Ionis.

Comments: On Oct. 25, 2020, Mirati Therapeutics reported updated clinical data of adagrasib. Preliminary efficacy data as of August 30, 2020 in patients with advanced non-small cell lung cancer (NSCLC) treated with adagrasib as a monotherapy at a 600 mg BID dose: Patients had a median of two prior systemic treatments, including all patients receiving prior treatment with platinum-based chemotherapy regimens and 92% of patients receiving prior treatment with an anti-PD-1 /L1 inhibitor. Efficacy data from pooled Phase 1/1b cohort and Phase 2 registration-enabling cohort (n=51): 45% (23/51) confirmed objective response rate (ORR); 70% (16/23) of responders had a best tumor response greater than 40%; 96% (49/51) disease control rate (DCR); 3.6 months median duration of follow-up: 65% (33/51) of patients remain on treatment; 83% (19/23) of responders have not progressed and remain on treatment. Adagrasib 600mg BID was well tolerated in monotherapy and combination trials with pembrolizumab, cetuximab and TNO-155, a SHP-2 inhibitor. In a pooled assessment of 110 patients harboring a G12C mutation in NSCLC, CRC and other solid tumors, monotherapy adagrasib has been well tolerated. Side effects included nausea (52%), diarrhea (58%), vomiting (36%), fatigue (42%), and increased levels of an enzyme that indicates minor liver irritation (20%). The only serious adverse side effect to occur in more than one patient was low sodium in the blood, which occurred in two patients. 4.5% of treatment-related adverse events led to discontinuation.

Mirati plans on submitting a New Drug Application for accelerated approval of adagrasib as a monotherapy treatment for patients in 2nd / 3rd line NSCLC in the second half of 2021. It is in monotherapy and combination trials for earlier lines of therapy in NSCLC and colorectal cancer (CRC). The Ph1/2 KRYSTAL-01 study is evaluating adagrasib with Keytruda in first-line NSCLC and with Erbitux in second-line CRC. KRAS G12C mutations are found in approximately 3-4% of patients with CRC.

3. arimoclomol (Miplyffa - Orphazyme)

Current Status: NDA filed. Orphan drug. Breakthrough therapy designation. June 18, 2021: complete response letter. Approval possible in 2022.

Route of Administration/Dosing: Oral (150mg to 600mg per day depending on weight and divided into three doses daily)

Proposed Indication(s): treatment of Niemann-Pick Disease Type C (NPC)

Mechanism of Action: heat shock factor 1 (HSF1) stimulant; Because arimoclomol crosses the blood-brain barrier, its concentrations in central nervous system (CNS) fluid approximately match those in blood. Additionally, it is 80% to 90% bioavailable, allowing for small doses to be effective. In stressed cells, it boosts and lengthens the activity of HSF1, which controls production of heat shock proteins (HSP). Increased levels of HSP help to readjust misfolded proteins, remove damaged material, enhance cellular repair and increase liposome activity.

Patient Impact: NPC is one of several very rare inherited lysosomal storage conditions that are difficult to diagnose. Patients who have it cannot break down lipids, including cholesterol, which collects in the liver, lungs and spleen. Other lipids lodge in the brain, causing difficulties with muscle tone and movement, speech, swallowing and walking. Patients, who gradually lose nerve function, get progressively worse as lipids accumulate. Symptoms may be noticeable at birth. Infants who have NPC may have jaundice, some have foam cells in the lungs and many have enlarged livers and/or spleens. Vertical gaze palsy (the inability to move the eyes up and down) may also be an early symptom. Epilepsy and mental health conditions are fairly common, as well. For many patients, problems often mistaken for behavioral and learning disorders begin in middle or late childhood. Those who are diagnosed in teen or adult years are more likely to have depression or schizophrenia-like symptoms. In general, the earlier the symptoms appear, the more severe the condition and the faster its progression. NPC nearly always is fatal -- usually before the age of 40. At an estimated one case of NPC in 120,000 live births, fewer than 50 new cases are discovered in the U.S each year. The total U.S. patient population is believed to be about 200, although many cases may be misdiagnosed as other conditions with similar symptoms.

Cost Estimates (per Patient): $500,000/yr

Current Therapies: Zavesca® (miglustat - Actelion) capsules, which is approved in Europe for treating NPC, is used off-label in the U.S. However, no drugs that affect progression of NPC presently are FDA approved in the United States. Therapy consists of controlling symptoms with treatment plans tailored to each individual and typically managed by several medical specialists. Drugs that lower cholesterol are not effective in reducing lipid deposits from NPC.

Pipeline Product(s): There are no other drugs in late-phase development for NPC.

Comments: On Feb. 6, 2019, CytRx Corporation highlighted positive Phase II/III clinical trial data from arimoclomol licensee Orphazyme A/S. Arimoclomal was studied in a 12-month double-blinded, placebo-controlled phase II/III trial that enrolled 44 patients with NPC over the age of two years. All patients continued receiving their usual treatment. In this full data set analysis, treatment with arimoclomol adjunct to routine clinical care resulted in a 74% reduction in disease progression (p-value=0.0506) as measured by the primary endpoint, 5-domain NPC Clinical Severity Scale (NPC-CSS). In the predefined subgroup of patients of 4 years and older (44 out of 50 randomized patients in the trial), the treatment difference was statistically significant with a minimal disease progression at month 12 in the arimoclomol-treated group (p-value =0.0219). A highly statistically significant treatment difference was observed in another predefined subgroup analysis, requested by the EMA, that compared arimoclomol to placebo control in patients receiving miglustat as a part of routine clinical care (p-value =0.0071). In agreement with the FDA, treatment response defined as no change or improved on the Clinical Global Impression of Improvement scale (CGI-I) was included as a co-primary endpoint. A responder rate of more than 50% in the placebo control group impeded the ability to show an overall effect on this endpoint. However, when considering patients who severely progressed during the trial, only 10.7% of the arimoclomol-treated patients got 'much worse' or 'very much worse' compared to 26.7% in the placebo control group. Forty-one patients continued in an open-label extension of the trial; with all taking arimoclomal for an additional 12 months. While disease progression slowed for all patients, those who had two full years of active treatment generally showed better results than participants who previously received placebos. The implication is that earlier treatment with arimoclomol delays the disease process. Overall, baseline characteristics were well-balanced across treatment arms. Arimoclomol was well-tolerated with a similar incidence of adverse events (AEs) for arimoclomol (88.2%) and placebo control (81.3%). Serious AEs occurred less frequently in the arimoclomol group (14.7%) compared to placebo control (37.5%). On July 21, 2020, CytRx Corporation highlighted that Orphayzme A/S announced they have completed their rolling submission of their New Drug Application (NDA) with the U.S. Food

and Drug Administration (FDA) for arimoclomol for the treatment of Niemann-Pick Disease Type-C (NPC). Orphazyme is also developing arimoclomol for amyotrophic lateral sclerosis (ALS), Gaucher disease and sporadic Inclusion Body Myositis. (sIBM). On December 27, 2020, Orphazyme announced that the FDA has extended the review period of the NDA for arimoclomol for the treatment of Niemann-Pick Disease Type C (NPC) by a standard extension period of three months. This extension is necessary for the FDA to complete its review of recently submitted QT study, hepatic and renal safety trial data. The updated Prescription Drug User Fee Act (PDUFA) target action date is June 17, 2021. On June 18, 2021, Orphazyme announced it had received a Complete Response Letter (CRL) from the U.S. Food and Drug Administration (FDA) following its review of the new drug application for arimoclomol, a heat shock protein amplifier intended for the treatment of Niemann-Pick disease type C (NPC). The FDA issued the CRL based on needing additional qualitative and quantitative evidence to further substantiate the validity and interpretation of the 5-domain NPC Clinical Severity Scale (NPCCSS) and, in particular, the swallow domain. Further, the FDA noted in the CRL that additional data are needed to bolster confirmatory evidence beyond the single phase 2/3 clinical trial to support the benefit-risk assessment of the NDA.

4. bardoxolone methyl (Reata Pharmaceuticals)

Current Status: Orphan drug. NDA filed. Approval expected by Feb. 25, 2022

Route of Administration/Dosing: oral capsules (titrated up to a maximum dose of 20mg or 30mg once daily)

Proposed Indication(s): to treat chronic kidney disease (CKD) due to Alport syndrome

Mechanism of Action: Nuclear factor erythroid 2-related factor 2 (Nrf2) activator. By stimulating the activity of Nrf2, bardoxolone reduces inflammation and oxidative stress, while enhancing mitochondrial function.

Patient Impact: Each kidney contains multiple sets of glomeruli – capillary nodes that filter water and waste products out of the blood. Kidney function is measured by estimated glomerular filtration rate (eGFR), which approximates the amount of blood running through the glomeruli each minute based on an average body surface area (BSA) of 1.73m2. Naturally decreasing with age, eGFR averages about 107mL/min at age 30 declining to around 75mL/min by age 70. It also varies according to other factors, such as gender and race -- with women and African Americans tending to have lower rates. Generally, an eGFR less than 60mL/min correlates with advanced CKD. Kidney failure occurs at 15mL/min or less.

The Alport Syndrome Foundation (ASF) estimates that between 30,000 and 60,000 Americans have some degree of Alport syndrome. Mutations in any of three genes that encode proteins to build type IV collagen, a major component of glomeruli, cause irreversible weakening and changes in the kidney structures around glomeruli. The most prevalent mutation is carried on X chromosomes, so it is much more common for men than women. As damage to the kidney structures increases, kidney function gradually decreases, allowing more waste products of metabolism to remain in the blood. Eventually, cumulative kidney damage can result in end-stage renal disease (ESRD) that requires dialysis and/or a kidney transplant. According to the ASF, about one-half of patients who have severe Alport syndrome will need dialysis in their mid-twenties -- increasing to 90% by age 40. Type IV collagen also is an important component for parts of the ears and eyes, so patients who have Alport syndrome usually have hearing and vision problems, as well. Most have hypertension and blood in their urine; advanced cases also are likely to cause protein to leak into the urine.

Cost Estimates (per Patient): $55,000/yr

Current Therapies: No pharmaceutical treatments currently are FDA approved for treating the underlying cause of Alport syndrome. Present therapy consists of symptom control to delay the progression of kidney damage. Most patients manage high blood pressure with a sodium-limited diet and treatment with an antihypertensive such as an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB).

Many patients, particularly men, who have Alport syndrome eventually need kidney dialysis due to ESRD. Kidney transplants also are an option, with high rates of patient survival and approximately 45% of kidney transplants remaining functional for at least 20 years among patients who have Alport syndrome.

Pipeline Product(s): Sanofi's lademirsen is a single stranded, chemically modified oligonucleotide that is in Phase II development as a subcutaneous injection for the treatment of Alport syndrome. Approval is possible in 2025.

Comments: On Nov. 9, 2020, Reata announced that the Phase III CARDINAL study of bardoxolone methyl in patients with chronic kidney disease (CKD) caused by Alport syndrome met its primary and key secondary endpoints at the end of Year 2. The phase III part of the CARDINAL clinical trial included 157 patients between the ages of 12 years and 70 years who had Alport syndrome and eGFRs from 30mL/min to 90mL/min. Patients took between 5mg and 30mg of bardoxolone or a placebo daily for 48 weeks, followed by a four-week interval of no drug treatment and then 48 more treatment weeks. Four weeks after the end of the complete study period, eGFR averaged 7.7mL/min2 higher than their eGFRs at study entry for actively treated patients, compared to an average loss of 8.5 mL/min for those taking a placebo. Average eGFR for patients who continued bardoxolone throughout the entire two years increased by 11.3mL/min from baseline. Across all treated patients, the risk of kidney failure fell by approximately 50%. Fourteen patients, who continued treatment for an additional year in the EAGLE study, maintained an average increase of 11.0 mL/min in eGFR at the end of 156 weeks. Bardoxolone was generally reported to be well tolerated in this study, and the safety profile was similar to that observed in prior trials. Seventy-five patients (97%) receiving bardoxolone and 77 patients (96%) receiving placebo experienced an adverse event (AE). Ten patients (13%) receiving bardoxolone and four patients (5%) receiving placebo discontinued study drug due to an AE, and no individual AE contributed to more than two discontinuations in either group. The reported AEs were generally mild to moderate in intensity, and the most common AEs observed more frequently in patients treated with bardoxolone compared to patients treated with placebo were muscle spasms and increases in aminotransferases. Eight patients (10%) receiving bardoxolone and 15

patients (19%) receiving placebo experienced a treatment-emergent serious adverse event (SAE). No SAEs were reported in pediatric patients treated with bardoxolone. No fluid overload or major adverse cardiac events were reported in patients treated with bardoxolone. Blood pressure was not significantly different between the two groups. The urinary albumin-to-creatinine ratio (UACR) was not significantly different between treatment groups at Week 100 or Week 104. Non-kidney symptoms associated with Alport syndrome, including psychiatric, hearing, vestibular, and ocular AEs, occurred less frequently in bardoxolone-treated patients. Bardoxolone is also being studied in FALCON, a Phase III study for the treatment of autosomal dominant polycystic kidney disease, AYAME, a Phase III study for the treatment of diabetic kidney disease and BARCONA, a Phase II study for the treatment in patients suffering from COVID-19 conducted by researchers at NYU Grossman School of Medicine. On Apr. 26, 2021, Reata Pharmaceuticals announced that FDA granted standard review of bardoxolone for the treatment of patients with chronic kidney disease caused by Alport syndrome. Approval is expected by February 25, 2022. The FDA is planning to hold an Advisory Committee meeting to discuss the medication.

5. betibeglogene autotemcel (Zynteglo – Bluebird Bio)

Current Status: Orphan drug. Breakthrough therapy. Phase 3. Completion of a rolling BLA is expected in mid-2021.

Route of Administration/Dosing: One time intravenous (IV) infusion

Proposed Indication(s): β-globin gene therapy for the treatment of transfusion-dependent β thalassemia.

Mechanism of Action: lentiviral vector gene therapy. Upon extraction of the patients own CD34+ hematopoietic stem cells, the cells are genetically modified using a lentiviral gene vector to deliver the ß A-T87Q beta-globin gene to these cells. Once modified, they are returned to the patient

Patient Impact: β-thalassemia is estimated to affect approximately 1 in 100,000 individuals in the general population. The disorder is particularly prevalent in the Mediterranean, Middle East, Africa, central Asia, the Indian subcontinent and the Far East. Individuals in other parts of the world whose families are from these regions carry a greater risk of having β-thalassemia. In the United States, thalassemia's prevalence is approximately 1 in 272,000 or about 1,000 people.

Cost Estimates (per Patient): $2 million+

Current Therapies: Current treatment of beta thalassemia may include regular blood transfusions, chelation therapy to remove excess iron from the body due to the transfusions, surgery to remove spleen and/or gallbladder (if needed), and possible bone marrow transplant.

Pipeline Product(s): CRISPR Therapeutics and Vertex's CTX-001 (one time IV infusion) and Orchard Therapeutics' OTL-300 (one time intra-bone injection) are gene therapies in development for transfusion-dependent β thalassemia; they may reach the market in 2023. Acceleron and Celgene's luspatercept, a subcutaneously administered erythroid maturation agent, is currently under FDA review for the treatment of adult patients with very low to intermediate risk myelodysplastic syndromes (MDS)-associated anemia who have ring sideroblasts and require red blood cell (RBC) transfusions and for the treatment of adult patients with beta-thalassemia-associated anemia who require red blood cell transfusions. This product is currently under FDA review for beta-thalassemia-associated anemia with a PDUFA date of Dec. 4, 2019. The PDUFA date for MDS-associated anemia is Apr. 4, 2020.

Comments: Zynteglo is made from stem cells taken from the patient's blood, which are modified by a virus that carries working copies of the beta-globin gene into the cells. When these modified cells are given back to the patient (autologous stem cell transplant), they are transported in the bloodstream to the bone marrow where they start to make healthy red blood cells that produce beta-globin. In June 2019, Zynteglo was granted conditional marketing approval by the European Commission, for the treatment of patients 12 years and older with transfusion-dependent β-thalassemia (TDT), who do not have a β0/β0 genotype, and for whom hematopoietic stem cell (HSC) transplantation is appropriate but a human leukocyte antigen (HLA)-matched related HSC donor is not available.

On June 14, 2019, Bluebird Bio announced updated results from the completed Phase 1/2 Northstar (HGB-204) study, and new data from the Phase 3 Northstar-2 (HGB-207) and Phase 3 Northstar-3 (HGB-212) clinical studies of its LentiGlobin® (Zynteglo) gene therapy for patients with transfusion-dependent β-thalassemia (TDT), at the 24th European Hematology Association (EHA) Congress in Amsterdam, the Netherlands. The results reported for the completed Phase 1/2 Northstar (HGB-204) study reflect data as of December 13, 2018; of the 18 patients in the study, 10 patients do not have a β0/β0 genotype and eight have a β0/β0 genotype. All 18 patients have completed the two-year study and enrolled in the long-term follow-up study, LTF-303. Eight of 10 treated patients who do not have a β0/β0 genotype achieved transfusion independence (TI), meaning they had not received a transfusion for at least 12 months or more and maintained a weighted average Hb ≥9 g/dL. These eight patients had a median weighted average Hb during TI of 10.3 g/dL (min–max: 9.3–13.2 g/dL) and continued to maintain TI for up to 45 months. In patients who have a β0/β0 genotype, three of the eight achieved TI and maintained a median weighted average Hb ranging from 9.5–10.1 g/dL for a median duration of 16.4 months(min–max: 16.1–20.8 months). An exploratory assessment was conducted to assess liver iron concentration (LIC) in the 11 patients from the Northstar study who achieved TI. Increased iron levels are a consequence of frequent transfusions. High iron levels can cause organ damage, which many patients with TDT are at risk of and must manage through chelation regimens. LIC was measured at baseline and then every 12 months after treatment with LentiGlobin. Patients reinitiated iron chelation therapy at a median of 13 months after LentiGlobin infusion (min–max: 2–16 months). Over time, LIC began to decrease in all 11 patients with the largest decrease observed in patients who had 48 months of data available (n=4). A median 56 percent reduction (min–max: 38–83 percent) was reported in these four patients. As of April 12, 2019, 11 patients with TDT and a β0/β0 genotype or an IVS-I-110 mutation had been treated in the Phase 3

Northstar-3 study. The one patient evaluable for TI achieved and maintained it and had a total Hb of 13.6 g/dL at the Month 16 follow-up. Five patients had stopped transfusions for at least three months and had Hb levels of 10.2–13.6 g/dL at the time of the last study visit (5 – 16 months post-treatment). Of these patients, all of those who reached six months of follow-up (n=4) had HbAT87Q levels of at least 8 g/dL. Non-serious adverse events (Aes) observed during clinical studies that were attributed to LentiGlobin for TDT were hot flush, dyspnea, abdominal pain, pain in extremities and non-cardiac chest pain. One serious adverse event (SAE) of thrombocytopenia was considered possibly related to LentiGlobin for TDT. Additional Aes observed in clinical studies were consistent with the known side effects of HSC collection and bone marrow ablation with busulfan, including SAEs of veno-occlusive disease. This product is currently in Phase 3 development in the U.S. Completion of BLA filing is expected in mid-2021 with approval possible in early-2022. This product was granted orphan drug and breakthrough therapy designations.

6. bimekizumab (UCB)

Current Status: BLA filed. Approval expected by October 15, 2021.

Route of Administration/Dosing: subcutaneous (SC) injection (320mg every four weeks; self-administered)

Proposed Indication(s): moderate-to-severe plaque psoriasis

Mechanism of Action: Interleukin (IL)-17A and IL-17F inhibitor

Patient Impact: Psoriasis is an autoimmune disease that results from chronic overactivity of the immune system, causing an overproduction of skin cells. It is not contagious, but currently it cannot cured. Plaque psoriasis, which affects approximately eight million patients in the U.S., is characterized by itchy, red, scaly patches on the skin. Moderate-to-severe plaque psoriasis accounts for nearly 35% of psoriasis cases.

Often diagnosed when patients are in their mid-teens to mid-20s, psoriasis can occur at any age. It affects both genders about equally, and it is found in all ethnic groups. Chronic inflammation associated with psoriasis contributes to other medical conditions, such as cardiovascular (CV) disease and depression. Around one-third of patients who have psoriasis will develop psoriatic arthritis (PsA), which causes pain, stiffness and swelling in joints along with other symptoms.

Cost Estimates (per Patient): $65,000/yr

Current Therapies: Otezla® (apremilast - Amgen), an oral phosphodiesterase-4 (PDE-4) inhibitor that works inside cells to decrease inflammation. It is approved for psoriatic arthritis, plaque psoriasis and mouth sores that are caused by Behçet's disease. Injectable IL-23 inhibitors for treating moderate-to-severe plaque psoriasis include Skyrizi™ (risankizumab-rzaa – AbbVie/Boehringer Ingelheim), Tremfya® (guselkumab - Janssen) and Ilumya™ (tildrakizumab-asmn – Sun Pharma). Stelara® (ustekinumab - Janssen) targets IL-23 and interleukin-12 (IL-12) for treating moderate-to-severe plaque psoriasis. Injectable IL-17 inhibitors for treating moderate-to-severe plaque psoriasis include Cosentyx® (secukinumab – Novartis), Taltz® (ixekizumab – Lilly) and Siliq™ (brodalumab — Ortho Dermatologics). Several injectable TNF inhibitors are approved for moderate-to-severe plaque psoriasis (e.g., Enbrel, Humira, Cimzia).

Pipeline Product(s): Bristol Myers Squibb's deucravacitinib is an oral tyrosine kinase 2 (TYK2) inhibitor that is in Phase III development for the treatment of moderate-to-severe plaque psoriasis. Approval is possible in late-2021 or early-2022. Lilly's mirikizumab is an interleukin-23p19 inhibitor in Phase III development for moderate-to-severe plaque psoriasis. Approval is possible in late-2021 or early-2022.

Comments: FDA filing for bimekizumab included results from three phase III clinical trials, which all met their primary and secondary endpoints. In the placebo-controlled BE VIVID study, bimekizumab was compared with Stelara® (ustekinumab – Janssen). For the first 16 weeks, participants received either placebo, 320mg of bimekizumab once every four weeks or Stelara 45mg to 90mg (depending on body weight) once every 12 weeks after two loading doses four weeks apart. The placebo-treated patients all were started on bimekizumab at week 16. At that point, 85.0% of patients using bimekizumab had achieved PASI 90 – a 90% or more improvement in the Psoriasis Area and Severity Index and 58.6% had a PASI 100 (complete clearance of psoriatic plaques). Among patients using Stelara, the results were 49.7% and 20.9%, respectively. Responses to bimekizumab generally were quicker, as well, with 76.9% of patients treated with it responding within four weeks. At 52 weeks, 64.2% of patients using bimekizumab were at PSAI 100 vs 38.0% of Stelara-treated patients. The most frequently reported adverse events with bimekizumab through week 52 in BE VIVID were nasopharyngitis (21.8 percent), oral candidiasis (15.2 percent), and upper respiratory tract infections (9.1 percent). The majority of adverse events were mild to moderate in intensity. The vast majority of patients (94.7 percent) did not discontinue treatment. The incidence of serious treatment-emergent adverse events (TEAEs) was 6.1 percent with bimekizumab versus 7.4 percent with ustekinumab at week 52. BE READY was a placebo-controlled trial that enrolled 435 patients. Four-fifths of them used 320mg of bimekizumab once every four weeks for 16 weeks. The others were given placebo. Treated patients who showed at least PASI 90 were then reassigned to bimekizumab at 320mg every four weeks, 320mg once every eight weeks or placebo for 40 more weeks. Results for both treatment groups were similar – 86.8% of those on four-week dosing and 91.0% on eight-week schedules were still at PASI 90 or better at 56 weeks. Only 16.2% of patients given placebo for the final 40 weeks were able to maintain PASI 90. In BE READY, the most frequently reported adverse events with bimekizumab between week 16 and week 56 were nasopharyngitis (10.4 percent for the Q4W group; 23 percent for the Q8W group), oral candidiasis (11.3 percent Q4W; 9.0 percent Q8W), and upper respiratory tract infections (11.3 percent Q4W; 8.0 percent Q8W). The majority of adverse events were mild to moderate in intensity. The vast majority of patients (100 percent Q4W; 98 percent Q8W) did not discontinue treatment. The incidence of serious TEAEs with

bimekizumab was 4.7 percent for the Q4W group and 3.0 percent for the Q8W group versus 3.8 percent with placebo at week 56. Bimekizumab was tested against Humira® (adalimumab – AbbVie) in the BE SURE study. After 16 weeks of treatment, 86.2% of patients using bimekizumab were at PASI 90 as opposed to 47.2% of those receiving Humira. At week 24, 66.8% of patients on bimekizumab were at PASI 100 compared to 29.6% of those using Humira. Patients who moved to bimekizumab at 24 weeks achieved improved skin clearance more quickly compared to patients who continued on Humira. Through weeks 0–24, the active comparator period, treatment emergent adverse events (TEAEs) and serious TEAEs were comparable for patients receiving bimekizumab (71.5 percent and 1.6 percent, respectively) and adalimumab (69.8 percent and 3.1 percent). A fourth Phase III trial, BE RADIANT, assessed bimekizumab against Cosentyx® (secukinumab – Novartis) for achieving PASI 100. Although full results are not yet available, bimekizumab was better at achieving and maintaining PASI 100 through 48 weeks of blinded treatment followed by a 96-week open-label extension. On Sept. 22, 2020, UCB, announced that the FDA accepted the Biologics License Application (BLA) for bimekizumab for the treatment of adults with moderate to severe plaque psoriasis. Approval is expected by October 15, 2021. Bimekizumab is also in development for ankylosing spondylitis, non-radiographic axial spondyloarthritis and psoriatic arthritis (PsA). On April 23, 2021, UCB announced that The New England Journal of Medicine has published two manuscripts with results from BE RADIANT and BE SURE, two Phase 3 studies evaluating the efficacy and safety profile of bimekizumab in the treatment of adults with moderate to severe plaque psoriasis. The Phase 3b BE RADIANT study compared the efficacy and safety of bimekizumab to secukinumab in adults with moderate to severe plaque psoriasis. The study met its primary endpoint, with significantly more patients treated with bimekizumab achieving complete skin clearance, as measured by a 100 percent improvement from baseline in the Psoriasis Area and Severity Index (PASI 100) at week 16, compared to those treated with secukinumab (61.7 percent versus 48.9 percent, respectively; $p<0.001$). Across the study duration, the most common treatment-emergent adverse events (TEAEs) with bimekizumab were upper respiratory tract infections* (38.9 percent), oral candidiasis (19.3 percent) and urinary tract infection (6.7 percent). 1 Oral candidiasis cases were predominantly mild or moderate and none led to discontinuation. 1 Over 48 weeks, the incidence of serious TEAEs was 5.9 percent with bimekizumab and 5.7 percent with secukinumab. The Phase 3 BE SURE study compared the efficacy and safety of bimekizumab to adalimumab in adults with moderate to severe plaque psoriasis. BE SURE met its co-primary endpoints, demonstrating that bimekizumab-treated patients achieved superior levels of skin clearance, at week 16, compared to those who received adalimumab, as measured by PASI 90 and Investigator's Global Assessment (IGA) response of clear or almost clear skin (IGA 0/1); $p<0.001$ for both comparisons. No new safety signals were identified. Through week 56, there were no suicidal ideation/behavior, inflammatory bowel disease, or major adverse cardiac events reported in patients treated with bimekizumab. On Apr. 28, 2021, UCB announced that the FDA has set the Prescription Drug User Fee Act (PDUFA) date for UCB's Biologics License Application (BLA) for bimekizumab for the treatment of adults with moderate to severe plaque psoriasis at October 15, 2021.

7. ciltacabtagene autoleucel (JNJ-4528 – Janssen)

Current Status: Orphan drug. Breakthrough therapy. BLA filed. Priority review granted. Approval expected by Nov. 29, 2021.

Route of Administration/Dosing: intravenous (IV) infusion (one-time at a target dose of 0.75 * 10^6 CAR-positive viable T cells/kg)

Proposed Indication(s): treatment of patients with relapsed or refractory multiple myeloma

Mechanism of Action: B cell maturation antigen (BCMA)-directed chimeric antigen receptor T cell (CAR-T) therapy

Patient Impact: Multiple myeloma is an incurable blood cancer that affects a type of white blood cell called plasma cells, which are found in the bone marrow. When damaged, these plasma cells rapidly spread and replace normal cells with tumors in the bone marrow. In 2020, it is estimated that 32,270 people will be diagnosed and 12,830 will die from the disease in the U.S. While some patients with multiple myeloma have no symptoms, most patients are diagnosed due to symptoms, which can include bone fracture or pain, low red blood cell counts, tiredness, high calcium levels, kidney problems or infections. Despite advances in five-year survival rates in the past two decades, this blood cancer has remained a persistent challenge to treat using traditional techniques because of its cyclical and progressive nature, as well as its ability to mutate and adapt over time.

Cost Estimates (per Patient): $420,000

Current Therapies: There are currently three additional CAR-T cell therapies available on the U.S. market. Kymriah (tisagenlecleucel-T - Novartis) and Yescarta (axicabtagene ciloleucel - Gilead) were approved in 2017 for treating acute lymphoblastic leukemia (ALL) and non-Hodgkin's lymphoma (NHL), respectively. Kymriah was later approved for NHL. Kite's Tecartus (brexucabtagene autoleucel) is a CAR-T that was approved in July 2020 for mantle cell lymphoma. The treatment of multiple myeloma consists of a regimen containing proteasome inhibitors (PIs), Velcade® (bortezomib) and Kyprolis® (carfilzomib), immunomodulatory drugs (IMiDs), Revlimid® (lenalidomide) and Pomalyst® (pomalidomide), the anti-CD38 monoclonal antibody Darzalex® (daratumumab), as well as alkylating agents and corticosteroids. Xpovio (selinexor - Karyopharm) was approved in June 2019 for treating penta-refractory multiple myeloma. On Aug. 5, 2020, GlaxoSmithKline's Blenrep (belantamab mafodotin-blmf) was approved as monotherapy for relapsed or refractory multiple myeloma after four or more previous treatments that include an anti-CD38 monoclonal antibody, a proteasome inhibitor and an immunomodulatory agent. Recommended dosing is as a 30-minute intravenous (IV) infusion of 2.5mg/kg once every three weeks. It is an antibody-drug conjugate that is the first drug in a new class called B-cell maturation antigen (anti-BCMA) agents. Bluebird Bio and BMS's Abecma® (idecabtagene vicleucel) is a BCMS-directed CAR-T cell therapy that was approved on Mar. 26, 2021 for multiple myeloma.

Pipeline Product(s): There are no other BCMA-directed CAR-T cell therapies in late-phase development for multiple myeloma.

Comments: On May 13, 2020, Janssen announced updated results from the Phase 1b/2 CARTITUDE-1 study evaluating the efficacy and safety of JNJ-4528. CARTITUDE-1 is an open-label, multicenter study evaluating the safety and efficacy of JNJ-4528 in adults with relapsed or refractory multiple myeloma, 97 percent of whom were refractory to the last line of treatment; 86 percent of whom were triple-class refractory, meaning their cancer did not, or no longer responds to an immunomodulatory agent (IMiD), a proteasome inhibitor (PI) and an anti-CD38 antibody. Longer-term follow-up results from the Phase 1b portion of the study (n=29) show that all patients responded to treatment and that the responses were deep and durable with 86 percent of patients achieving stringent complete response at a median follow-up of 11.5 months and 86 percent of patients being alive and progression free at 9 months. The 100 percent overall response rate (ORR) included 97 percent of patients achieving a very good partial response or better and three percent achieving a partial response. Responses were observed among heavily pretreated patients (n=29) at a low dose of CAR-T cells (median administered dose 0.72x106 CAR+ viable T cells/kg). Patients evaluated had received a median of five (range, 3-18) prior treatment regimens; 86 percent were triple-refractory and 28 percent were penta-refractory. The median time to first response was one month (range, 1-3), and 81 percent of evaluable patients (n=16) achieved minimal residual disease (MRD)-negative disease status at 10-5 or 10-6 at the time of first suspected complete response. The most common adverse events (Aes) observed in CARTITUDE-1 were neutropenia (100 percent) and cytokine release syndrome (CRS, 93 percent). In patients who experienced Grade 3 and above Aes, the most common were neutropenia (100 percent), thrombocytopenia (69 percent) and leukopenia (66 percent). The median time of onset of CRS was seven days (range, 2-12) post-infusion, with a majority of patients experiencing Grade 1-2 CRS and two patients experiencing Grade 3 or greater CRS.

Neurotoxicity consistent with immune effector cell-associated neurotoxicity syndrome (ICANS) was observed in 3 patients (10 percent), including one patient (3 percent) with Grade 3 or greater toxicity. Three deaths were reported during the Phase 1b study: one due to CRS, one due to acute myeloid leukemia (not treatment-related) and one due to progressive disease. On Dec. 21, 2020, Janssen announced the initiation of a rolling submission of its Biologics License Application (BLA) to the FDA for ciltacabtagene autoleucel (cilta-cel), an infused B-cell maturation antigen (BCMA)-directed chimeric antigen receptor T cell (CAR-T) therapy, for the treatment of adults with relapsed and/or refractory multiple myeloma. Once Janssen completes the submission, an expedited FDA review is expected. On May 26, 2021, it was announced that Janssen's ciltacabtagene autoleucel has been granted priority review by FDA. Approval is expected by Nov. 29, 2021. On June 1, 2021, Janssen announced new data for ciltacabtagene autoleucel. Updated results from the Phase 1b/2 CARTITUDE-1 study (n=97) with a longer-term follow-up at a median of 18 months showed an overall response rate (ORR) of 98 percent, with 80 percent of patients achieving a complete response (sCR). These data also showed 66 percent of patients were progression free and alive at 18 months (95 percent Confidence Interval [CI], range, 54.9–75.0). The latest findings to be presented at the American Society of Clinical Oncology (ASCO) Annual Meeting, showed an overall survival (OS) of 81 percent (95 percent CI, range, 71.4–87.6)1 and response rates comparable across prespecified subgroups and lines of treatment. The most common hematologic adverse events (AEs) observed in the CARTITUDE-1 study were neutropenia (96 percent); anemia (81 percent); thrombocytopenia (79 percent); leukopenia (62 percent); and lymphopenia (53 percent). Cytokine release syndrome (CRS) of any grade was observed in 95 percent of patients with a median duration of four days (range, 1-97), and 99 percent of which resolved within 14 days of onset.1 Of the 92 patients with CRS, 95 percent experienced Grade 1/2 events. Neurotoxicity of any grade was observed in 21 percent (n=20) of patients, with Grade 3 or higher neurotoxicity observed in 10 percent (n=10) of patients. Findings from Cohort A (n=20) in the Phase 2 CARTITUDE-2 (NCT04133636) study evaluating the safety and efficacy of cilta-cel in patients with multiple myeloma whose disease progressed after one to three prior lines of therapy, and who were lenalidomide refractory, will be presented for the first time at ASCO. Results from this cohort showed early and deep responses at a median of 5.8 months of follow-up2, and an ORR of 95 percent with 45 percent of patients achieving a sCR, 30 percent of patients achieving a CR, 10 percent of patients achieving a VGPR, and 10 percent of patients achieving a PR. The overall safety profile, including incidence of CRS and most common hematologic AEs, was consistent with observations in the CARTITUDE clinical development program.

8. deucravacitinib (Bristol Myers Squibb)

Current Status: Phase III. NDA filing expected in 2021.

Route of Administration/Dosing: Oral (6mg once daily)

Proposed Indication(s): moderate to severe plaque psoriasis

Mechanism of Action: tyrosine kinase 2 (TYK2) inhibitor; it inhibits the interleukin (IL)-12, IL-23 and Type 1 interferon (IFN) pathways, which are implicated in the pathogenesis of psoriasis and other immune-mediated diseases

Patient Impact: Psoriasis is an autoimmune disease that results from chronic overactivity of the immune system, causing an overproduction of skin cells. It is not contagious, but currently it cannot cured. Plaque psoriasis, which affects approximately eight million patients in the U.S., is characterized by itchy, red, scaly patches on the skin. Moderate-to-severe plaque psoriasis accounts for nearly 35% of psoriasis cases.

Often diagnosed when patients are in their mid-teens to mid-20s, psoriasis can occur at any age. It affects both genders about equally, and it is found in all ethnic groups. Chronic inflammation associated with psoriasis contributes to other medical conditions, such as cardiovascular (CV) disease and depression. Around one-third of patients who have psoriasis will develop psoriatic arthritis (PsA), which causes pain, stiffness and swelling in joints along with other symptoms.

Cost Estimates (per Patient): $45,000/yr

Current Therapies: Otezla® (apremilast - Amgen), an oral phosphodiesterase-4 (PDE-4) inhibitor that works inside cells to decrease inflammation. It is approved for psoriatic arthritis, plaque psoriasis and mouth sores that are caused by Behçet's disease. Injectable IL-23 inhibitors for treating moderate-to-severe plaque psoriasis include Skyrizi™ (risankizumab-rzaa – AbbVie/Boehringer Ingelheim), Tremfya® (guselkumab - Janssen) and Ilumya™ (tildrakizumab-asmn – Sun Pharma). Stelara® (ustekinumab - Janssen) targets IL-23 and interleukin-12 (IL-12) for treating moderate-to-severe plaque psoriasis. Injectable IL-17 inhibitors for treating moderate-to-severe plaque psoriasis include Cosentyx® (secukinumab – Novartis), Taltz® (ixekizumab – Lilly) and Siliq™ (brodalumab — Ortho Dermatologics). Several injectable TNF inhibitors are approved for moderate-to-severe plaque psoriasis (e.g., Enbrel, Humira, Cimzia).

Pipeline Product(s): UCB's bimekizumab is an IL-17A and IL-17F inhibitor that is expected to be approved by July 22, 2021 for the treatment of moderate-to-severe plaque psoriasis. It's administered by SC injection. Lilly's mirikizumab is an interleukin-23p19 inhibitor in Phase III development for moderate-to-severe plaque psoriasis. Approval is possible in late-2021 or early-2022.

Comments: On Nov. 2, 2020, Bristol Myers Squibb announced positive results from POETYK PSO-1, the first pivotal Phase 3 trial evaluating deucravacitinib for the treatment of patients with moderate to severe plaque psoriasis. It is a multi-center, randomized, double-blind, placebo- and active comparator-controlled Phase 3 study with 666 participants. POETYK PSO-1 evaluated 6mg of deucravacitinib once daily and met both co-primary endpoints versus placebo, with more patients achieving Psoriasis Area and Severity Index (PASI) 75, defined as at least a 75 percent improvement in PASI, and a static Physician's Global Assessment (sPGA) score of clear or almost clear (sPGA 0/1) after 16 weeks of treatment with deucravacitinib. The trial also met multiple key secondary endpoints, including showing deucravacitinib was superior to Otezla® (apremilast) in the proportion of patients reaching a PASI 75 response and sPGA 0/1 at Week 16. The overall safety profile of deucravacitinib in the POETYK PSO-1 trial was consistent with previously reported Phase 2 results. In a Phase 2 study, with results reported Nov. 9, 2020, deucravacitinib was well-tolerated. In the study, there were no serious adverse events reported in deucravacitinib-treated patients. The most common treatment-emergent adverse events for patients who received deucravacitinib 6 mg or 12 mg versus placebo, respectively, were nasopharyngitis (5.7%, 17.9%, 7.6%), rash (4.3%, 6.0%, 0%) and headache (7.1%, 1.5%, 4.5%). On Feb. 2, 2021, Bristol Myers Squibb announced positive results from POETYK PSO-2, the second pivotal Phase 3 trial evaluating deucravacitinib for the treatment of patients with moderate to severe plaque psoriasis. The multi-center, randomized, double-blind study enrolled 1,020 patients. POETYK PSO-2 evaluated deucravacitinib 6mg once daily and met both co-primary endpoints versus placebo, with significantly more patients achieving Psoriasis Area and Severity Index (PASI 75), defined as at least a 75 percent improvement of baseline PASI, and a static Physician's Global Assessment (sPGA) score of clear or almost clear (sPGA 0/1) after 16 weeks of treatment with deucravacitinib. The trial also met multiple key secondary endpoints, including showing deucravacitinib 6mg once daily was superior to Otezla® (apremilast) in the proportion of patients reaching PASI 75 and sPGA 0/1 at Week 16. The overall safety profile of deucravacitinib in POETYK PSO-2 remains consistent with previously reported results and consistent with the mechanism of action of deucravacitinib. Deucravacitinib is in Phase II development for

psoriatic arthritis, lupus and inflammatory bowel disease.

9. efgartigimod (Argenx)

Current Status: Orphan drug. BLA filed. Approval expected by Dec. 17, 2021

Route of Administration/Dosing: Intravenous (IV) Infusion. Initial treatment cycle consisting of four weekly infusions (10mg/kg) then each subsequent cycle is individualized.

Proposed Indication(s): Treatment of patients with generalized Myasthenia gravis (gMG).

Mechanism of Action: Neonatal Fc receptor (FcRn) inhibitor. The neonatal Fc receptors (FcRn) binds immunoglobulins (IgGs) and pathogenic IgGs rescuing them from cell recycling and lysosomal degradation extending their half-life. Efgartigimod antagonizes neonatal Fc receptors (FcRn) which compete with immunoglobulin-G1 (IgG1), increasing clearance and reducing pathogenic IgGs by blocking cell recycling, a key contributor to the pathogenesis Myasthenia gravis (MG).

Patient Impact: MG is an autoimmune disease that is caused by poor nerve signaling resulting in the weakness of the voluntary muscles. Acetylcholine is a neurotransmitter that plays a key role in sending nerve signals to muscles helping with contraction, but in MG, antibodies are produced against acetylcholine that disrupts or block signal transmission on their respective receptors. The lack of acetylcholine causes the voluntary muscles to weaken and within 18 months, more than 85% of people will progress to multiple muscle groups being affected known as, generalized myasthenia gravis (gMG). Around 10 to 40% of cases will be limited to the eye muscles or drooping of one or both eyelids. As the disease progresses people can have trouble walking, moving arms or hands, vision disturbances, changing facial expressions, swallowing and shortness of breath. Muscle weakness typically worsens throughout the day and is not limited to a single muscle group; however, patients will not usually complain of generalized fatigue. Some patients will have spontaneous improvement at the early stages of the disease, but typically, patients will fluctuate between inactive and active states of the disease until symptoms become fixed in an atrophic or burnout stage. If the muscles that help control breathing do become affected it can be life threatening. MG is thought to affect approximately 65,000 Americans, but prevalence is probably higher since it is often underdiagnosed. MG can affect anyone at any age, but typically will affect women who are under 40 years of age and men over 60 years of age. It is not fully understood what triggers MG, but it is understood that genes may play a role and in some cases, it may be linked to thymus gland tumors or abnormalities.

Cost Estimates (per Patient): $450,000/yr

Current Therapies: Current treatments for MG include Mestinon®, Mestinon®-Timespan® (pyridostigmine bromide as tablet, solution and extended-release tablet – Bausch Health, generics), Regonol® (pyridostigmine bromide injection – Novartis). Corticosteroids and immunosuppressants can be used such as RAYOS® (prednisone delayed-release – Horizon Therapeutics), Deltasone® (prednisone – Sonoma Pharmaceuticals, generics), Decadron® - (dexamethasone – Merck & Co., generics), Medrol® (methylprednisolone – Pfizer, generics), Cortone® (cortisone –Merck & Co., generics), (Imuran® (azathioprine – Sebela, generics), Cellcept® - mycophenolate mofetil – Genentech, generics), or Sandimmune® (cyclosporine – Novartis, generics), Gengraf® (cyclosporine modified – Abbvie, generics), Bloxiverz® (neostigmine – Avadel Legacy). The only product approved by the U.S. Food and Drug Administration (FDA) for MG is Soliris® (eculizumab – Alexion Pharmaceuticals). Sometimes, intravenous immune globulins (IVIg) may be used and examples include, (Carimune®/Carimune NF®– CSL Behring, Gammagard®/Gammagard S/D® -Shire, Asceniv® - ADMA Biologics, Bivigam® - ADMA Biologics, Cutaquig® - Pfizer, Cuvitru® - Shire, Flebogamma DIF® - Grifols USA, GamaSTAN® - Grifols USA, Gammaked® - Kedrion, Gammaplex® - Bio Products, Gamunex-C® - Grifols USA, Hizentra® - CSL Behring, Octagam® - Octapharma USA, Panzyga® - Octapharma USA, Privigen® - CSL Behring, Xembify® - Grifols USA). Other treatment approaches include plasma exchange (PLEX), or plasmapheresis to remove the pathogenic IgGs. If the thymus gland is believed to play a role in the disease, surgical removal may be considered to improve long-term outcomes; however, results are not seen for years.

Pipeline Product(s): Catalyst/Jazz Pharmaceuticals' Firdapse® (amifampridine) oral tablet was a phase III trial for MG did not statistically meet its endpoints, but the company plans to redesign the trial protocol in 2021 and meet with the FDA to see if there is a path forward. Rozanolixizumab is another FcRn inhibitor in phase III being investigated by UCB as an IV or SC treatment for MG. Approval is possible in 2024. Alexion's Ultomiris® (ravulizumab-cwvz) for intravenous use is seeking a new indication for gMG and plans to file a BLA in 2021. Viela bio is seeking an additional indication for their intravenous drug, Uplinza® (inebilizumab – cdon), which is in phase III trial. Zilucoplan, a once-daily, self-administered SC injection from Ra Pharmaceuticals is being developed and is currently in phase III with Orphan Designation.

Comments: Support for BLA filing was announced on May 26, 2020, in a phase III randomized, double-blind, placebo-controlled trial, called ADAPT. The trial evaluated safety, efficacy, and quality of life on normal activities in patients who have general muscle weakness due to myasthenia gravis (gMG). The trial was completed in North America, Europe and Japan in 167 adult patients. Patients had confirmed gMG, regardless of AChR antibody status with a Myasthenia Gravis Activities of Daily Living (MG-ADL) score of five or greater. The MG-ADL, is an eight item questionnaire that monitors the severity of MG. If a patient was on at least one treatment for their gMG before the trial, they were required to stay at that stable dose for the entirety of the study. For 26 weeks, patients were randomized 1:1 to receive efgartigimod or placebo. Patients received an initial treatment cycle followed by individualized subsequent treatments. Each cycle consisted of four weekly infusions of efgartigimod (10mg/kg) IV or placebo. The primary endpoint was the number of AChR-Ab+ patients with at least a two-point improvement in their MG-ADL score for four or more consecutive weeks. The study met its endpoint with statistical significance focused on patients treated with efgartigimod who are AChR-Ab+ having a 67.7% improvement in MG-ADL score vs. 29.7% in placebo ($p<0.0001$). Of the MG-ADL scores, 40% of the treated patients achieved a minimal symptom expression score defined as zero (no symptoms) or one compared to 11.1% for the placebo group. Sustained response was observed for those patients meeting the primary endpoint measured as 88.6% who achieved a six-week response, 56.8% who achieved an eight-week response and 34.1% who achieved a 12-week response. Also, patients showed a response on the Quantitative Myasthenia Gravis (QMG) test, defined as a three-point improvement or more, in 63.1% of treated AChR-Ab+ vs. 14.1% in placebo. The QMG test is a standardized test that measures the severe impairment due to MG. Secondary endpoints showed a statistically significant improvement in MG-ADL responses in the overall population, in both AChR-Ab+/- patients. Other secondary endpoints met include, time on trial in MG-ADL improvement of two or more and onset MG-ADL observed in the first two weeks. The time to qualify for retreatment did not meet its secondary endpoint. For a patient that received a second treatment cycle 70.6% of them were MG-ADL responders vs. 25.6% placebo. Overall, 90% of patients went on to the open-label phase extension of the trial. For patients who were AChR-Ab- achieved a similar MG-ADL score; however, a greater placebo response was measured. The company is going to include this efficacy data to support approval, even though not statistically significant due to the strong response in the treatment group. The subjectivity of MG-ADL scores could have been influenced by placebo-effect type improvement, desperation for approved treatments or heterogeneity of the population according to investigators for the company. An update to the study was announced on October 3, 2020, showing that 55.6% of efgartigimod treated patients had MG-ADL scores of five points or more and 50% had a QMG score of six points or more, with 33.9% having a nine-point or more improvement. The repeatability of response was seen in AChR-Ab+ patient's MG-ADL scores, with the first treatment cycle seeing (67.7% efgartigimod vs. 29.7% placebo) and in the second treatment cycle (70.6% efgartigimod vs. 25.6% placebo). Overall, 78.5% of the treated patients responded according to the MG-ADL score in the first two cycles. A clinical benefit in AChR-Ab- patients showed further evidence with 52.6% of efgartigimod- treated patients having a QMG score response compared to 36.8% of placebo. A post-hoc analysis of the seronegative group also showed 47.4% had a response in both QMG and MG-ADL scores vs. 21.1% of placebo patients. The safety of efgartigimod was established showing that it was well tolerated and had comparable data to placebo with no adverse events (AE's), including no elevation in total cholesterol, HDL and LDL. Argenx is working on a subcutaneous (SC) version.

10. eladocagene exuparvovec (PTC Therapeutics)

Current Status: Orphan drug. Phase III. Filing expected in 2H:2021.

Route of Administration/Dosing: Infused through a surgical procedure directly into the putamen, parts of the brain that affect learning and movement/1.8 × 10^11 vector genomes (vg) delivered as four 0.080 mL (0.45 × 10^11 vg) infusions (two per putamen).

Proposed Indication(s): to replace an enzyme, aromatic-L-amino-acid decarboxylase (AADC), for patients who have AADC deficiencies

Mechanism of Action: Eladocagene exuparvovec is a recombinant adeno-associated virus vector gene therapy that uses human DNA to replace AADC.

Patient Impact: AACD deficiency is extremely rare; about 100 patients with this disease have been identified in the U.S. It results from mutations in the dopa decarboxylase (DDC) gene, which cause shortages of the enzyme, AADC. As a result, levels of dopamine and serotonin, two neurotransmitters that help pass information between nerve cells, are decreased. Because symptoms of AADC are very similar to those of other conditions, including cerebral palsy and epilepsy, diagnosing it may be difficult. Children who have severe deficiencies of AADC seldom survive into their teens.

Usually becoming evident in the first few months of life, AADC deficiency results in low energy, involuntary movements, poor sleep, weak or stiff muscles and the failure to reach typical achievements, such as learning to sit up, talk and walk. Many patients have oculogyric crises, which are typified by uncontrollable eye, head and neck movements, intense irritability, muscle spasms, pain and seizures. Such crises tend to occur every few days and they can last for several hours. Other body functions, such as blood pressure and temperature, also may be affected -- with many patients experiencing low blood sugar, low blood pressure or excessive sweating. For many patients, symptoms appear to increase when they are tired.

Cost Estimates (per Patient): $4M for one-time infusion

Current Therapies: No treatments are FDA approved to correct AADC deficiency.

Therapies presently focus on increasing available neurotransmitters and relieving symptoms. Initial treatment usually includes vitamin B6 (pyridoxine), because it enhances any AADC production that the patient has. To increase dopamine, drugs such as bromocriptine and Neupro® (rotigotine transdermal patches) are used off-label. Although they also are not approved to treat AADC deficiency, monoamine oxidase inhibitors, including selegiline and tranylcypromine, may be used to delay the metabolism of dopamine and serotonin. Doses for children often have to be compounded since most of the oral drugs are not available in pediatric strengths or dosage forms.

Patients may need additional medications to control seizures, manage blood pressure and blood sugar, improve sleep and keep other symptoms in check. Physical, occupational, and speech therapies may also be helpful.

Pipeline Product(s): There are no other pipeline drugs in late-phase development for AADC deficiency.

Comments: On Oct. 24, 2019, PTC Therapeutics announced results from eladocagene exuparvovec in patients living with AADC deficiency. Results from three open-label clinical trials of eladocagene exuparvovec were pooled for analysis. The 26 patients who were treated ranged in age from 21 months old to eight and one-half years old at the beginning of the studies. None of the participants could restrict abnormal head movements, sit up, stand or walk before being treated. At one year after treatment, oculogyric crises had decreased for most patients and most had gained weight. All but three developed some degree of dyskinesia (unusual body movements), which was not considered to be severe for any of the children and which gradually dissipated over about ten months for most of them.

A sub-analysis for two studies included 18 patients followed for two years after therapy. Eight study participants had at least five years of data after treatment. In the two-year group, eight children could completely limit their head movements, six could sit up alone and three could stand unassisted. Among those whose treatment had been five years previously, four could control their head movements, four could sit up and two could stand without help.

11. futibatinib (Taiho Oncology)

Current Status: Orphan drug. Breakthrough therapy. Phase III. Approval expected in 2022.

Route of Administration/Dosing: Oral (20mg once daily)

Proposed Indication(s): Second- and later-line treatment of intrahepatic cholangiocarcinoma (iCCA) in patients with FGFR2 fusions

Mechanism of Action: fibroblast growth factor (FGFR) 1-4 inhibitor

Patient Impact: Cholangiocarcinoma is a rare cancer that forms in the bile duct. It is classified based on its origin: intrahepatic cholangiocarcinoma ("iCCA") occurs in the bile duct inside the liver and extrahepatic cholangiocarcinoma occurs in the bile duct outside the liver. Patients with cholangiocarcinoma are often diagnosed at a late or advanced stage when the prognosis is poor. Approximately 8,000 patients are diagnosed with cholangiocarcinoma each year in the United States. About 25% of patients with CCA have iCCA. FGFR2 genetic aberrations are present in approximately 15% to 20% of people who have this disease. Currently, treatment options are limited, and the five-year survival rate is only 9%.

Cost Estimates (per Patient): $250,000/yr

Current Therapies: The main treatment for CCA is surgery. Radiation therapy and chemotherapy may be used if the cancer cannot be entirely removed with surgery and in cases where the edges of the tissues removed at the operation show cancer cells (also called a positive margin). Both stage III and stage IV cancers cannot be completely removed surgically. Currently, standard treatment options are limited to radiation, palliative therapy, liver transplantation, surgery, chemotherapy and interventional radiology. First-line chemotherapy for locally advanced or metastatic CCA is the combination of gemcitabine and cisplatin chemotherapy; however, median survival is less than 1 year. Second-line therapies in CCA have shown limited efficacy. Incyte Pharmaceuticals' Pemazyre™ (pemigatinib), an oral FGFR 1, 2 and 3 inhibitor, was approved on Apr. 17, 2020, to treat adults who have previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or other rearrangement as detected by an FDA-approved test. On May 28, 2021, the U.S. Food and Drug Administration (FDA) granted Accelerated Approval for Truseltiq™ (infigratinib) capsules. An oral fibroblast growth factor 2 (FGFR2) inhibitor, it is indicated for treating adults who have inoperable cholangiocarcinoma (bile duct cancer) that has spread despite previous therapy. It is taken on 28-day cycles, with a 125mg dose on each of the first 21 days followed by one week off of treatment. It should be taken at least one hour before or two hours after eating. BridgeBio Pharma and Helsinn Therapeutics co-market Truseltiq in the United States.

Pipeline Product(s): Basilea Pharmaceutica' derazantinib is an oral FGFR inhibitor that is in Phase II development for the first or second-line treatment of cholangiocarcinoma. Approval is possible in 2023+.

Comments: On Apr. 11, 2021, Taiho Oncology announced efficacy and safety results from the Phase 2 FOENIX-CCA2 trial. In the trial, 103 patients with locally advanced or metastatic unresectable iCCA harboring FGFR2 gene rearrangements including fusions who had received one or more prior lines of systemic therapy received futibatinib 20 mg once daily until disease progression or unacceptable toxicity. The study met its primary endpoint of a greater than 20% objective response rate (ORR) assessed by independent central review with an ORR of 41.7%. Secondary endpoints of duration of response (DOR) and disease control rate (DCR) were also reported; responses were durable, with a median DOR of 9.7 months and 72% of responses ≥6 months, and a DCR of 82.5%. Median progression-free survival (PFS) was 9.0 months and median overall survival (OS) was 21.7 months, with 72% of patients alive at 12 months. Common treatment-related adverse events (TRAEs) were hyperphosphatemia (85%), alopecia (33%) and dry mouth (30%). The most frequent grade 3 TRAE was hyperphosphatemia (30%), which resolved in patients with adequate management. One grade 4 TRAE of increased ALT was reported and there were no treatment related deaths. The FDA granted breakthrough therapy designation based on the results of this study. Futibatinib is currently in a Phase III study comparing it to gemcitabine-cisplatin chemotherapy as first-line treatment of patients with advanced, metastatic, or recurrent unresectable iCCA harboring FGFR2 gene rearrangements.

12. inclisiran (Leqvio - Novartis)

Current Status: NDA filed. Complete response letter issued Dec. 18, 2020. Resubmitted in July 2021. Approval expected Jan. 1, 2022

Route of Administration/Dosing: Subcutaneous (SC) injection (300mg on days 1 and 90, followed by one 300mg injection once every six months by a healthcare professional)

Proposed Indication(s): treatment of adults with atherosclerotic cardiovascular disease (ASCVD or heterozygous familial hypercholesterolemia (HeFH) who have elevated LDL-C while being on a maximum tolerated dose of a lipid-lowering therapies (LLT)

Mechanism of Action: small interfering RNA (siRNA) therapy that lowers low-density lipoprotein cholesterol (LDL-C)

Patient Impact: According to the Centers for Disease Control and Prevention (CDC), more than 71 million American adults have high levels of LDL-C, a major risk factor for cardiovascular (CV) disease. About one-quarter of them cannot take HMG-CoA reductase inhibitors (statins) or cannot control their LDL-C adequately with maximum statin doses. FH is an inherited condition involving mutations in one of the genes that regulate the body's clearance of cholesterol. It causes very high levels of cholesterol, which can result in heart disease for relatively young individuals. Its two major forms are heterozygous familial hypercholesterolemia (HeFH) and homozygous familial hypercholesterolemia (HoFH). By far the most common, HeFH is believed to affect one in 500 to one in 250 people, or approximately 650,000 to 1.3 million Americans. It is caused by one defective gene. Both HF genes are mutated for patients who have the more serious HoFH form of the condition (approximately one person in 300,000). Heart disease may be apparent for HoFH patients as early as their teens. It's estimated that there are more than 11 million patients in the U.S. with familial hypercholesterolemia and/or clinical ASCVD.

Cost Estimates (per Patient): $5,500/yr

Current Therapies: Two other PCSK9 inhibitors are approved by the FDA. Praluent® (alirocumab – Sanofi/Regeneron) was FDA approved on Jul. 24, 2015, and Repatha® (evolocumab – Amgen) on Aug. 27, 2015, to be used along with diet and other LDL-lowering therapies for specific subsets of patients who require additional lowering of LDL-C. Later, they each received additional indications still along with a low-cholesterol diet to reduce LDL-C. Either alone or with other lipid-lowering therapies, both are FDA approved to treat adults who have primary hyperlipidemia, including FH, and to decrease the risk of heart attacks, strokes and coronary revascularization in adults with established CV disease. Both Praluent and Repatha are monoclonal antibodies that have a different mechanism of action than inclisiran and both must be used more often – either once a month or once every two weeks by SC injection. They attach to PCSK9, preventing it from occupying LDL receptors and increasing the liver's ability to trap and eliminate LDL-C.

Pipeline Product(s): CiVi Biopharma's CiVi-007 is an antisense RNAi oligonucleotide targeting PCSK9 that's in Phase II development for the treatment of hypercholesterolemia. It's not expected to reach the market for several

Comments: Inclisiran has been tested in several clinical trials, including three major phase III studies. Over 1,600 adults participated in the 18-month long ORION-11 Study. All had either ASCVD or risk equivalents, such as diabetes; and 96.2% already were on statin therapy. On day 510 (17 months) of the study, those who were given 300mg of inclisiran on days 1, 90 (three months), 270 (nine months) and 450 (15 months) had average LDL-C levels 49% lower than when the study began. LDL-C levels for patients who got placebo injections averaged 4% higher. In general, side effects were similar between the two groups with the exception of skin events (primarily irritation at the injection site), which affected 4.7% of patients on the active drug, but only 0.5% of the patients using placebo. The ORION -10 trial included 1,561 patients age 18 or older who have ASCVD and whose LDL-C remained at or above 70mg/dL even though they were taking the highest doses of statins that they could. Some took ezetimibe, as well. More than 90% of participants had coronary artery disease (CAD). After 17 months, patients who were given two doses of inclisiran at a three-month interval and then two doses a year saw an average reduction in LDL-C of over 50%, compared to a slight increase (1% to 3%) in the group receiving placebos. ORION -9 enrolled 482 adult patients who have heterozygous familial hypercholesterolemia (HeFH) One-half of patients were randomized to 300mg of inclisiran on the first day, at three months, at nine months and at 15 months. The others received placebo injections on the same schedule. Average LDL-C levels for patients receiving inclisiran were 41% lower than at the start of the study, but LDL-C increased by 8% for those given a placebo injection. All patients continued on high doses of a statin. On Dec. 18, 2020, Novartis announced that the U.S. Food and Drug Administration (FDA) has issued a complete response letter (CRL) regarding the new drug application (NDA) for inclisiran, a subcutaneous small interfering RNA (siRNA) therapy that is in development for the treatment of hyperlipidemia in adults who have elevated low-density lipoprotein

cholesterol (LDL-C) while being on a maximum tolerated dose of a statin therapy. The CRL is due to unresolved facility inspection-related conditions and not safety or efficacy issues. In July 2021, Novartis resubmitted the application for approval with a new manufacturing facility. Approval is expected by Jan. 1, 2022. Cardiovascular outcomes data are expected in 2026.

13. obeticholic acid (Intercept Pharmaceuticals)

Current Status: Breakthrough therapy for NASH with liver fibrosis. CRL. Approval in 2022+

Route of Administration/Dosing: Oral (10mg or 25mg once daily)

Proposed Indication(s): treatment of fibrosis due to nonalcoholic steatohepatitis (NASH)

Mechanism of Action: farnesoid X receptor (FXR) agonist

Patient Impact: Nonalcoholic fatty liver disease (NAFLD), a common form of chronic liver disease, is characterized by fat buildup in the liver. Many patients have only simple steatosis, a form of the condition that remains relatively mild. Its more severe progressive form, NASH, damages liver cells and causes inflammation, potentially resulting in fibrosis, cirrhosis, end-stage liver disease, liver transplant, liver cancer and liver-related death. Neither condition has definite symptoms, so they may not be diagnosed until damage is extensive. Although it is very similar to liver disease caused by excessive alcohol consumption, NASH occurs in persons who drink little or no alcohol. Some genetic factors related to NAFLD/NASH have been identified, and developing them is highly associated with several metabolic conditions that include obesity, type 2 diabetes, hypertension and high cholesterol. As a result, the first line of treatment for NAFLD/NASH is diet modification, increased physical activity and weight loss. Other current management recommendations are to control related conditions.

Currently, the only broadly accepted and definitive method for diagnosing NASH is a liver biopsy, which allows for the evaluation of cellular structure and the assessment of liver disease. However, this invasive procedure is not without pain and risks that include infections and bleeding. Additionally, the test evaluates only the portion of the liver directly sampled, which does not necessarily represent the condition of the entire liver and introduces the possibility of sampling errors. No FDA-approved diagnostic tests specifically are designed for the identification of patients with NASH. However, the majority of patients currently are diagnosed with non-invasive tests (NIT) such as blood test [e.g., liver function tests: alanine aminotransferase (ALT) and aspartate aminotransferase (AST)] and imaging (e.g., ultrasound, FibroScan, CT scan, MRI). According to Intercept, less than 10% of patients with ICD-10 codes for NASH have had a liver biopsy. Several NITs, including biomarkers (blood tests), for diagnosing NASH are in development.

According to Intercept, there are about 19M patients in the US with NASH and about 16M of these patients have some levels of fibrosis. Of these 16M patients, 11.2M are thought to have early fibrosis and are unlikely to require pharmaceutical treatment, and 1.5M have compensated cirrhosis. It's estimated that there are around 3M NASH patients with advanced fibrosis (F3 or F3-like, without cirrhosis) in the US, of which around 500,000 patients are thought to be under the care of a hepatologist or gastroenterologist. These 500,000 patients are Intercept's target patient population for obeticholic acid.

Cost Estimates (per Patient): $15K-$20K/yr

Current Therapies: The first line of treatment for NAFLD/NASH is diet modification, increased physical activity and weight loss. Other current management recommendations are to control related conditions. There are no drugs currently approved to treat NASH.

Pipeline Product(s): There are several drugs in development for NASH. Oral drugs for NASH in Phase III development include: Genfit's elafibranor, a dual peroxisome proliferator-activated alpha and delta receptor agonist (PPARα/δ agonist); Allergan's cenicriviroc is a dual chemokine receptor 5 (CCR5) and chemokine receptor 2 (CCR2) antagonist; Madrigal's resmetirom is a thyroid hormone receptor (THR) β -selective agonist; Galmed's Aramchol (arachidyl amido cholanoic acid) is a novel fatty acid bile acid conjugate. These could potentially reach the market in 2021. It's more likely that Aramchol will be approved in 2023.

Comments: On Jan. 29, 2015, Intercept Pharmaceuticals announced that obeticholic acid (OCA) received a breakthrough therapy designation from the FDA for the treatment of patients with NASH with liver fibrosis. On Nov. 08, 2019, Intercept Pharmaceuticals announced additional Phase 3 REGENERATE data. Patients in the REGENERATE primary intent-to-treat (ITT) population (n=931) with stage 2 and 3 fibrosis were randomized 1:1:1 to receive OCA 25 mg (n=308), OCA 10 mg (n=312) or placebo (n=311) once daily over 18 months. As previously reported, in the primary efficacy analysis, once-daily OCA 25 mg met the primary endpoint of fibrosis improvement (≥1 stage) with no worsening of NASH in 23.1% of patients compared to 11.9% of placebo patients at the planned 18-month interim analysis (p=0.0002 vs. placebo). In a new analysis of the interim data presented at The Liver Meeting, OCA-treated patients in the primary ITT group showed time- and dose-dependent improvements compared to placebo across commercially available noninvasive tests, including blood tests of fibrosis (Fibrosis-4 [FIB-4] index, AST to platelet

ratio index [APRI], and FibroSURE®) as early as three months after treatment initiation. In addition, vibration-controlled transient elastography [VCTE], an imaging assessment of liver stiffness and a surrogate of fibrosis, decreased from baseline in both OCA groups but increased with placebo at 18 months. In a responder analysis, improvements in noninvasive tests mirrored shifts in fibrosis stage, with the greatest improvements observed in patients achieving >1 fibrosis stage reduction. In contrast to patients treated with placebo, OCA-treated patients with no change in fibrosis stage also had marked improvement in noninvasive tests. The authors concluded that the improvements observed in histologic non-responders suggest OCA's therapeutic benefit may not be adequately captured by categorical histologic fibrosis staging at 18 months. On Dec. 05, 2019, Intercept Pharmaceuticals announced that the positive results from the interim analysis of the Phase 3 REGENERATE study have been published in The Lancet. This is the first peer-reviewed publication of positive results from a pivotal study evaluating an investigational therapy for NASH. REGENERATE is an ongoing study that will continue through clinical outcomes for verification and description of clinical benefit. Data from the 18-month interim analysis of the study served as the basis for the New Drug Application (NDA) for OCA for the treatment of fibrosis due to NASH, which was accepted by the FDA in November 2019. The safety population of the interim analysis included 1,968 randomized patients who received at least one dose of investigational product (OCA or placebo). Adverse events were generally mild to moderate in severity and the most common were consistent with the known profile of OCA. The frequency of serious adverse events was similar across treatment arms (11% in placebo, 11% in OCA 10 mg and 14% in OCA 25 mg). The most common adverse event reported was dose-related pruritus (placebo, 19%; OCA 10 mg, 28%; OCA 25 mg, 51%). The large majority of pruritus events were mild to moderate, with severe pruritus occurring in a small number of patients. On May 22, 2020, Intercept announced that the June 9 virtual FDA advisory committee has been postponed. FDA requested additional data that Intercept will submit quickly. FDA is expected to extend the Prescription Drug User Fee Act (PDUFA; FDA action) date beyond June 26, 2020. On June 29, 2020, Intercept announced that FDA issued a Complete Response Letter (CRL) for obeticholic acid. FDA noted that based on currently available data, the potential benefits don't outweigh potential risks; additional safety and efficacy data were requested. Approval is now likely delayed until 2022.

14. pegunigalsidase alfa (Protalix BioTherapeutics)

Current Status: BLA filed. Orphan drug. Breakthrough therapy. Apr. 28, 2021: complete response letter. Approval may be delayed until early 2022.

Route of Administration/Dosing: Intravenous (IV) every two weeks at a dose of 1mg/kg or 2mg/kg every four weeks

Proposed Indication(s): treatment of Fabry disease

Mechanism of Action: Pegunigalsidase alfa is a proprietary plant cell-expressed, PEGylated, chemically modified recombinant alpha-galactosidase-A enzyme that is designed to be a more stable enzyme than currently marketed enzyme replacement therapies for Fabry disease.

Patient Impact: Fabry disease (FD) belongs to a group of lysosomal storage disorders. It is a rare genetic disease caused by mutations in galactosidase alpha gene (GLA), resulting in little to no α-galactosidase-A (α-Gal-A), a lysosomal enzyme. As a result, lysosomes are unable to break down and repurpose old cell materials, such as globotriaosylceramide (GL3) and glycosphingolipids. The fatty material, (GL3) can build-up within blood vessels and organs, such as the kidneys, heart and the central nervous system. There are two types of (FD), categorized as type 1 or "classic phenotype", which occurs at a young age and type 2 or "late-onset" phenotype. In both phenotypes, patients will have a decreased life expectancy typically due to renal failure, heart disease or cerebrovascular disease. Type 1 (FD) occurs early in childhood with nerve pain that occurs in the hands and feet which is exacerbated by increased activity, illness or stress. Furthermore, patients suffer from symptoms such as decreased sweating, gastrointestinal symptoms, whirl-like lesions of the eye, and small red or blue spots on the lower trunk area of the body, called angiokeratomas. Type 2 (FD) patients will develop heart disease or kidney disease by the age of 30 years or older, but lack many of the symptoms seen in type 1 (FD), so may go undiagnosed until organ failure is detected. (FD) typically affects males more severely than females due to their X-linked mutation. FD affects an estimated 1 in 40,000 to 60,000 males, while female prevalence remains unknown. There are about 7,000 patients in the US with Fabry disease.

Cost Estimates (per Patient): $300,000/yr

Current Therapies: Sanofi Genzyme's Fabrazyme® (agalsidase beta) was approved for (FD) on October 9, 2003. It is intravenously administered at a dose of 1mg/kg every two weeks. Fabrazyme is an enzyme replacement therapy (ERT) that works by lowering the amount of globotriaosylceramide (GL-3) that builds up and damages organs such as the kidney. The patent expired on September 27, 2015, therefore, biosimilar competition could be approved at any time. Amicus' Galafold® (migalastat) is the only approved oral therapy for the treatment of (FD) who has a certain genetic variant in GLA that is responsive to the drug. The dose for Galafold is 123mg taken orally every other day at the same time on an empty stomach. Galafold was approved on August 10, 2018, and has an annual cost of $315,000 per year. Galafold works by binding to α-Gal and acts as a chaperone therapy, helping fold and stabilize the enzyme.

Pipeline Product(s): Idorsia Pharmaceuticals lucerastat is an oral drug in phase III development with Orphan drug designation. Lucerastat works by inhibiting glucosylceramide synthase to treat (FD) regardless of the genetic mutation type. So far, it has shown benefit in blood levels of GL3, improved neuropathic pain and gastrointestinal symptoms. The dose for lucerastat is 1000mg orally twice per day. It is expected to be approved second half of 2021.

Comments: Pegunigalsidase alfa has been studied multiple clinical trials including three major phase III trials. The BRIDGE study showed an improvement in renal function when switched from agalsidase alfa (Replagal - Takeda) to pegunigalsidase alfa, measured as mean annualized estimated Glomerular Filtration Rate (eGFR) in both males and females. Overall, the study met its primary and secondary endpoints evaluating the safety and effectiveness of pegunigalsidase alfa on renal function. Twenty-two patients were evaluated in the study, an open-label, single-arm switch over study where patients were given 1mg/kg every two weeks. The average eGFR slope improved in agalsidase alfa a patients from -5.90 mL/min/1.73m2/year compared to -1.19mL/min/1.73m2/year while on Pegunigalsidase alfa. Male patients improved -6.36 mL/min/1.73m2/year to 1.73 mL/min/1.73m2/year and female patients saw benefit from 5.03 mL/min/1.73m2/year to 0.21 mL/min/1.73m2/year. Most adverse drug reactions (ADRs) were self-limiting with the exception of two patients who withdrew due to hypersensitivity reactions. The BRIGHT study is an open-label, switch over trial evaluating the efficacy, safety and pharmacokinetics of pegunigalsidase alfa at 2mg/kg administered intravenous every four weeks for 52 weeks in patients with Fabry disease who are also on enzyme replacement therapy (ERT). The company plans to have results by the fourth quarter 2020. Another phase III study, BALANCE, is a randomized , double-blind, head to head, active control study evaluating 80 patients who have declining renal function on the superiority of pegunigalsidase alfa over agalsidase beta (Fabrazyme® - Sanofi Genzyme) on renal function, measured by the average change in slope of (eGFR) over 24

months. The BALANCE study should have results in the second quarter of 2022. On Nov. 27, 2020, Protalix BioTherapeutics announced that the U.S. Food and Drug Administration (FDA) has extended the Prescription Drug User Fee Act (PDUFA) date for review of the Company's Biologics License Application (BLA) seeking accelerated approval of pegunigalsidase alfa for the proposed treatment of adult patients with Fabry disease. The FDA extended the PDUFA action date by three months to April 27, 2021, from January 27, 2021. On Dec. 30, 2020, Protalix BioTherapeutics and Chiesi announced final study results from the BRIDGE study, a Phase III 12 month open-label, single arm switch-over study evaluating the safety and efficacy of pegunigalsidase alfa, 1 mg/kg infused every two weeks, in up to 22 Fabry patients previously treated with agalsidase alfa (Replagal® - Takeda) for at least two years and on a stable dose for at least six months. Final results of the data generated in the study showed substantial improvement in renal function as measured by mean annualized estimated Glomerular Filtration Rate (eGFR slope) in both male and female patients who were switched from agalsidase alfa to pegunigalsidase alfa. Male patients improved from -6.36 mL/min/1.73m2/year to -1.73 mL/min/1.73m2/year and female patients improved from -5.03 mL/min/1.73m2/year to -0.21 mL/min/1.73m2/year. Of the 22 patients enrolled in the BRIDGE study, the majority of treatment emergent adverse events were mild or moderate in severity, with two patients (9.1%) withdrawing from the therapy due to hypersensitivity reaction that was resolved. The most common moderate treatment emergent adverse events were nasopharyngitis, headache and dyspnea. The FDA is not currently planning to hold an advisory committee meeting to discuss the application. On Feb. 23, 2021, Protalix BioTherapeutics, Inc. and Chiesi Global Rare Diseases announced positive topline results from the BRIGHT study. The BRIGHT study is a Phase III 12-month, open-label, switch-over study designed to evaluate the safety, efficacy and pharmacokinetics of pegunigalsidase alfa treatment, 2 mg/kg every four weeks, in up to 30 patients with Fabry disease previously treated with a commercially available enzyme replacement therapy (ERT) (agalsidase alfa – Replagal® or agalsidase beta – Fabrazyme®), for at least three years and on a stable dose administered every two weeks. Topline results indicate that 2 mg/kg of pegunigalsidase alfa administered by intravenous infusion every four weeks was found to be well tolerated among treated patients, and stable clinical presentation was maintained in adult Fabry patients. No new patients developed treatment-induced anti-drug antibodies (ADA) following the switch to pegunigalsidase alfa treatment. Study outcome measures showed plasma lyso–Gb3 concentrations remained stable during the study with a mean change of 3.01 nM from baseline (19.36 nM) to Week 52 (22.23 nM). Mean absolute change of eGFR values were stable during the 52–week treatment period, with a mean change from baseline of –1.27 mL/min/1.73 m2. Following a survey of participants using the Quality of Life EQ-5D-5L questionnaire, responses indicate that patient perception of their own health remained high and stable throughout the 52–week study duration, with overall health mean (SE) scores of 78.3 (3.1) and 82.1 (2.9) at baseline and Week 52, respectively, in a 0 to 100 scale. Using the short-form Brief Pain Inventory (BPI) questionnaire, approximately 75% of study participants had an improvement or no change in average pain severity at Week 52 (compared to baseline). The short-form BPI interference items also remained stable during the study. Pain-related results indicate that there was no increase and/or relapse in pain. No Fabry clinical events were reported during the study. The Company intends to report final data on the BRIGHT study in the second half of 2021. On Apr. 28, 2021, Protalix BioTherapeutics announced that it received a Complete Response Letter (CRL) received from the FDA. It was not due to any concerns relating to the potential safety or efficacy of pegunigalsidase alfa. The FDA noted that an inspection of Protalix's manufacturing facility in Carmiel, Israel, including the FDA's subsequent assessment of any related findings, is required before the FDA can approve the BLA. Due to travel restrictions, the FDA was unable to conduct the required inspection during the review cycle. The FDA explained that it will continue to monitor the public health situation as well as travel restrictions, and is actively working to define an approach for scheduling outstanding inspections.

15. sutimlimab (Sanofi)

Current Status: Orphan drug. Breakthrough therapy. BLA filed. Complete response letter. Approval expected in H1:2022

Route of Administration/Dosing: intravenous (IV) infusion (6.5gm or 7.5gm, depending on the patient's weight; on the first and seventh days of treatment, then once every other week)

Proposed Indication(s): cold agglutinin disease (CAD)

Mechanism of Action: C1s inhibitor; sutimlimab works by inhibiting C1s, a complement-cascade protease, to block signals for inflammation and cell destruction.

Patient Impact: CAD is a type of nonhereditary autoimmune hemolytic anemia. For patients who have it, an antibody, immunoglobulin M (IgM), sticks to the surface of red blood cells (RBCs). The complement part of the immune system attacks IgM when the patients experience low body temperatures. Usually diagnosed among older adults, primary cases of CAD probably result from abnormal B-cell production in bone marrow. The condition can be secondary to other conditions, such as autoimmune diseases, infections or some types of cancer, as well. At a prevalence of around 16 per 1 million people, an estimated 5,200 Individuals in the U.S. may be affected, but one-half or more of patients have mild forms of the condition. Typical symptoms include chronic anemia, fatigue and shortness of breath. Those who have it are more likely to experience blood clots. Symptoms tend to be variable, with most patients having periods of remission and episodes of more active disease. Acute hemolytic crisis – the sudden loss of more RBCs than the body can replace – can be life-threatening.

Cost Estimates (per Patient): $300,000+/yr

Current Therapies: Lifestyle factors, such as avoiding cold temperatures and protecting the head, fingers and toes from chills, are generally effective in preventing episodes for patients who have milder forms of CAD. For those who have CAD that is caused by another disorder, treating the underlying condition can reduce or even eliminate attacks. About one-half of patients who have severe cases of CAD receive blood transfusions to restore RBCs.

Presently, no drugs are FDA approved to treat the causes of severe primary CAD. Some patients have been treated off-label with short courses of rituximab or other cancer drugs. Although many patients responded and the responses typically lasted around a year or longer, treatment effectiveness decreased for subsequent episodes and some of the drugs can cause serious side effects. Soliris® (eculizumab), a drug indicated to prevent breakdown of RBCs for patients who have rare chronic blood conditions, also sometimes is used -- especially as rescue for very severe CAD episodes. It introduces the risk of infections, though; and treatment with it probably would need to be continual. More research is needed before any of the tested drugs can be recommended for general treatment.

Pipeline Product(s): Apellis' pegcetacoplan is a complement factor C3 inhibitor in Phase 2 development for the treatment of autoimmune hemolytic anemia. It's given as a twice weekly SC injection. Approval is possible for this indication in 2022.

Comments: The open-label, phase III CARDINAL clinical trial is being conducted in two parts. First, 24 patients who needed blood transfusions within six months to manage severe primary CAD were treated with sutimlimab on the first day, one week later and then once every two weeks for a total of 26 weeks. For 13 patients, hemoglobin levels either reached at least 12gm/dL or improved by at least 2gm/dL. Normal hemoglobin ranges from about 14gm/dL to 17gm/dL for men and about 12gm/dL to 15gm/dL for women. Additionally, bilirubin levels (an indicator of RBC destruction) stabilized to near normal counts after about three weeks of treatment for most patients. After five weeks of treatment, 17 patients did not need any transfusions for the remainder of the study. Patients also reported less fatigue. Positive effects developed quickly and persisted throughout the trial. In data from the phase III CARDINAL trial, intravenous administration of sutimlimab in 24 patients with cold agglutinin disease resulted in at least one treatment emergent adverse event (TEAE) in 22 patients. At least one treatment emergent serious adverse event (TESAE) was reported in seven patients, however, as per investigator none were related to sutimlimab. Additionally, at least one TESAE of infection was experienced by two patients which were assessed to be in unrelated to sutimlimab by investigator. No meningococcal infections were identified and no patient discontinued sutimlimab due to infection. Twenty-two (91.7%) patients experienced ≥1 treatment-emergent adverse event (TEAE), with 7 (29.2%) patients experiencing a serious TEAE (TESAE). There were no TESAEs assessed as related to sutimlimab. There was 1 death in a patient with hepatic cancer that was assessed as unrelated to the study drug. Serious infections were reported, but no meningococcal infections were identified. There were no thromboembolisms and decreases in mean D-dimer and thrombin-antithrombin III complex thrombotic markers were observed Twenty-two patients now are continuing

treatment to establish the long-term effectiveness and safety of sutimlimab. Results for the second part of the study should available in 2021. A separate phase III trial, Cadenza, is comparing treatment with sutimlimab vs. placebo for patients who have primary CAD, but who did not need blood transfusions within six months of entering the study. It, too, has a 26-week stage followed by a year-long extension to evaluate safety and duration of response. In the second part, all patients will be receiving sutimlimab. On Nov. 14, 2020, Sanofi announced that FDA issued a Complete Response Letter (CRL) regarding the Biologics License Application (BLA) for sutimlimab. The FDA noted deficiencies in the facility that will be manufacturing the medication for Sanofi. Approval is likely delayed until 2021. On June 11, 2021, Sanofi announced results from Part A of CADENZA, a pivotal Phase 3 double-blind, placebo-controlled study evaluating the safety and efficacy of sutimlimab in people with cold agglutinin disease (CAD) without a recent history of blood transfusion (within the prior six months). The data demonstrated treatment with sutimlimab resulted in rapid and sustained inhibition of C1-activated hemolysis in people with CAD, noted within one week of treatment, and clinically significant improvements in hemoglobin and fatigue when compared to placebo during the course of the study. The primary efficacy outcome was the proportion of patients who met all three of the following components: improvement in hemoglobin ≥1.5 g/dL from baseline at treatment assessment timepoint, (average of Weeks 23, 25, and 26); avoidance of transfusions from Week 5 through Week 26; and avoidance of other CAD-related therapies beyond what was permitted from Week 5 through Week 26. The secondary efficacy measures assessed improvement from baseline in key indicators of the disease process including hemoglobin, bilirubin, lactate dehydrogenase (LDH) levels, and quality of life as measured by Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Score. Seventy-three percent (n=16) of patients treated with sutimlimab met the primary composite endpoint, demonstrating improvement in hemoglobin ≥1.5 g/dL from baseline at treatment assessment timepoint (Weeks 23, 25, and 26); avoidance of transfusions from Week 5 through Week 26; and avoidance of other CAD-related therapies beyond what was permitted from Week 5 through Week 26 compared to 15% (n=3) in the placebo group (Odds Ratio=15.9, 95% CI: 2.9 to 88.0, p<0.001). Data showed sutimlimab increased and sustained mean hemoglobin levels from baseline to treatment assessment timepoint (Week 26) representing a statistically significant least squares (LS) mean difference of 2.6 g/dL (p<0.001; 95% CI:1.8 to 3.4) when compared with placebo. Hemoglobin improved rapidly, with a LS mean increase from baseline of ≥1 g/dL by Week 1 and ≥2 g/dL by Week 3. Overall mean hemoglobin levels were maintained >11 g/dL from Week 3 through treatment assessment timepoint, demonstrating a sustained effect throughout the remainder of the treatment period. A statistically significant improvement in fatigue as measured by FACIT-Fatigue assessment was achieved in patients treated with sutimlimab when compared to the placebo group, 10.8 points versus 1.9, respectively, with a LS mean difference of 8.9 points (p<0.001; 95% CI:4.0 to 13.9). A 5 or greater point increase in FACIT-Fatigue score suggests a clinically important change. Patients treated with sutimlimab had greater mean reductions in bilirubin, a key marker of hemolysis, from baseline to treatment assessment timepoint as compared with the placebo group (-22.1 µmol/L versus -1.8 µmol/L, respectively). Mean bilirubin levels were normalized below the upper limit of normal within 1 to 3 weeks in the sutimlimab group (upper limit of reference range 20.5 µmol/L) and maintained levels below the upper limit of normal to week 26. Treatment with sutimlimab led to meaningful improvements in LDH, an additional hemolysis marker, from baseline to treatment assessment timepoint compared to placebo (-150.8 U/L versus +7.6 U/L). Twenty-one patients (95.5%) in the sutimlimab group and 20 patients (100%) in the placebo group experienced at least one treatment emergent adverse event (TEAE). Three patients (13.6%) in the sutimlimab group experienced at least one treatment-emergent serious adverse event (TESAE) (n=4), including one TESAE assessed by the investigator as related to sutimlimab (cerebral venous thrombosis in a patient with a history of diabetes). One patient (5%) in the placebo group had three TESAEs. Treatment emergent adverse events reported more often in the sutimlimab group vs. placebo (difference of ≥ 3 patients between groups) were: headache (23% versus 10%), hypertension (23% versus 0%), rhinitis (18% versus 0%), Raynaud's phenomenon (18% versus 0%), and acrocyanosis (14% versus 0%). No deaths or meningococcal infections were reported. Sanofi plans to resubmit its Biologics License Application with the U.S FDA in the second half of 2021. Approval is expected in the 1H:2022.

16. teplizumab (Provention Bio)

Current Status: Breakthrough Therapy and Orphan Drug Designations. BLA filed. Priority Review.July 2, 2021: Complete Response Letter. Approval likely delayed until 4Q:2021 or 1Q:2022.

Route of Administration/Dosing: Intravenous (IV) infusion. Two courses are given six months apart. Each course includes daily infusions for 12 to 14 days. Given at doses of 51 mcg per square meter of body-surface area day 0 and titrating to 826 mcg per square meter of body-surface by day 4 and continue to day 13.

Proposed Indication(s): Prevent or delay clinical type one diabetes (T1D) in at-risk individuals

Mechanism of Action: Humanized anti-CD-3 specific monoclonal antibody that binds to and eliminates autoreactive T-cells while sparing regulatory T-cells

Patient Impact: Newly diagnosed T1D, also known as juvenile diabetes, is considered an orphan indication due to its high disease burden and unmet need in the U.S. Over 75% of people with T1D have poor control of their blood glucose levels, considered an HbA1c >7%. Poor control leads to complications that can result in kidney disease, cardiovascular disease, retinopathy and metabolic syndrome. Around half of the newly diagnosed T1D patients present with diabetic ketoacidosis (DKA), a life-threatening condition. For patients who are diagnosed before the age of 10 years old their life expectancy is estimated to be reduced by sixteen years. T1D is the second most common chronic childhood disease, behind asthma only. An estimated 64,000 new cases of T1D is diagnosed in the U.S. annually with 1 million to 1.5 million who currently have T1D. The average medical costs for someone with T1D is $16,752, annually. There is a genetic predisposition to inheriting T1D and an environmental trigger that leads to certain autoantibodies that lead to the self-destruction of the β-cells in the islets of Langerhans of the pancreas. Caucasians have the highest rate of inheriting T1D, mostly due to the presence of autoimmune related HLA-DR3 and HLA-DR4 genes. Known environmental triggers are not for certain, however, it is believed that around 60% of cases are associated with coxsackievirus B infection. Other environmental triggers can include living in cold weather climates and diet early in life. Over 300,000 people have two or more autoantibodies that put them at risk and of those, 200,000 also having dysglycemia. Provention Bio believes teplizumab could have a target population of 30,000 annually, representing about 15% of the 200,000 who have two or more autoantibodies, dysglycemia and would be genetic relatives at risk for TD1. The company also believes that awareness will lead to further screening of T1D relatives and could encourage broader testing globally with a total addressable patient population of 2.3 million people.

Cost Estimates (per Patient): $500,000 per patient over two cycles

Current Therapies: There is no prevention for T1D or disease modifying agents. Insulin is the backbone treatment for T1D with rapid-acting analogs typically recommended versus regular human insulin for T1D. Examples of rapid acting insulins include; Admelog® (insulin lispro injection – Sanofi-Aventis), Apidra® (insulin glulisine injection – Sanofi-Aventis), Fiasp® (insulin aspart injection – Novo Nordisk), Humalog® (insulin lispro injection – Eli Lilly [U-100 and U-200], authorized generics for U-100), Humalog® 50/50 mix (50% insulin lispro protamine suspension/50% insulin lispro injection – Eli Lilly), Humalog® Mix 75/25 (75% insulin lispro protamine suspension/25% insulin lispro injection – Eli Lilly, authorized generic), Lyumjev™ (insulin lispro-aabc injection – Eli Lilly), NovoLog® (insulin aspart injection – Novo Nordisk, authorized generic) and NovoLog Mix 70/30® (70% insulin aspart protamine suspension/30% insulin aspart injection – Novo Nordisk, authorized generic). Some analogs may be used in insulin pumps. Examples of human or regular insulin include; Humulin® N (NPH, human insulin isophane suspension [recombinant DNA {rDNA} origin] injection [vials and KwikPen] – Lilly), Humulin® R (regular insulin human injection [rDNA origin] U-100 and U-500 [vials] – Lilly), Humulin® 70/30 (70% NPH, human insulin isophane suspension and 30% regular human insulin injection [rDNA origin] [vials and KwikPen] – Lilly), Novolinreplace N and ReliOn® Novolin N® (NPH, human insulin isophane suspension [rDNA origin] injection [vials and FlexPen] – Novo Nordisk), Novolin® R and ReliOn® Novolin R® (regular human insulin injection [rDNA origin] solution [vials and FlexPen] – Novo Nordisk) and Novolin® 70/30 and ReliOn® Novolin 70/30® (70% NPH, human insulin isophane suspension and 30% regular human insulin [rDNA origin] injection [vials and FlexPen] – Novo Nordisk). Affreza® (insulin human - Mannkind) oral inhalation powder is a rapid acting insulin that is absorbed through the lungs. Long-acting insulin analogs include Levemir® (insulin detemir injection – Novo Nordisk), Lantus® (insulin glargine injection – Sanofi Aventis), Basaglar® (insulin glargine injection – Eli Lilly), Tresiba® (insulin degludec injection – Novo Nordisk) [U-100 and U-200], Toujeo® (insulin glargine – Sanofi Aventis) and Semglee® (insulin glargine injection – Viatris). Symlin® (pramlintide acetate pen injection – Astra Zeneca), a synthetic analog of amylin, is the only non-insulin approved for T1D. In addition to insulin, therapy patients may control blood glucose levels with finger stick monitoring, continuous glucose monitoring (CGM), diet and exercise. An “artificial pancreas” or “closed loop system” are terms used to describe insulin pumps when combined with CGM

to control T1D.

Pipeline Product(s): There are no drugs in late-phase development to prevent or delay T1D in at-risk individuals. Celltrans is developing donislecel, an allogenic human islets of Langerhans transplantation for patients with brittle T1D. Celltrans has a FDA advisory committee meeting scheduled to discuss the BLA on April 15, 2021. Once-weekly subcutaneous (SC) basal insulin icodec is being developed by Novo Nordisk and is currently in Phase III with projected approval in 2024. Biosimilars in development for other approved insulins include; SC insulin aspart from Lannett, Sanofi and Mylan/Biocon (Kixelle®). Semglee® (insulin glargine injection –Viatris) is seeking interchangeability with SC insulin glargine with a PDUFA date August 31, 2021. Lannett is also developing a biosimilar for SC insulin glargine, currently in phase III, with an estimated approval in 2023. Oramed is developing an orally administered insulin, which is currently in phase 3 with projected approval in 2025.

Comments: The National Institutes of Health (NIH), National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) and Juvenile Diabetes Research Foundation (JDRF) sponsored the phase II pivotal trial, named "At-Risk", which enrolled 76 non-diabetic participants at high risk for T1D. Patients were 8 to 49 years of age (72% under the age of 18), who had two or more T1D autoantibodies and dysglycemia, were double-blinded and randomized 1:1 to receive one 14-day course of teplizumab or placebo. After 40 participants developed T1D, the study was un-blinded to analyze the data and then blinded again, indefinitely. At the 2.5-year follow-up, 50% of teplizumab treated patients remained free of clinical T1D versus 22% in the placebo group, respectively. In patients treated with teplizumab, the median time to develop clinical T1D was approximately 5 years (59.6 months) versus 2 years (27.1 months) in the placebo group. Onset of clinical T1D was delayed by almost 3 years (32.5 months) in treated patients with one patient who has yet to develop T1D more than 8.5 years after starting treatment. Additionally, patients treated with teplizumab saw beta cell function improvement, increased C-peptide levels and improved insulin secretory capacity reflecting normal beta cell glucose sensitivity. Adverse events (AEs) were similar from previous trials, with decreased lymphocyte count with nadir by day 5 in 72.3% of patients. The reduction in blood cell counts improved by day 45 in the majority of patients. Rash that spontaneously resolves occurred in 36% of treated patients. Epstein-Barr virus (EBV) reactivation is common for anti-CD3 monoclonal antibodies. In the trial, quantifiable EBV DNA was found in blood samples in 50% of the teplizumab treated patients with just one patient who had symptoms. On average EBV levels decreased by day 77. Also, Provention Bio plans to develop and expand teplizumab for the treatment of newly diagnosed T1D patients. On April 8, 2021, Provention Bio announced that FDA recently identified deficiencies in the application for approval. The pharmacokinetic (PK) profiles of the drugs used in the bridging study were not comparable and that additional data would be required. It's possible that approval could be delayed for up to one year. On May 27, 2021, the FDA's Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) voted 10 yes and 7 no that the benefits of teplizumab outweigh the risks in support of approval to delay clinical type 1 diabetes mellitus. The EMDAC based its recommendation on safety and efficacy data from the pivotal TN-10 Study in which a single 14-day course of teplizumab delayed insulin-dependent, clinical-stage disease by a median of at least two years in presymptomatic patients with Stage 2 type 1 diabetes (T1D) compared to placebo. If approved, teplizumab will be the first disease-modifying therapy in T1D. On July 2, 2021, the FDA issued a Complete Response Letter (CRL) for Provention Bio's Biologics License Application (BLA) for teplizumab for the delay of clinical type 1 diabetes (T1D) in at-risk individuals. The FDA stated that a single, low-dose pharmacokinetic/pharmacodynamic (PK/PD) bridging study in healthy volunteers to compare planned commercial product with drug product originating from drug substance manufactured for historic clinical trials had failed to show PK comparability. The FDA indicated that the company needs to establish PK comparability appropriately between the intended commercial product and the clinical trial product or provide other data that adequately justify why PK comparability is not necessary. Provention Bio plans to collect this data from a PK/PD substudy in patients receiving 12-days of therapy in the ongoing Phase 3 PROTECT trial in newly diagnosed T1D patients later in the third quarter. The FDA also requested updated safety information as part of the BLA resubmission, likely related to the higher incidence of diabetic ketoacidosis in treated patients in the clinical trial vs. placebo. Provention Bio indicated that product quality issued cited by the FDA have already been addressed in amendments submitted by the company or can be addressed in the short-term. There are also manufacturing issues that need to be resolved prior to approval. Approval is likely delayed until 4Q:2021 or 1Q:2022.

17. tezepelumab (Amgen/AstraZeneca)

Current Status: Breakthrough therapy. BLA submitted May 10, 2021. Priority review. Approval expected by Jan. 10, 2022.

Route of Administration/Dosing: subcutaneous (SC) injection (210mg once every four weeks)

Proposed Indication(s): Treatment of patients with severe, uncontrolled asthma

Mechanism of Action: thymic stromal lymphopoietin (TSLP) inhibitor; monoclonal antibody that inhibits an inflammatory cytokine believed to initiate and prolong the inflammatory processes involved in asthma

Patient Impact: Allergens, dust, viruses and other irritants may prompt the production of TSLP, which then triggers immune cells to release inflammatory substances. Many patients who have severe asthma also have high levels of biomarkers, such as immunoglobulin E (IgE) and/or eosinophils (a type of white blood cells) in their blood. Another indicator of asthma's severity is fractional exhaled nitric oxide (FeNO), a sign of airway inflammation measured through a breath test. However, about one-third of those whose asthma is not well managed by current medications are believed to have numerous inflammation triggers or ones that do not have clear markers. High levels of TSLP seem to correlate with more severe asthma.

Amgen estimates that about one million U.S. patients have severe asthma that cannot be managed despite adherence to currently available treatments. Although patients who have severe, uncontrolled asthma represent only a small percentage of patients who have asthma, they account for as much as one-half of direct and indirect costs associated with the condition.

Cost Estimates (per Patient): $35,000/yr

Current Therapies: Most patients who have severe asthma presently are treated with high and/or more frequent doses of an ICS, such as Flovent® HFA (fluticasone) Inhalation Suspension, and a second type of asthma controller, such as montelukast tablets or Serevent® Diskus (salmeterol) Powder for Inhalation. Several inhalers, including Symbicort® (budesonide/formoterol) Inhalation Aerosol and Advair Diskus® (fluticasone/salmeterol) Powder for Inhalation, combine more than one type of medication in a single inhaler. Many patients also need OCS to manage asthma.
Other biologics that are FDA approved in combination with additional asthma drugs to treat some forms of severe asthma include: Xolair® (omalizumab - Genentech) injection. Approved in June 2003, Xolair interferes with IgE to treat patients as young as six years old for asthma symptoms not controlled by an ICS. It is given SC once every two weeks or four weeks, with doses depending on IgE levels and weight. Nucala® (mepolizumab – GlaxoSmithKline) injection. An interleukin-5 (IL-5) antagonist monoclonal antibody administered SC once every four weeks at 100mg for patients age 12 and older and 40mg for younger patients, Nucala was FDA approved in November 2015 for maintenance treatment of patients who have severe asthma with an eosinophilic phenotype. It is indicated for patients age six and older. Cinqair® (reslizumab – Teva) injection. Also an IL-5 inhibitor, Cinqair was approved in March 2016 as add-on maintenance treatment of adults who have severe eosinophilic asthma. It is given by weight-based IV infusions once every four weeks. Fasenra® (benralizumab – AstraZeneca) injection. As the third FDA-approved IL-5 blocker (November 2017), Fasrena is indicated for patients at least 12 years old who have severe asthma that has an eosinophilic phenotype. Dosing is 30mg SC once every eight weeks following three doses spaced four weeks apart. Dupixent® (dupilumab – Sanofi/Regeneron) injection is an IL-4α antagonist indicated in October 2018 as an add-on maintenance treatment for patients age 12 years and older who have moderate-to-severe eosinophilic asthma or who are dependent on OCS. Dosing is once every two weeks by SC injection. For patients weighing under 60kg (132 pounds) the dose is weight based; for heavier patients the dose is 300mg after one 600mg loading dose.

Pipeline Product(s): AB Science's masitinib is an oral tyrosine kinase inhibitor in Phase III development for the treatment of patients with severe, uncontrolled asthma. Approval is possible in 2022. Biosimiliars to Xolair may be launched in 2022.

Comments: Two phase III clinical trials and a follow-up collectively called PATHFINDER have been adding tezepelumab to standard treatments -- typically an inhaled corticosteroid (ICS), other asthma controllers and, often, an oral corticosteroid (OCS) -- for various populations who have severe, unmanaged asthma. In the trials, the most common side effects, which were similar in the placebo groups and the actively treated participants, included nasopharyngitis, upper respiratory infections and headaches. NAVIGATOR includes two groups of patients – one between the ages of 12 and 17 years, and one between 18 years old and 80 years old -- totaling more than 1,000 participants. At the beginning of the trial, all patients had uncontrolled asthma despite treatment with ICS and one or

more added drugs to control asthma episodes. Some took an OCS, as well. Following up to six weeks of screening, patients received either tezepelumab or placebo along with their usual medications for one year. Overall, tezepelumab-treated patients showed a 56% reduction in annualized asthma exacerbation rates (AAER). For patients whose eosinophil levels were low (less than 300 cells/microliter), AAERs decreased by 41%. Those with eosinophil levels of 300 cells/microliter, averaged decreases of 77% in AAERs and 85% in hospitalizations for asthma. Tezepelumab-treated patients also reported better asthma control, lung function and health-related quality of life (QoL). The 48-week-long, phase III SOURCE trial tested the effect of tezepelumab to reduce dependence on OCS for 150 adults who need maintenance therapy with both ICS and OCS plus a long-acting beta2 agonist (LABA) to manage asthma. Approximately one-third of patients had eosinophil levels of 300 cells/microliter or above. Patients were treated with tezepelumab or given a placebo once a month as OCS doses were tapered off over 36 weeks. Although the percentage of treated patient (54.1%) who were able to gradually eliminate 90% or more of their OCS was higher than the percentage of patients who got a placebo (46.1%), the difference was not statistically significant enough to meet criteria for success. DESTINATION is a two-year extension study to evaluate the safety of tezepelumab for patients who participated in either NAVIGATOR or SOURCE. Patients treated with tezepelumab will continue on it; those who received placebo will get either tezepelumab or placebo. All patients will keep using their other asthma controller medications. Other studies: In PATHWAY, a IIb trial, 82% of patients treated with tezepelumab plus their usual therapies felt their asthma was well controlled compared to 70% of those receiving a placebo. Actively treated patients also reported better QoL than patients receiving placebo (77% vs 64%). Across varying eosinophil, FeNO and other asthma indicator levels, up to 71% of asthma attacks were prevented in the actively treated group after 52 weeks of treatment. The phase II CASCADE study is examining the change in inflammatory cells, including eosinophils, in the airways of patients between 18 and 80 years old who have uncontrolled moderate-to-severe asthma and differing levels of biomarkers and FeNO.

18. tralokinumab (LEO Pharma)

Current Status: BLA filed. Complete response letter on Apr. 29, 2021. Approval likely delayed until Q4:2021 or Q1:2022

Route of Administration/Dosing: SC injection (300mg every 2 weeks)

Proposed Indication(s): treatment for moderate-to-severe atopic dermatitis (AD) in adults

Mechanism of Action: Interleukin-13 inhibitor

Patient Impact: Atopic dermatitis (AD) is a chronic skin disease characterized by inflammation of the skin and skin barrier defects. Children are often affected by AD during their first year of life and it will appear as dry, scaly patches on the scalp, arms and legs. The affected areas are often very itchy, which can range in severity, but is generally associated with inability to sleep and increased risk of skin infection. AD can be long-lasting and continue throughout adulthood. If left untreated, affected skin can become bumpy, discolored, and remain persistently itchy. The American Academy of Dermatology (AAD) estimates that between 10% and 20% of children and about 1% to 3% of adults are affected by AD. Most patients (90%) have disease onset before 5 years of age, as AD rarely begins in adulthood. Incidence of AD has increased 2- to 3-fold since the 1970s and is commonly associated with additional atopic manifestations, such as food allergies, allergic rhinitis, and asthma. About 20% of children who develop AD before 2 years of age will have persisting symptoms of disease and 17% will have intermittent symptoms by 7 years of age. In many cases, childhood AD resolves by the time a child reaches adulthood, but approximately 10% to 30% of patients will continue to have symptoms of disease throughout their lifetime.

Cost Estimates (per Patient): $40,000/yr

Current Therapies: Dupixent (dupilumab), a monoclonal antibody that antagonizes interleukin (IL)-4 and IL-13. Following a one-time loading dose of 600 mg (administered as two 300 mg subcutaneous injections), the recommended dose of Dupixent is 300 mg subcutaneously every other week. Other therapies to treat atopic dermatitis include topical steroids; phototherapy; topical immunomodulators (calcineurin inhibitors) such as Protopic (tacrolimus) and Elidel (pimecrolimus); Xolair (omalizumab), a monoclonal antibody that blocks IgG function that is sometimes used off label for AD. Methotrexate, cyclosporine, and mycophenylate mofetil are also sometimes used in patients with severe disease.

Pipeline Product(s): Lilly and Incyte's Olumiant (baricitinib) is a once-daily oral JAK inhibitor that has greater inhibitory potency at JAK1, JAK2, and tyrosine kinase (TYK)-2 relative to JAK3. It received FDA approval for moderately-to-severely active rheumatoid arthritis (RA) in May 2018 and is currently in phase III development for moderate-to-severe AD with approval possible in 2021. AbbVie's Rinvoq (upadacitinib) is a once-daily oral selective JAK1 inhibitor that was approved in Aug. 2019 for moderate-to-severe RA. It's currently in phase III development for moderate-to-severe AD with approval possible in 2021. Lilly and Incyte's Incyte (ruxolitinib) is an oral JAK inhibitor with approved indications for myelofibrosis, polycythemia vera, and steroid-refractory acute graft-versus-host disease. Ruxolitinib topical cream is currently in phase III development for moderate-to-severe AD. Approval is possible in 2021. Xbiotech's bermekimab is a monoclonal antibody that selectively inhibits IL-1-alpha. Bermekimab is a novel agent in phase II development for atopic dermatitis. Approval is possible in 2023. Dermira's lebrikizumab is a monoclonal antibody that targets IL-13 and is currently in phase II development for AD with approval possible in 2023.

Comments: On Dec. 11, 2019, LEO Pharma A/S announced that tralokinumab met all primary and secondary endpoints in its three pivotal Phase 3 studies (ECZTRA 1-3) for the treatment of moderate-to-severe atopic dermatitis (AD) in adults. During the studies, the overall adverse event rate was comparable between tralokinumab and placebo. ECZTRA 1 and ECZTRA 2 (ECZema TRAlokinumab studies no. 1 and 2), are randomized, double-blind, placebo-controlled, multinational, 52-week studies, which included 802 and 794 adult patients respectively, to evaluate the efficacy and safety of tralokinumab as monotherapy in adults with moderate-to-severe AD who are candidates for systemic therapy. ECZTRA 3 is a randomized, double-blind, placebo-controlled, multinational 32-week study, which included 380 adult patients, to evaluate the efficacy and safety of tralokinumab in combination with topical corticosteroids (TCS) in patients with moderate-to-severe AD who are candidates for systemic therapy. The primary endpoints in the three studies were an Investigator Global Assessment (IGA) score of clear (0) or almost clear (1) skin at week 16 and at least a 75 percent or greater change from baseline in their Eczema Area and Severity Index (EASI) score at week 16. A change from baseline to week 16 in SCORing of Atopic Dermatitis (SCORAD), Pruritus Numeric Rating Scale (NRS) of at least 4, and Dermatology Life Quality Index (DLQI) were secondary endpoints. Results from the phase III ECZTRA 1 trial (n=802) showed that the overall frequency (76% for tralokinumab and 77% for placebo) and severity of AEs in ECZTRA 1 were comparable across the treatment groups over 16 weeks. The most commonly

reported AEs that were higher with tralokinumab included viral upper respiratory tract infections (23% tralokinumab; 21% placebo) and conjunctivitis (7% tralokinumab; 2% placebo). In the phase III ECZTRA 2 trial (n=794), the overall frequency (62% for tralokinumab and 66% for placebo) and severity of AEs in ECZTRA 2 were comparable across the treatment groups over 16 weeks. The most commonly reported AEs that were higher with tralokinumab included upper respiratory tract infections (10% tralokinumab; 9% placebo) and conjunctivitis (3% tralokinumab; 2% placebo). In the phase III ECZTRA 3 combination trial (n=380), the overall frequency (71% for tralokinumab plus topical corticosteroid (TCS) and 67% for placebo plus TCS) and severity of AEs were comparable across the treatment groups over 16 weeks. The most commonly reported AEs that were higher with tralokinumab plus TCS included viral upper respiratory tract infections (19% tralokinumab plus TCS; 11% placebo plus TCS), conjunctivitis (11% tralokinumab plus TCS; 3% placebo plus TCS), headache (9% tralokinumab plus TCS; 5% placebo plus TCS), upper respiratory tract infections (8% tralokinumab plus TCS; 5% placebo plus TCS) and injection site reactions (7% tralokinumab plus TCS; 0.0% placebo plus TCS). Tralokinumab plus TCS was associated with lower rates of severe and serious infections and eczema herpeticum versus placebo plus TCS. On July 9, 2020, LEO Pharma announced that the Biologics License Application (BLA) for tralokinumab for the treatment of adults with moderate-to-severe atopic dermatitis (AD) has been accepted for review by the FDA. The FDA has set a target action date in the second quarter of 2021. According to the manufacturer, the PDUFA date is Apr. 27, 2021. On Apr. 29, 2021, LEO Pharma announced that the FDA has issued a Complete Response Letter requesting additional data relating to a device component of tralokinumab. FDA did not request any new data on the clinical efficacy or safety of the drug. LEO plans to provide this info as quickly as possible. Approval is likely delayed until the fourth quarter of 2021 or the first quarter of 2022

19. valoctocogene roxaparvovec (Roctavian – BioMarin Pharmaceuticals)

Current Status: Orphan drug. Breakthrough therapy. Aug. 2020: Complete response letter. Resubmission expected in Q2:2022. Approval likely delayed until late 2022 or early 2023

Route of Administration/Dosing: intravenous (IV) infusion [one-time; 6x1013 vector genomes (vg)/kg]

Proposed Indication(s): treatment of adult patients with severe hemophilia A

Mechanism of Action: Valrox is a gene therapy. Through an adeno-associated virus (AAV) vector that can penetrate cells without harming them, it replaces the missing gene needed to produce factor VIII.

Patient Impact: Hemophilia is a mainly inherited condition that affects about 16,000 Americans – predominantly boys and men. Around one-third of newly diagnosed patients do not have a family history of the disorder, however. Their hemophilia results from a new mutation. For patients who have hemophilia, A deficiency in one or more natural clotting factors means that their blood does not clot properly. Uncontrolled and often spontaneous bleeding causes sometimes intense pain, irreversible joint damage and potentially life-threatening hemorrhages. In hemophilia A, patients do not produce enough of a protein designated as factor VIII. Approximately four-fifths of patients who have hemophilia have the A type, which tends to be more severe than other types. Up to 35% of patients who have hemophilia A develop inhibitors, antibodies that reduce the effectiveness of factor VIII replacement. Approximately 50-60% of patients have severe hemophilia A (factor VIII < 2% of normal). According to BioMarin, about 2,400 patients in the US will be candidates for treatment with Valrox.

Cost Estimates (per Patient): $2-3 million

Current Therapies: Hemophilia presently cannot be cured. However, several recombinant factor VIII products have been approved by the FDA to treat and prevent bleeds. Most are administered by IV infusion, usually two times to four times a week to prevent bleeding episodes. To control acute bleeding, varying amounts are infused depending on severity of the bleed. Infused factor VII products include Advate (Baxalta), Kogenate FS (Bayer), Kovaltry® (Bayer), Novoeight® (Novo Nordisk), Nuwiq® (coagulation factor VIII [Factor VIII] - Octapharma), Recombinate (Baxalta) and Xyntha® Solofuse® (Pfizer). Long-acting formulations, Adynovate® (antihemophilic Factor [Recombinant], PEGylated – Baxalta), Afstyla® antihemophilic factor [recombinant], single chain – CSL Behring), Eloctate® (antihemophilic factor [Recombinant], Fc Fusion Protein – Bioverativ) and Jivi® (antihemophilic factor [recombinant], PEGylated-aucl - Bayer) also are available. Other infused factor VIII products on the market are derived from human plasma and some also include another clotting factor.

Genentech's Hemlibra® (emicizumab-kxwh) currently is the only subcutaneously (SC) administered (weekly) product for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A that has developed factor VIII inhibitors. Later approved for patients with hemophilia A without inhibitors.

Pipeline Product(s): Other gene therapies for hemophilia A in the pipeline include DTX-201 (Ultragenyx/Bayer), giroctocogene fitelparvovec (Sangamo/Pfizer), SPK-8011 (Spark Therapeutics) and TAK-754 (Takeda). These may compete in the market in 2022+.

Comments: On July 8, 2019, BioMarin announced that it plans to submit its BLA to FDA in 4Q:2019. Filing will be based on the updated three-year Phase 1/2 data and the recently completed Phase 3 interim analysis of patients treated with valoctocogene roxaparvovec. The three-year update of the 6e13 vg/kg dose cohort in the Phase 1/2 study demonstrated that bleed rate control and reduction in Factor VIII usage was maintained for a third year following a single administration of valoctocogene roxaparvovec. In the year prior to study entry, the mean Annualized Bleed Rate (ABR) was 16.3 and the median was 16.5. Over three years, the ABR was reduced to a mean of 0.6 and a median of zero. This represents a 96% reduction in participants' mean ABR, and there is 100% resolution of target joints. There was also a 96% reduction in participants' mean annualized Factor VIII usage rate over three years, and all participants remain off Factor VIII prophylaxis. Factor VIII levels sustained over a three-year period were sufficient to achieve striking hemostatic efficacy. Factor VIII expression has entered a plateau phase where the rate of decline has substantially slowed, which could be indicative of durable, long-term expression. Overall, valoctocogene roxaparvovec is well-tolerated. No participants developed inhibitors to Factor VIII, and no participants withdrew from the study. All participants have remained off Factor VIII prophylaxis. Corticosteroid use was transient with no long-lasting clinical sequelae. No participants have developed thrombotic events. Transient liver biomarker abnormalities and infusion-associated reactions have been the primary treatment-related adverse events, with no emergence of any delayed adverse events. A phase III study, GENEr8-1, is enrolling patients with a goal of 130 participants by mid-autumn 2019. In preliminary results released at the end of May, 2019, eight of the 16 study patients who had been

treated 26 weeks earlier with 6x1013 vg/kg of valrox, achieved the study's goal to increase factor VIII levels to 40 IU/dL. Estimates are that annual averages for both the bleeding rate and the use of factor VIII replacement will drop by at least 80%. Although over 30% of the 22 patients now in the study have reported side effects such as elevated liver enzymes, nausea, headache and back pain; only three side effects were considered to be severe. No one has withdrawn from the study and no patients have developed inhibitors to factor VIII. The Phase III study is expected to complete enrollment in the fourth quarter of 2019, with one-year data from 130 patients expected by the end of 2020 or in early 2021. A second phase III trial, GENEr8-2, which was testing a lower dose (4x1013 vg/kg) of valrox for 40 patients, has been discontinued in favor of the higher dose. On Dec. 23, 2019, BioMarin announced that the company submitted a Biologics License Application (BLA) to the FDA for valoctocogene roxaparvovec for adults with hemophilia A. Approval is expected by Aug. 21, 2020. On May 31, 2020, BioMarin announced an update to its previously reported results of an open-label Phase 1/2 study of valoctocogene roxaparvovec. The four-year update for the 6e13 vg/kg and three-year update for the 4e13 vg/kg cohorts demonstrated that all subjects in both cohorts remain off prophylactic Factor VIII treatment since receiving their single dose of valoctocogene roxaparvovec. Cumulative mean annualized bleed rates (ABR) remain less than one (1) in both cohorts and below pre-treatment baseline levels. The mean ABR in year four for the 6e13 vg/kg cohort was 1.3, and the mean ABR in year three for the 4e13 vg/kg cohort was 0.5. Over the past year, six of the seven participants in the 6e13 vg/kg cohort and five of the six participants in the 4e13 vg/kg cohort remain free of spontaneous bleeds. Factor VIII activity levels declined commensurate with the most recent years' observations and remain in a range to provide hemostatic efficacy. Overall, the safety profile of valoctocogene roxaparvovec remains consistent with previously reported data with no delayed-onset treatment related events. No participants developed inhibitors to Factor VIII, and no participants withdrew from the study. No participants have developed thrombotic events. The most common adverse events associated with valoctocogene roxaparvovec occurred early and included transient infusion-associated reactions and transient, asymptomatic, and mild to moderate rise in the levels of certain proteins and enzymes measured in liver function tests with no long-lasting clinical sequelae. On Aug. 19, 2020, BioMarin announced that the FDA issued a Complete Response Letter (CRL) for valoctocogene roxaparvovec. FDA is requesting two-year data from BioMarin's ongoing Phase III study to determine if there's sufficient evidence of a durable effect using Annualized Bleeding Rate (ABR) as the primary endpoint. Results from the Phase III study are expected in Nov. 2021. Approval is likely delayed until 2022. On Jan. 10, 2021, BioMarin announced positive topline results from its ongoing global Phase 3 GENEr8-1 study of valoctocogene roxaparvovec in 134 participants. All participants in the study received a single dose of valoctocogene roxaparvovec and completed a year or more of follow-up. Data from the study with a mean follow-up of 71.6 weeks showed that in the pre-specified primary analysis for Annualized Bleeding Rate (ABR) a single dose of valoctocogene roxaparvovec significantly reduced ABR by 84% from a prospectively collected 4.8 (median 2.8) at baseline to 0.8 (median 0.0) bleeding episodes per year (p-value <0.0001), among a pre-specified group of prior participants in a non-interventional baseline observational study (rollover population; N=112). 80% of participants were bleed-free starting at week five after treatment. Valoctocogene roxaparvovec also significantly reduced the mean annualized Factor VIII in the rollover population by 99% from 135.9 (median 128.6) to 2.0 (median 0.0) infusions per year (p-value <0.0001). At the end of the first year post-infusion with valoctocogene roxaparvovec, participants in the modified intent-to-treat (mITT) population (N=132) had a mean endogenous Factor VIII expression level of 42.9 (SD 45.5, median 23.9) IU/dL, as measured by the chromogenic substrate (CS) assay, supporting the marked clinical benefits observed with abrogation of bleeding episodes and Factor VIII infusion rate. Factor VIII expression declined at a slower rate compared to the Phase 1/2 study, and remained in a range to provide hemostatic efficacy. In a subset of the mITT population that had been dosed at least two years prior to the data cut date (N=17), Factor VIII expression declined from a mean of 42.2 (SD 50.9, median 23.9) IU/dL at the end of year one to a mean of 24.4 (SD 29.2, median 14.7) IU/dL at the end of year two with continued hemostatic efficacy demonstrated by a mean ABR of 0.9 (median 0.0) bleeding episodes per year. Overall, in the Phase 3 study, valoctocogene roxaparvovec has been well tolerated by the 134 participants who received a single 6e13 vg/kg dose. No participants developed inhibitors to Factor VIII, or thromboembolic events. One participant was lost to follow-up. Infusion-related reactions were effectively mitigated by managing infusion rates. Alanine aminotransferase (ALT) elevation (115 participants, 86%), a laboratory test of liver function, remained the most common adverse event (AE). Other common adverse events were headache (51 participants, 38%), nausea (50 participants, 37%), aspartate aminotransferase (AST) elevation (47 participants, 35%), arthralgia (38 participants, 28%) and fatigue (37 participants, 27%). Twenty-two (16.4%) participants experienced a total of 43 serious adverse events (SAEs), and all SAEs resolved. Common, steroid-related side effects can occur with temporary use of corticosteroid (or alternative immunosuppressants) to manage ALT elevation. On Apr. 29, 2021, BioMarin announced that it plans to resubmit its application for approval to FDA in the second quarter of 2022, followed by a 6 month FDA review. Approval is expected in late-2022 or early-2023. On May 19, 2021, BioMarin announced an update to its previously reported results from an open-label Phase 1/2 study. Five-

year and four-year post-treatment follow-up of the 6e13 vg/kg and 4e13 vg/kg cohorts, respectively, shows a sustained treatment benefit of valoctocogene roxaparvovec. All participants in both cohorts remain off prophylactic Factor VIII treatment. Mean cumulative annualized bleed rates (ABR) remain less than one in the 6e13 vg/kg cohort and substantially below pre-treatment baseline levels; the mean ABR in year five for the 6e13 vg/kg cohort was 0.7 with an ABR reduction of 95% and Factor VIII use reduction of 96% through five years, compared to pre-infusion. The mean ABR in year four for the 4e13 vg/kg cohort was 1.7 with a mean cumulative ABR reduction of 92% and Factor VIII use reduction of 95% through four years, compared to pre-infusion. Factor VIII activity levels declined commensurate with the most recent years' observations and continue to remain in a range to provide hemostatic efficacy. BioMarin is targeting a Biologics License Application (BLA) submission in the second quarter of 2022 assuming favorable Phase III study results, followed by an expected six-month review procedure by the FDA. On July 19, 2021, BioMarin announced new data for valoctocogene roxaparvovec. GENEr8-1 is a pivotal Phase 3 study with 134 participants. All patients have received a single dose and completes a year or more follow-up. Over 90 percent (N=134) of all participants in the GENEr8-1 study had an annualized bleed rate (ABR) of zero or a lower bleed rate than baseline after week 4 after treatment with valoctocogene roxaparvovec. Mean annualized Factor VIII utilization rate, among a pre-specified group of prior participants in a non-interventional baseline observational study (rollover population; N=112) decreased from baseline on Factor VIII prophylaxis by 99% from 3961.2 (median 3754.4) to 56.9 (median 0) IU/kg/year after week 4 after treatment with valoctocogene roxaparvovec (p-value <0.001). As previously shared in January 2021, data from the pre-specified rollover population (N=112) in the GENEr8-1 study with a mean follow-up of 71.6 weeks demonstrated that in the pre-specified primary analysis for ABR, calculated through each subject's last assessment, a single dose of valoctocogene roxaparvovec significantly reduced mean ABR by 84% from a prospectively collected 4.8 (median 2.8) at baseline to 0.8 (median 0.0) bleeding episodes per year (p-value <0.001). In addition, the mean annualized Factor VIII infusion rate was reduced by 99% from 135.9 (median 128.6) to 2.0 (median 0.0) infusions per year (p-value <0.001). Overall, in the Phase 3 study, valoctocogene roxaparvovec has been well tolerated by the 134 participants who received a single 6e13 vg/kg dose. No participants withdrew due to adverse events. No participants developed inhibitors to Factor VIII, or experienced thromboembolic events. One participant was lost to follow-up. Infusion reactions were defined as any AEs occurring within 48 hours post-infusion. The most common infusion reactions were nausea (14.2%), fatigue (7.5%), and headache (6.0%). Systemic hypersensitivity during or following infusion was mitigated by slowing or pausing infusion and treating with supportive medications, as indicated. All four (3.0%) participants with an interruption due to infusion-related symptoms were able to complete their infusion. Twenty-two (16.4%) participants experienced a total of 43 serious adverse events (SAEs), and all SAEs resolved.

20. vosoritide (Voxzogo - BioMarin)

Current Status: Orphan drug. Review was extended three months to Nov. 20, 2021.

Route of Administration/Dosing: subcutaneous (SC) self-injection (15mcg/kg once daily)

Proposed Indication(s): for the treatment of children who have achondroplasia

Mechanism of Action: C-type Natriuretic Peptide (CNP) analog. In achondroplasia, fibroblast growth receptor factor 3 (FGFR3) is overactive, severely decreasing bone development. Vosoritide is a long-acting derivative of CNP, a naturally produced substance that regulates the growth of bones. By blocking FGFR3 receptors, it helps to reduce the activity of FGFR3 for children whose bones have not yet stopped growing.

Patient Impact: The most common form of disproportionate short stature in humans, achondroplasia results from mutations of FGFR3 genes. It is inherited for about one-fifth of individuals who have it, but the majority of cases are random. Characteristics of achondroplasia are due to malformation of bones. They include overall shortness (usually under five feet), short arms, short bowed legs, spinal curvature and unusually large heads with bulging foreheads and flattened facial areas (frontal bossing). Individuals who have it also may have breathing and lung conditions, such as sleep apnea, mainly resulting from narrow upper airways and small ribcages. Ear infections are more common, as well.

Achondroplasia affects about one birth in 10,000 to 30,000; or around 100 to 400 babies per year in the United States. Among the estimated 30,000 Americans living with the condition, roughly one-quarter of individuals are under the age of 18 – the years when growth plates in bones typically remain open, allowing for increases in height.

Cost Estimates (per Patient): $350,000/yr

Current Therapies: No treatments are FDA approved specifically to treat achondroplasia. Off-label therapy with growth hormones is not particularly successful for most children. Some children may need surgical procedures to correct spinal abnormalities that threated mobility. However, surgery to lengthen bones, which requires multiple operations, increases height by only few inches. Additionally, operations frequently have complications such as infections, fractures and uneven limb length. Other current therapies are used only to manage achondroplasia's symptoms and co-morbidities.

Pipeline Product(s): Ascendis Pharma's ACP-015 is an antagonist of fibroblast-growth-factor-receptor 3 (FGFR3) that is in Phase II development for the treatment of achondroplasia. It's administered as a weekly SC injection. Approval is possible in 2023.

Comments: In December 2017, a phase III continuation study enrolled 121 children (ages five years to 14 years) with achondroplasia. Participants were randomized to receive either 15mcg/kg of vosoritide or a placebo injected SC once daily. On Dec. 16, 2019, BioMarin reported final Phase III trial results. Treated children averaged 1.6cm (about 0.6 inch) more growth during the first year than those receiving placebo injections. All but two of the children are continuing to receive vosoritide in the study's extension until the planned end date of December 2024. In the study, vosoritide was generally well tolerated. The majority of adverse events (Aes) were mild and no serious adverse events were reported as study drug-related. Injection site reactions were the most common drug-related Aes, and all were transient. No clinically significant blood pressure decreases or new safety findings were observed. In a phase II clinical trial of 35 children, a daily dose of 15mcg/kg or 30mcg/kg maintained increased growth rates for as long as 42 months. The average increase was between 1.1cm (about one-half inch) and 2.3cm (slightly less than one inch) per year. The 30mcg dose did not offer any advantages over 15mcg/day, and its chance of side effects was much higher, so subsequent trials will focus on the 15mcg/kg. Started in 2018, a separate phase II study is comparing treatment with vosoritide with placebo for approximately 70 children. Results are expected in May 2021. On Aug. 20, 2020, BioMarin announced that it has submitted a New Drug Application (NDA) to the FDA for vosoritide for children with achondroplasia, the most common form of disproportionate short stature in humans. If standard review, approval is expected by Aug. 20, 2021. Some experts anticipate rapid uptake, with 50% of eligible patients on the drug within the first year on the market. On Dec. 21, 2020, BioMarin announced that children in the open-label long-term extension of the Phase 3 study of vosoritide maintained an increase in Annual Growth Velocity (AGV) through the second year of continuous treatment. These analyses are the result of the combination of data of the same patients enrolled in three consecutive trials. In the first trial, a "run in" period consisted of longitudinal measurement of height in all patients prior to receiving treatment. After at least six months observation in the run-in trial, 121 patients were randomized 1:1 to receive either placebo or vosoritide at a dose of 15 ug/kg/day. One year later, patients previously receiving placebo were crossed over to receive vosoritide in an open-label treatment extension study, while those

patients previously on vosoritide remained on treatment. A first analysis, comparing all children randomized and treated with vosoritide for two years (n=52) to all children from the run-in study who were randomized to receive placebo with an untreated observation period of two years (n=38), showed improvement in one-year height change in the treated group relative to the untreated group that was similar in the second year of treatment, 1.79 cm, as in the first year of treatment, 1.73 cm. The cumulative height gain over the 2-year treatment period was 3.52 cm compared to untreated children, which is the sum of the first year (1.73) and the second year (1.79). On Apr. 15, 2021, BioMarin announced that its Phase 2 extension study of vosoritide for achondroplasia showed that improvement in growth velocity is sustained over 5 years of treatment and does not reduce the total duration of the growth period. Bone age progressed normally and posterior-anterior (PA) X-rays of the hand annually showed no significant changes in bone mineral content or bone mineral density. The mean (±SD) increase in annualized growth velocity (AGV) observed over 60 months of treatment was 1.35 (±1.07) cm/year. There was an overall mean (±SD) increase in height Z-score (which measures the height deficit in standard deviations relative to the mean for age and gender-matched average stature children) at 60 months of 0.78 (±0.70) using the CDC standards for average stature children. Vosoritide was well tolerated at the doses of 15 and 30 µg/kg/day, and the safety profile remained unchanged with no new types of adverse events (Aes) developing over time, and no serious Aes were related to therapy. No new safety findings have emerged, and clinically inconsequential blood pressure changes were mild, transient and self-limiting, On Apr. 29, 2021, BioMarin announced that the FDA extended its review of vosoritide by three months to allow it additional time to review recently submitted two-year results from a Phase 3 extension study. Vosoritide is a SC C-type Natriuretic Peptide (CNP) analog for the treatment of children who have achondroplasia, the most common form of disproportionate short stature. Approval is now expected by Nov. 20, 2021.