PIPELINE REPORT

Specialty Drugs

July 2018

PIPELINE DRUG	CURRENT STATUS	ANTICIPATED APPROVAL	WHAT IS THIS DRUG BEING DEVELOPED FOR?
AVXS 101 (Novartis)	Phase 3	2018	Gene therapy using an adeno-associated virus vector (AAV9) containing the SMN1 transgene for the treatment of spinal muscular atrophy (SMA); IV infusion (one-time) Breakthrough Therapy Orphan Drug
baricitinib (Olumiant - Lilly / Incyte	NDA Filed	2018 Approved 5/29/2018	Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis (RA); oral (once daily)
binimetinib / encorafenib (Mektovi / Braftovi - Array BioPharma)	NDA Filed	2018 06/30/2018	MEK inhibitor for the treatment of advanced and unresectable or metastatic malignant cutaneous melanoma harboring NRAS mutations; oral (twice daily) Orphan Drug PGx
cannabidiol (Epidiolex - GW Pharmaceuticals)	NDA Filed	2018 Approved 06/25/2018	Epidiolex contains the cannabinoid, cannabidiol, for treatment of seizures associated with Lennox-Gastaut syndrome (LGS) and Dravet syndrome; oral therapy Breakthrough Therapy Orphan Drug
cemiplimab (Sanofi/Regeneron)	BLA Filed	2018 10/28/2018	Programmed Death-1 (PD-1) inhibitor for the treatment of adults with metastatic or locally advanced and unresectable cutaneous squamous cell carcinoma (CSCC); IV infusion Breakthrough Therapy
duvelisib (Verastem)	NDA Filed	2018 10/05/2018	Phosphoinositide-3-kinase (PI3K)-delta and PI3K-gamma inhibitor for the treatment of patients with relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma and relapsed or refractory follicular lymphoma; oral Orphan Drug
entinostat (Syndax Pharmaceuticals)	Phase 3	2018	Histone deacetylase inhibitor for the second-line treatment of postmenopausal women with advanced ER+ breast cancer with exemestane; oral (once weekly) Breakthrough Therapy PGx
erenumab (Aimovig - Amgen/Novartis)	BLA Filed	2018 Approved 05/17/2018	A calcitonin gene-related peptide (CGRP) receptor antagonist monoclonal antibody for prevention of migraine in patients with four or more migraine days per month; subcutaneous injection (monthly)
fremanezumab (Teva)	BLA Filed	2018 06/16/2018	Anti-CGRP mAb for the prevention of chronic and high frequency episodic migraines; subcutaneous therapy
inotersen (Tegedi - Ionis Pharmaceuticals/Akacea)	NDA Filed	2018 10/06/2018	Antisense oligonucleotides that targets transthyretin (TTR) for treating hereditary amyloid transthyretin-mediated (hATTR) amyloidosis; SC injection (once weekly) Orphan Drug

PGx = Pharmacogenetic test in development

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ivosidenib (Tibsovo - Agios Pharmaceuticals)	NDA Filed	2018 08/21/2018	Isocitrate dehydrogenase 1 inhibitor for the treatment of relapsed or refractory (R/R) acute myeloid leukemia (AML) with an isocitrate dehydrogenase 1 (IDH1) mutation; oral Orphan Drug PGx
lanadelumab (Shire)	BLA Filed	2018 08/26/2018	Fully human Monoclonal Antibody (MAb) that inhibits plasma kallikrein for the prevention of hereditary angioedema attacks; SC (every 2 weeks) Breakthrough Therapy Orphan Drug PGx
larotrectinib (Bayer/Loxo Oncology)	NDA Filed	2018 11/26/2018	Tropomyosin receptor kinase (TRK) inhibitor for the treatment of unresectable or metastatic solid tumors with TRK-fusion proteins; oral Breakthrough Therapy Orphan Drug PGx
lisocabtagene maraleucel (JCAR017 - Celgene)	Phase 2	2018	CD19-directed CAR T for the treatment of patients with relapsed/refractory (R/R) aggressive large B-cell non-Hodgkin lymphoma (NHL); IV infusion (one time) Breakthrough Therapy
lorlatinib (Pfizer)	NDA Filed	2018 08/12/2018	Anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor (TKI) for the treatment of patients with ALK-positive metastatic non-small cell lung cancer (NSCLC), previously treated with one or more ALK TKIs; oral Breakthrough Therapy Orphan Drug
migalastat (Galafold - Amicus)	NDA Filed	2018 08/13/2018	Alpha-galactosidase A enhancer for the treatment of Fabry disease; oral (every other day) Orphan Drug PGx
ozanimod (Celgene)	Phase 3	2019	Sphingosine 1-phosphate (S1P) receptor modulator for the treatment of relapsing MS; oral
patisiran (Alnylam)	NDA Filed	2018 08/11/2018	RNAi therapeutic targeting the transthyretin (TTR) gene for treating hereditary amyloid transthyretin-mediated (hATTR) amyloidosis: IV infusion Breakthrough Therapy Orphan Drug
pegvaliase (Palynziq - BioMarin)	BLA Filed	2018 Approved 05/24/2018	Pegylated recombinant phenylalanine ammonia lyase for the treatment of severe phenylketonuria (PKU); SC Orphan Drug
romosozumab (Evenity - Amgen /UCB)	Complete Response	2018	Humanized antibody that targets and inhibits sclerostin for the treatment of postmenopausal osteoporosis; SC (once monthly for 1 year)

PGx = Pharmacogenetic test in development

PIPELINE REPORT

Specialty Drug Detail - July 2018

AVXS 101 (Novartis)

Current Status: Phase III. Orphan drug. Breakthrough therapy. BLA filing possible in mid-2018 with approval in late-2018 or early-2019

Route of Administration/Dosing: IV infusion (1.1x10^14 vg/kg; one time)

Proposed Indication(s): Treatment of patients with spinal muscular atrophy (SMA) Type 1 who are less than 6 months of age and are genetically defined by nonfunctional survival motor neuron 1 gene (SMN1) with 1 or 2 copies of survival motor neuron 2 gene (SMN2).

Mechanism of Action: AVXS-101 is a gene therapy designed to deliver a functional copy of the SMN1 gene to motor neuron cells in SMA patients. AVXS-101 comprises the shell of a genetically engineered virus, the adeno-associated virus (AAV) 9, called a capsid, that delivers a normal copy of the SMN1 gene to the brain via the bloodstream. Once the SMN1 gene (called a transgene because it comes from an external source) reaches patients' cells, it supplements those cells' own production of SMN protein. The SMN1 transgene in AVXS-101 consists of double-stranded DNA, meaning it takes the same form as natural genes and can be activated more quickly, producing faster, more efficient therapy. AVXS-101 includes the genetic instructions to activate the transgene so that SMN protein production is continuous and sustainable.

Patient Impact: Spinal Muscular Atrophy (SMA) is characterized by loss of motor neurons in the spinal cord and lower brain stem, resulting in severe and progressive muscular atrophy and weakness. Ultimately, individuals with the most severe type of SMA can become paralyzed and have difficulty performing the basic functions of life, like breathing and swallowing. Due to a loss of, or defect in the SMN1 gene, people with SMA do not produce enough survival motor neuron (SMN) protein, which is critical for the maintenance of motor neurons. The severity of SMA correlates with the amount of SMN protein. People with Type 1 SMA, the most severe life-threatening form, produce very little SMN protein and do not achieve the ability to sit without support or live beyond 2 years without respiratory support. People with Type 2 and Type 3 produce greater amounts of SMN protein and have less severe, but still life-altering forms of SMA. This disease affects approximately 30,000 to 35,000 patients in the United States, Europe and Japan. There are no approved treatments for SMA. One in 50 people, the equivalent of about six million people in the United States, are carriers of a defective SMN1 gene, which is unable to produce fully functional SMN protein. Carriers experience no symptoms and do not develop the disease. However, when both parents are carriers, there is a one in four chance that their child will have SMA. In the U.S., there are approximately 500 SMA births per year and 22-25 SMA Type 1 births per month.

Cost Estimate: $700,000 - $1,000,000+

Current Therapies: Ionis Pharmaceuticals and Biogen's Spinraza (nusinersen) was approved by the FDA on December 23, 2016. It is currently the only drug indicated to treat spinal muscular atrophy (SMA). It is a survival motor neuron-2 (SMN2)-directed antisense oligonucleotide to increase the amounts of SMN2, a similar protein to the missing SMN1. Spinraza is administered as a series of 4 intrathecal injections over the first two months of therapy and then a maintenance dose every 4 months. Spinraza costs approximately $625-750K for patients in the first year followed by $375K in subsequent years.

Pipeline Product(s): Novartis' branaplam is an oral survival of motor neuron-2 (SMN2) splicing modulator for the treatment of type 1 spinal muscular atrophy. Branaplam increases the amount of functional SMN protein produced by the "back-up" gene, SMN2, through modifying its splicing. Branaplam is in Phase III development with approval possible in 2020. Genentech's RG7916 is another oral SMN2 splicing modulator for the treatment of adults and adolescents with Type 2 and Type 3 SMA who have been previously treated with a SMN2-targeting therapy (i.e., Spinraza). RG7916 is in Phase II development with approval possible in 2021.

Comments: In May 2014, AveXis and Nationwide Children's Hospital initiated a phase I trial to evaluate the safety and efficacy of and efficacy of intravenous AVXS 101 in patients with SMA type 1. The non-randomized, open-label trial enrolled 15 patients in two cohorts, in the US. In March 2017, AveXis released topline results from the gene transfer trial. Cohort 1 included three patients dosed at 6.7x1013 vg/kg, and aged six to seven months at the time of dosing. Cohort 2 included 12 patients dosed at 2.0x1014 vg/kg, and aged one to eight months at the time of dosing. The top-line results demonstrated that AVXS 101 led to mean increases from baseline

in observed motor function improvement, as measured by the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) scores of 7.7 points in cohort 1 and 24.7 points in cohort 2. In Cohort 2 mean increases of 9.8 points was observed in CHOP INTEND, after one month of gene therapy and of 15.4 points after three months of gene therapy. 92%, 83% and 17% of patients in Cohort 2 achieved CHOP INTEND scores of at least 40 points, 50 points, and 60 points, respectively. Patients with 60 points score were considered to be the normal range as a proposed therapeutic dose range. The two patients achieved the maximum CHOP INTEND score of 64. Updated results from an open-label, dose-escalation phase I trial showed that the treatment with AVXS 101 in the proposed therapeutic-dose cohort caused achievement of head control in 92% patients (11/12), 75% patients (9/12) could roll a minimum of 180 degrees from back to both left and right, and 92% patients (11/12) could sit with assistance. In the end-of-study assessment, 75% patients (9/12) could sit unassisted for at least five seconds, 58% (7/12) could sit unassisted for at least 10 seconds and 42% (5/12) could sit unassisted for 30 seconds or more. Two patients could walk independently and also could stand with support, stand alone and walk with support. In cohort 2, 6/7 (86%) patients that did not require feeding support before treatment continued without feeding support after treatment; 7/10 (70%) patients that did not require bi-level positive airway pressure (BiPAP) support before treatment continued without any BiPAP after treatment. In cohort 2, 11 of 12 (92%) patients were fed orally, and 6/12 (50%) patients were exclusively fed orally; and 8/12 (67%) patients were able to speak. In cohort 2, 10/12 patients (83%) could sit unassisted for at least five seconds, 9/12 (75%) patients could sit unassisted for at least 10 seconds and 8/12 patients (67%) could sit unassisted for 30 seconds or more in the post-January 2017 analysis. Updated results from an open-label, dose-escalation phase I trial of AVXS 101 observed no reported adverse events related to elevations in LFEs and two patients had grade 1 or 2 elevation in LFEs. One patient experienced a grade 4 elevation in LFE, also had a concomitant viral infection and was required additional prednisolone therapy until the LFEs returned to the normal range. All adverse events (AEs) and serious AEs (SAEs) related to elevated LFEs were isolated elevations in serum transaminases, clinically asymptomatic and resolved with prednisolone treatment. No elevations in total bilirubin, gamma-glutamyl transferase or alkaline phosphatase were seen and Hy's law was not met. The median event-free age of all 15 patients was 14.9 months, (Cohort 1 = 25.7 months, Cohort 2 = 11.7months). In August 2017, AveXis initiated a long-term follow-up safety trial of patients enrolled in the trial. This trial will determine the safety for 15 years and is enrolling patients by invitation in the US. In September 2017, AveXis initiated a pivotal phase III STR1VE trial to evaluate safety and efficacy of a onetime IV infusion of AVXS 101 of 1.1 x 1014 vg/kg in patients with spinal muscular atrophy type 1. The open-label, single-dose trial intends to enroll minimum of 15 patients in the US, who are less than six months of age at the time of gene therapy and who have one or two copies of the SMN2 backup gene as determined by genetic testing and biallelic SMN1 gene deletion or point mutations. The co-primary endpoint of the trial include achievement of the developmental milestone of independent sitting for at least 30 seconds at 18 months of age and event-free survival at 14 months of age, with an event defined as either death or at least 16 hours per day of required ventilation support for breathing for 14 consecutive days in the absence of acute reversible illness or perioperatively. The trial was initiated based on data submitted and reviewed by FDA. In December 2017, AveXis initiated the STRONG phase I trial, following the IND approval from the US FDA. The trial will evaluate the safety and tolerability of intrathecal administration of AVXS 101, in patients with spinal muscular atrophy with 3 copies of SMN2. The non-randomized, open label trial intends to enroll approximately 27 infants and children in the US. Phase I development of intrathecal formulation for the treatment of SMA type 2 is ongoing in the US. On April 9, 2018, it was announced that Novartis is purchasing AveXis.

baricitinib (Olumiant - Lilly / Incyte)

Current Status: April 14, 2017: Complete response letter. Resubmitted application in Decmber 2017. Approved May 29, 2018

Route of Administration/Dosing: oral (2mg once daily)

Proposed Indication(s): Treatment of moderate-to-severe rheumatoid arthritis (RA)

Mechanism of Action: JAK1 and JAK2 inhibitor

Patient Impact: Rheumatoid arthritis is an autoimmune disease characterized by inflammation and progressive destruction of joints. Patients with RA have a decreased life expectancy from infection, cancer (especially lymphoma), and vascular disease. More than 2 million Americans are afflicted with RA.

PIPELINE REPORT

Specialty Drug Detail - July 2018

Cost Estimate: $40,000 - $50,000 per year

Current Therapies: Baricitinib will primarily compete with Pfizer's Xeljanz (tofacitinib) an oral, twice-daily JAK inhibitor that was approved in 2012 for the treatment of moderate-to-severe RA. Current treatment of RA includes the use of non-steroidal anti-inflammatory drugs, oral disease-modifying anti-rheumatic drugs such as methotrexate, and injectable biological response modifiers that target selected mediators implicated in the pathogenesis of RA. Pfizer's Xeljanz XR is a long-acting (once daily) formulation that was approved in February 2016.

Pipeline Product(s): The following are oral drugs in Phase II development that may compete in the RA market in 2019+: Galapagos' filgotinib (JAK1 inhibitor; Phase II), and AbbVie's upadacitinib (JAK1 inhibitor; Phase III).

Comments: On November 7, 2015, Lilly and Incyte announced positive results from its phase 3 RA-BEAM study. RA-BEAM evaluated the safety and efficacy of baricitinib (4mg once daily) in patients with active disease despite treatment with methotrexate, compared to placebo for 24 weeks or adalimumab [Humira® (adalimumab) 40mg SC every other week] for 52 weeks. The study met its primary objective of demonstrating superiority compared to placebo after 12 weeks of treatment based on ACR20 response – a standard clinical measure that represents at least a 20 percent improvement in RA disease activity. Baricitinib was also superior to adalimumab on key secondary objectives of ACR20 response and improvement in DAS28-hsCRP score after 12 weeks of treatment. Improvements in mean number of swollen and tender joints and a reduction in pain were seen as early as one week for baricitinib versus placebo. At 52 weeks, baricitinib significantly improved all seven components of the ACR composite score compared to adalimumab, including reducing the number of tender and swollen joints, reducing patients' pain and improving physical function. Patient-reported outcomes, including degree of tiredness and the severity and duration of morning joint stiffness, assessed daily for the first 12 weeks of the study, were all significantly improved with baricitinib compared to adalimumab. Compared to placebo, serious adverse events rates were similar for baricitinib and lower for adalimumab; serious infection rates were similar across groups. There were no cases of gastrointestinal perforations. One event of tuberculosis was reported in each of the baricitinib and adalimumab groups. Rates of treatment-emergent adverse events, including infections, were higher for baricitinib and adalimumab compared to placebo. The most common adverse events observed with baricitinib were nasopharyngitis and bronchitis. Discontinuations due to adverse events occurred with similar frequency across treatment groups. On November 7, 2015, Lilly and Incyte also announced positive results from its pivotal phase 3 RA-BEGIN study. In the RA-BEGIN trial, 584 patients who had limited or no prior treatment with methotrexate and who had never received other conventional or biologic disease-modifying antirheumatic drugs (DMARDs) were randomized to methotrexate once weekly (n=210), baricitinib 4 mg once daily (n=159) or baricitinib daily in combination with methotrexate weekly (n=215) for up to 52 weeks. The weekly methotrexate dose was increased from 10 mg to 20 mg over 8 weeks. Improvements compared to methotrexate were seen for baricitinib alone or in combination with methotrexate as early as week 1 for all components of the ACR response (swollen and tender joint counts, pain, patient and physician global assessment of disease activity and physical function). These improvements were maintained at weeks 24 and 52. The incidence of treatment-emergent adverse events and serious adverse events, including serious infections, was similar across treatment groups through week 52. No cases of tuberculosis or spontaneous gastrointestinal perforation were reported during the study. The most common adverse events observed were consistent with previous studies of baricitinib in RA. Compared to methotrexate, baricitinib monotherapy was associated with lower rates of liver abnormalities, lymphopenia and adverse events leading to interruption, while the combination of baricitinib plus methotrexate was associated with increases in non-serious infections and adverse events leading to permanent discontinuation. On January 19, 2016, Lilly and Incyte announced that Lilly has submitted a new drug application (NDA) to the U.S. Food and Drug Administration (FDA) for the approval of oral once-daily baricitinib for the treatment of moderately-to-severely active rheumatoid arthritis (RA). FDA approval is expected by January 19, 2017. On March 31, 2016, Eli Lilly and Incyte announced that results from the Phase 3 RA-BEACON study were published in the New England Journal of Medicine. The RA-BEACON study enrolled 527 patients with of moderate-to-severe rheumatoid arthritis (RA) who previously had failed at least one tumor necrosis factor (TNF) inhibitor, and included 199 patients who also had received prior treatment with one or more non-anti-TNF biologic agents. Patients received baricitinib 2 mg or 4 mg or placebo daily, in addition to their existing background therapies, for 24 weeks. The study met its primary endpoint of improved ACR 20 response for baricitinib compared with placebo at week 12. ACR 20 response rates were as follows (P≤0.001 for each baricitinib dose versus placebo): 55 percent for baricitinib 4 mg, 49 percent for baricitinib 2 mg, and 27 percent for placebo. Through 24 weeks, the rate of treatment-emergent adverse events (AEs) was higher for baricitinib 4 mg (77 percent) and baricitinib 2 mg (71 percent) than for placebo (64 percent). Discontinuation rates due to AEs were 6 percent, 4 percent and 4 percent,

respectively. The most common adverse events reported for baricitinib-treated patients included headache, upper respiratory infections and nasopharyngitis. There were no opportunistic infections, cases of tuberculosis or gastrointestinal perforations. Rates of serious adverse events were 10 percent for baricitinib 4 mg, 4 percent for baricitinib 2 mg and 7 percent for placebo. One death was reported in the baricitinib 4 mg dose group (stroke). On June 9, 2016, Lilly and Incyte announced that data from a pivotal long-term extension study, RA-BEYOND demonstrate that baricitinib was superior to placebo at inhibiting progressive radiographic joint damage in patients with RA. The most robust benefits across measures of progressive joint damage were observed for the 4 mg baricitinib dose. Structural joint damage was evaluated using van der Heijde modified Sharp scores, which quantify bone erosion and joint space narrowing in X-rays of patients' hands and feet. To account for treatment changes or missing scores, two different statistical methods were used, linear extrapolation (LE) and last observation carried forward (LOCF). Using LE, both baricitinib dose groups showed statistically significantly reduced rates of progression at weeks 24 and 48 compared to placebo. Using LOCF, only the 4 mg dose showed statistically significant reduction in progression of joint damage at weeks 24 and 48. On June 9, 2016, Lilly and Incyte announced that in two phase 3 trials patients with RA treated with baricitinib reported significant improvements in quality of life symptoms and other patient-reported outcomes compared to methotrexate or adalimumab (Humira®). Patients with RA also reported improvement in productivity at work. In these studies, significant improvements in patient-reported measures, including pain, physical function, tiredness and morning joint stiffness, were observed as early as one week after initial treatment with baricitinib. On November 2, 2016, Lilly and Incyte announced that new data from RA-BEACON – a pivotal phase 3 study of baricitinib in the treatment of moderate-to-severe rheumatoid arthritis (RA) – showed baricitinib demonstrated significant improvement in patient-reported outcomes and health-related quality of life (HRQOL) measures, fatigue and pain compared with placebo. The RA-BEACON study included patients who had insufficient response or intolerance to previous treatment with biologic disease-modifying antirheumatic drugs (bDMARDs), including tumor necrosis factor (TNF) inhibitors. In these patients, treatment with baricitinib through 24 weeks significantly improved most patient-reported outcomes compared with placebo, and patients receiving baricitinib 4 mg showed the most rapid and greatest change. Previously, baricitinib has also shown significant clinical efficacy in these patients. On November 7, 2016, Lilly and Incyte announced that that in two phase 3 trials, RA-BEAM and RA-BUILD, patients with rheumatoid arthritis (RA) treated with baricitinib experienced significant improvements in patient-reported outcomes, including joint pain, severity of morning joint stiffness and tiredness, compared to placebo and adalimumab (Humira®). In the RA-BEAM trial, once-daily baricitinib (4 mg) significantly improved joint pain, severity of morning joint stiffness and tiredness, compared to placebo, as early as day 3 and significantly improved duration of morning joint stiffness by day 5. With the same dose of baricitinib, these improvements were significantly greater than adalimumab by day 17 (joint pain), day 19 (severity of morning joint stiffness) and day 21 (tiredness). In RA-BEAM, compared to placebo, serious adverse events (SAEs) rates were similar for baricitinib and lower for adalimumab; serious infection rates were similar across groups. There were no cases of gastrointestinal perforations. One event of tuberculosis was reported in each of the baricitinib and adalimumab groups. The most common adverse events observed with baricitinib were nasopharyngitis and bronchitis. Discontinuations due to adverse events occurred with similar frequency across treatment groups. In the RA-BUILD trial, baricitinib (4 mg) significantly improved joint pain, severity and duration of morning joint stiffness and tiredness by days 4, 4, 10 and 3, respectively, compared to placebo. In RA-BUILD, the incidence of SAEs with baricitinib treatment, including serious infections, was similar to placebo. There were no gastrointestinal perforations in the study. A single case of tuberculosis was reported in a patient receiving baricitinib. The most common adverse events observed were consistent with previous studies of baricitinib in RA. Discontinuation rates due to adverse events were similar between treatment groups. The RA-BUILD study enrolled 684 patients with moderate-to-severe RA who previously had an inadequate response to, or were intolerant of, at least one conventional synthetic disease-modifying antirheumatic drug (csDMARD) and had not received a biologic DMARD. Patients received either once-daily baricitinib (2 mg or 4 mg) or placebo, in addition to their background therapy. On January 13, 2017, Lilly and Incyte announced that FDA extended its review of baricitinib by three months to allow time to review additional data recently submitted by Lilly. Approval was expected by April 19, 2017. On April 14, 2017, Lilly and Incyte announced that FDA issued a complete response letter (CRL) for baricitinib. FDA noted that additional clinical data are needed to determine the most appropriate doses. The FDA also stated that additional data are necessary to further characterize safety concerns across treatment arms. On July 25, 2017, Lilly and Incyte announced that a new clinical study is necessary for a resubmission in order to further characterize the benefit/risk across doses, in light of the observed imbalance in thromboembolic events that occurred during the placebo-controlled period of the RA clinical program. This request for an additional clinical study does not impact the ongoing clinical trials for baricitinib. The NDA for RA contained the results of four positive Phase 3 clinical trials that met their primary endpoints and in which 3,100 patients were enrolled, across the full spectrum of RA patients from treatment-naïve to highly-treatment refractory. Thromboembolic events – diagnosed as deep venous thrombosis (DVT) and pulmonary embolism (PE) – were reported in five patients receiving baricitinib during the controlled period of two of seven completed Phase 2 or Phase 3 trials in RA. On August 30, 2017, Eli Lilly and Incyte

announced that, after discussions with the FDA, Lilly will resubmit the NDA for baricitinib before the end of January 2018. The resubmission package will include new safety and efficacy data. The companies anticipate the FDA will classify the application as a Class II resubmission, which will start a new six-month review cycle. Lilly resubmitted application in December 2017. Approval expected in June 2018. On April 23, 2018, FDA's Arthritis Advisory Committee voted 10-5 for approval of 2 mg baricitinib for adults with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or are intolerant to methotrexate. The committee voted 10-5 against approval of the 4 mg dose due to a higher incidence of deep vein thrombosis and pulmonary embolism events seen at this dose in pivotal trials.

binimetinib / encorafenib (Mektovi / Braftovi - Array BioPharma)

Current Status: Approval is expected by June 30, 2018

Route of Administration/Dosing: oral (45mg twice daily / 300mg once daily)

Proposed Indication(s): Treatment of patients with BRAF-mutant advanced, unresectable or metastatic melanoma

Mechanism of Action: MEK inhibitor / BRAF inhibitor

Patient Impact: Melanoma is a rare, but aggressive and deadly form of skin cancer. Each year in the United States, approximately 76,000 new cases of melanoma are diagnosed and nearly 10,000 patients will die from the disease. Approximately half of patients with melanoma skin cancer have a BRAF gene mutation.

Cost Estimate: $327,000/year

Current Therapies: Immunotherapy (Yervoy, Opdivo, Keytruda) and chemotherapy (e.g., dacarbazine). GSK's Mekinist (trametinib) is a MEK inhibitor that is approved for use with Tafinlar (dabrafenib) for patients with advanced melanoma with BRAF mutations. Genentech and Exelixis' Cotellic (cobimetinib) is a MEK inhibitor that is approved for use with Zelboraf (vemurafenib) for patients with advanced melanoma with BRAF mutations.

Pipeline Product(s): There are no other MEK inhibitors in late-phase development.

Comments: On June 30, 2016, Array BioPharma announced the submission of a New Drug Application (NDA) for binimetinib in patients with advanced NRAS-mutant melanoma to the FDA. The submission is based on results of the pivotal Phase 3 NEMO (NRAS MELANOMA AND MEK INHBITOR) study, which found binimetinib significantly extended median progression-free survival (PFS), the study's primary endpoint, as compared with dacarbazine. In the NEMO study, binimetinib significantly extended median PFS at 2.8 months, as compared with 1.5 months observed with dacarbazine [hazard ratio (HR)=0.62 (95% CI 0.47-0.80), pNRAS-mutant melanoma. In the pre-specified subset of patients who received prior treatment with immunotherapy, including ipilimumab, nivolumab or pembrolizumab, patients who received binimetinib experienced 5.5 months of median PFS (95% CI, 2.8–7.6), compared with 1.6 months for those receiving treatment with dacarbazine (95% CI, 1.5–2.8). Binimetinib also demonstrated significant improvement in overall response rate (ORR). Confirmed ORR was 15 percent (95% CI, 11-20 percent) in patients receiving binimetinib vs. 7 percent (95% CI, 3-13 percent) in patients receiving dacarbazine. Binimetinib also demonstrated significant improvement in disease control rate (DCR). DCR for patients receiving binimetinib was 58 percent (95% CI, 52-64 percent) vs. 25 percent (95% CI, 18-33 percent) for patients receiving dacarbazine. There was no statistically significant difference demonstrated in overall survival, the median overall survival (mOS) favored the binimetinib arm. Binimetinib was generally well-tolerated and the adverse events (AEs) reported were consistent with previous results in NRAS-mutant melanoma patients. Grade 3/4 AEs reported in greater than or equal to 5 percent of patients receiving binimetinib included increased creatine phosphokinase (CPK) and hypertension. Standard review was granted. The FDA action date is June 30, 2017. On March 19, 2017, Array announced that it has withdrawn from the FDA Division of Oncology Products its new drug application (NDA) for binimetinib monotherapy for the treatment of NRAS-mutant melanoma, a rare, mutationally-driven subset of skin cancer. Based on feedback from the agency, Array concluded that the clinical benefit demonstrated

in the Phase 3 NEMO clinical trial would not be found sufficient to support approval of the NRAS-mutant melanoma NDA. Ongoing clinical trials for binimetinib will continue. This action will not impact the planned Phase 3 COLUMBUS trial NDA of binimetinib, in combination with encorafenib, for the treatment of BRAF-mutant melanoma, which remains on track for mid-2017. On May 9, 2017, Array BioPharma announced top-line results from Part 2 of the Phase 3 COLUMBUS study evaluating binimetinib, a MEK inhibitor, and encorafenib, a BRAF inhibitor, in patients with BRAF-mutant advanced, unresectable or metastatic melanoma. The primary analysis of Part 2 compared progression free survival (PFS) in patients treated with binimetinib 45mg twice daily plus encorafenib 300mg daily (COMBO300) to patients treated with encorafenib 300mg daily as a single agent. The median PFS for patients treated with COMBO300 was 12.9 months compared to 9.2 months for patients treated with single agent encorafenib, with HR of 0.77 [95% CI 0.61-0.97, p=0.029]. Grade 3/4 AEs which occurred in more than 5 percent of patients receiving COMBO450 included increased gamma-glutamyltransferase (GGT), increased blood creatine phosphokinase (CK), and hypertension. The incidence of AEs of special interest (toxicities commonly associated with commercially available MEK+BRAF-inhibitor treatments), for patients receiving COMBO450 included: rash (23 percent), pyrexia (18 percent), retinal pigment epithelial detachment (13 percent) and photosensitivity (5 percent).

cannabidiol (Epidiolex - GW Pharmaceuticals)

Current Status: NDA filed, Orphan drug, Fast Track Designation. FDA APPROVED June 25, 2018

Route of Administration/Dosing: Oral therapy (liquid; 10-20mg/kg/day)

Proposed Indication(s): Adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) and Dravet syndrome, rare forms of epilepsy

Mechanism of Action: Formulation of purified cannabidiol (CBD). The antiepileptic mechanisms of CBD are not known, but may include effects on the equilibrative nucleoside transporter; the orphan G-protein-coupled receptor GPR55; the transient receptor potential of vanilloid type-1 channel; the 5-HT1a receptor; and the α3 and α1 glycine receptors. Cannabidiol is a molecule from the cannabis plant that does not have the psychoactive properties that create a "high."

Patient Impact: It is estimated that there are approximately 14,000-18,500 patients with LGS in the United States.
The incidence of Dravet syndrome is estimated at 1 in 40,000, or about 8,000 patients in the U.S. The onset of LGS typically occurs between ages of 3 to 5 years and can be caused by a number of conditions, including brain malformations, severe head injuries, central nervous system infections, and genetic neuro-degenerative or metabolic conditions. In up to 30 percent of patients, no cause can be found. Patients with LGS commonly have multiple seizure types including drop and convulsive seizures, which frequently lead to falls and injuries, and non-convulsive seizures. Resistance to anti-epileptic drugs (AEDs) is common in patients with LGS. Most children with LGS experience some degree of intellectual impairment, as well as developmental delays and aberrant behaviors. Dravet syndrome is a severe infantile-onset and highly treatment-resistant epileptic encephalopathy frequently associated with genetic mutations in the SCN1A sodium channels. Onset of Dravet syndrome occurs typically during the first year of life in previously healthy and developmentally normal infants. Initial seizures are often body temperature related, severe, and long-lasting. Over time, patients with Dravet syndrome often develop multiple types of seizures, including tonicclonic, myoclonic, and atypical absences and are prone to bouts of prolonged seizures including status epilepticus, which can be life threatening. Risk of premature death including SUDEP (sudden unexpected death in epilepsy) is elevated in patients with Dravet syndrome. Additionally, the majority will develop moderate to severe intellectual and development disabilities and require lifelong supervision and care. There are currently no FDA-approved treatments and nearly all patients continue to experience seizures and other medical needs throughout their lifetime.

Cost Estimate: $100,000+/year

Current Therapies: Antiepileptic medications such as first-line agents: clobazam and valproic acid; second-line agents: topiramate, ketogenic diet; third-line agents: clonazepam, levetiracetam, zonisamide and ethosuximide. Rescue medications to help stop seizures may include a benzodiazepine such as clonazepam, diazepam, lorazepam or midazolam.

PIPELINE REPORT

Specialty Drug Detail - July 2018

Pipeline Product(s): Aquestive's clobazam oral soluble film (OSF) formulation of benzodiazepine is pending approval for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients ages 2 and older. Approval is expected in September 2018. Zogenix's low dose fenfluramine (sympathomimetic amine) is in Phase 3 development for the treatment of seizures associated with Dravet syndrome; oral solution. Approval is expected in 2019.

Comments: Epidiolex is a pharmaceutical formulation of purified cannabidiol (CBD), which is in development for the treatment of several rare childhood-onset epilepsy disorders. GW has submitted a New Drug Application (NDA) with the FDA for Epidiolex as adjunctive treatment for seizures associated with LGS and Dravet syndrome with an expected approval and launch in 2018. To date, GW has received Orphan Drug Designation from the FDA for Epidiolex for the treatment of Dravet syndrome, LGS, Tuberous Sclerosis Complex (TSC) and Infantile Spasms (IS). Additionally, GW has received Fast Track Designation from the FDA for the treatment of Dravet syndrome and conditional grant of rare pediatric disease designation by FDA. Epidiolex is currently under FDA review with an action date of June 27, 2018. The Epidiolex NDA is supported with data from three positive Phase 3 studies in both Dravet and LGS, which demonstrated statistically significant reduction in monthly convulsive or drop seizures. On April 19, 2017, GW Pharmaceuticals presented positive results from a clinical trial in children and adults with Lennox-Gastaut syndrome (LGS). For the randomized, double-blind, placebo-controlled study, researchers followed 225 people with an average age of 16 for 14 weeks. The participants had an average of 85 drop seizures per month, had already tried an average of six epilepsy drugs that did not work for them and were taking an average of three epilepsy drugs during the study. Participants were given either a higher dose of 20 mg/kg daily cannabidiol, a lower dose of 10 mg/kg daily cannabidiol or placebo as an add-on to their current medications for 14 weeks. Those taking the higher dose had a 42 percent reduction in drop seizures overall, and for 40 percent, their seizures were reduced by half or more. Those taking the lower dose had a 37 percent reduction in drop seizures overall, and for 36 percent, seizures were reduced by half or more. Those taking the placebo had a 17 percent reduction in drop seizures, and for 15 percent, seizures were reduced by half or more. There were side effects for 94 percent of those taking the higher dose, 84 percent of those taking the lower dose and 72 percent of those taking placebo, but most side effects were reported as mild to moderate. The two most common were decreased appetite and sleepiness. Those receiving cannabidiol were up to 2.6 times more likely to say their overall condition had improved than those receiving the placebo, with up to 66 percent reporting improvement compared to 44 percent of those receiving the placebo. At the Annual Meeting of the American Epilepsy Society in December 2017, an AEs poster was presented regarding a pooled analysis of Epidiolex's two Phase III trials in Lennox-Gastaut syndrome which includes an analysis of response rates for the subgroup of patients on Epidiolex with concomitant clobazam compared to the subgroup of patients on Epidiolex without clobazam (Thiele et al). Even without clobazam, Epidiolex produced solid placebo-adjusted response rates. Response was characterized in terms of "25% responders", "50% responders", and "75% responders", meaning the proportion of patients who had a 25%, 50%, or 75% decrease in seizure frequency. For patients randomized to Epidiolex's 20mg/kg dose, the placebo-adjusted 50% response rate was 22% for patients on Epidiolex without clobazam, compared to 33% for patients on Epidiolex and clobazam. For patients randomized to 10 mg/kg Epidiolex, the placebo-adjusted 50% response rate was 25% for patients on Epidiolex without clobazam, compared to 27% for patients on Epidiolex with clobazam. Epidiolex is also being studied in a Phase II/III trial for use in Infantile Spasms (IS) and Phase III trial in tuberous sclerosis complex (TSC).

cemiplimab (Sanofi/Regeneron)

Current Status: Breakthrough therapy. Priority review granted. Approval expected by October 28, 2018.

Route of Administration/Dosing: Intravenous (IV) infusion over 30 minutes at 3mg/Kg once every two weeks for up to 48 weeks

Proposed Indication(s): Treatment of patients with unresectable, locally advanced or metastatic (nodal or distant) cutaneous squamous cell carcinoma (CSCC)

Mechanism of Action: Programmed death-1 (PD-1) monoclonal antibody checkpoint inhibitor

Patient Impact: Each year, roughly 700,000 people in the United States are diagnosed with cancer of squamous cells, which mainly

are in the outer layers of the skin. CSCC occurs most frequently on skin exposed repeatedly to ultraviolet (UV) light from the sun or tanning beds. Affected areas often include the face, hands and scalp and CSCC can appear as flat, scaly areas; raised patches; or reddened bumps. Less commonly, it can cause lumps similar to warts in places, such as between toes or in genital areas, that do not normally have UV exposure. Although it is treatable, CSCC can cause lesions and its treatment can leave scars that are unsightly. If untreated, it can spread – even into lymph nodes – but it is not usually life-threatening. Multiple sites and recurrences are common and advanced CSCC is responsible for 3,900 to 8,800 deaths per year in the U.S. Approximately 7,000 patients per year may be candidates for long term treatment with systemic therapy.

Cost Estimate: $150,000 per year

Current Therapies: For early CSCC patches, a topical medication, such as Efudex® (fluorouracil) cream 5%, may be applied daily for several weeks to destroy them. More advanced or extensive lesions are removed by surgery --including traditional methods and by other techniques using cautery (high heat), cryosurgery (freezing) and photodynamics (light therapy). Some CSCC may need radiation or electrochemotherapy, a process that typically involves injecting chemotherapy (chemo) drugs into the lesions and then subjecting the treated areas to electric currents to make them absorb more of the chemotherapy. For patients with CSCC that cannot be cured by surgery or radiation, there are no FDA-approved treatment options.

Pipeline Product(s): Merck's Keytruda (pembrolizumab) is in Phase II development for recurrent or metastatic cutaneous Squamous Cell Carcinoma (R/M CSCC) that is not amenable to surgery and/or radiation and/or systemic therapies. Approval is possible in 2021.

Comments: On December 13, 2017, Regeneron Pharmaceuticals and Sanofi announced positive topline results from a pivotal Phase 2 clinical study, EMPOWER-CSCC 1 of cemiplimab in 82 patients with advanced cutaneous squamous cell carcinoma (CSCC). EMPOWER-CSCC 1 is a single-arm, open-label clinical trial and remains active. Enrollment is complete in the study arm of patients with metastatic CSCC receiving a 3 mg/kg dose of cemiplimab every two weeks. Enrollment continues in the remaining two study arms of patients with metastatic CSCC receiving a 350 mg flat dose of cemiplimab every three weeks and patients with locally advanced and unresectable CSCC receiving a 3 mg/kg dose of cemiplimab every two weeks. Cemiplimab demonstrated an overall response rate (ORR) of 46.3%, as determined by independent review. The median duration of response (DOR) had not yet been reached at the data cut-off point (32 of 38 responses are ongoing). At the time of this analysis, all patients had a minimum follow up of 6 months. The safety profile in the study was generally consistent with approved anti-PD-1 agents. The companies announced that these pivotal data will form the basis of a rolling Biologics License Application (BLA) submission to the U.S. Food and Drug Administration (FDA), which has been initiated and is expected to be completed in the first quarter of 2018. These data confirm the positive Phase 1 clinical trial expansion cohort results reported at the 2017 American Society of Clinical Oncology (ASCO) Annual Meeting, which led to a Breakthrough Therapy Designation for cemiplimab in advanced CSCC in September 2017. BLA submission began in December 2017 and completed in September 2018. PDUFA date expected to be in September 2018. May be approved early since it's a breakthrough therapy. On April 30, 2018, Regeneron and Sanofi announced that the FDA has accepted the BLA for cemiplimab for the treatment of patients with metastatic cutaneous squamous cell carcinoma (CSCC) or patients with locally advanced CSCC who are not candidates for surgery and granted priority review. The target action date for the FDA decision is October 28, 2018.

duvelisib (Verastem)

Current Status: BNDA filed. Priority review granted. Approval expected by October 5, 2018

Route of Administration/Dosing: Oral (25 mg twice daily)

Proposed Indication(s): Treatment of patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and patients with relapsed/refractory follicular lymphoma

Mechanism of Action: Phosphoinositide 3-kinase (PI3K) inhibitor; duvelisib is selective for the delta and gamma isoforms of PI3K.

Duvelisib works by preventing the activation of PI3K delta/gamma pathway leading to a reduction in cellular proliferation. The delta and gamma isoforms are commonly overexpressed in hematologic malignancies.

Patient Impact: CLL is the most prevalent leukemia in adults in the US, with over 100,000 patients living with the disease. Over 21,000 individuals are diagnosed with CLL each year in the US, with the median age of 70 years at diagnosis. There is a large variation in survival among individual patients, ranging from several months to a normal life expectancy based upon prognostic factors. The five-year life expectancy rate for someone diagnosed with CLL ranges from 50-80%, and 10-year survival rate of 30-35%. Standard treatment of CLL is not expected to cure the disease; even when complete remission is obtained the leukemia typically recurs at some point. However, in 30% of CLL cases the disease remains indolent. A complication associated with treatment of CLL is a transformation of the leukemia to an aggressive type of Non-Hodgkin lymphoma (NLL) or acute myeloid leukemia (AML). In instances of refractory or relapsed CLL, the overall survival has been poor in many studies with a median of 1-2 years despite salvage therapy. About 14,000 cases of follicular lymphoma are diagnosed each year in the US.

Cost Estimate: $100,000/year

Current Therapies: Treatment options for CLL vary greatly, depending on the person's age, the disease risk group, and reason for treatment. Initial treatment often involves a regimen of intense chemotherapy combined with monoclonal antibodies such as fludarabine, cyclophosphamide, and rituximab (FCR). Second-line treatment for refractory or relapsed CLL involves combination of drugs not utilized during initial treatment, and for eligible patients a stem cell transplant may be an appropriate option. Gilead's Zydelig (idelalisib) is a PI3K inhibitor and Janssen and AbbVie's Imbruvica (ibrutinib) is a BTK inhibitor. Both are approved for CLL, Zydelig is also approved for FL. Kite/Gilead's Yescarta (axicabtagene ciloleucel) is a CAR-T therapy that was approved on October 18, 2017, for the treatment of adult patients with relapsed or refractory forms of non-Hodgkin lymphoma (NHL).

Pipeline Product(s): Ascenta Therapeutics has completed a Phase II study of its drug AT-101 in CLL. Cerdulatinib developed by Portola Pharmaceuticals is in Phase I/II clinical trials for patients with relapsed or refractory CLL.

Comments: On February 7, 2018, Verastem announced that a new drug application (NDA) has been submitted to the FDA for duvelisib for a full approval for the treatment of patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and an accelerated approval for the treatment of patients with relapsed/refractory follicular lymphoma. The NDA includes data from the phase III DUO trial and the phase II DYNAMO study. In DUO, duvelisib reduced the risk of disease progression or death by 48% versus ofatumumab (Arzerra - Novartis) in patients with relapsed/refractory CLL/SLL. In the overall population, the median progression-free survival (PFS) with the PI3K-delta and -gamma inhibitor was 3.4 months longer with duvelisib compared to ofatumumab. In patients with a 17p deletion (del [17p]), the median PFS benefit was 3.7 months. In the DYNAMO study, duvelisib demonstrated an overall response rate (ORR) of 46% (P <.0001) for patients with indolent non-Hodgkin lymphoma (iNHL), including 41% in patients with follicular lymphoma. The phase III DUO study randomized 319 patients with CLL/SLL in a 1:1 ratio to duvelisib at 25 mg twice daily until disease progression or unacceptable toxicity, or ofatumumab at 300 mg on day 1, followed by 7 weekly infusions and 4 monthly infusions of 2000 mg. The median PFS was 13.3 months in the duvelisib arm compared with 9.9 months in the ofatumumab arm (hazard ratio [HR], 0.52; P <.0001). In patients with del (17p), the median PFS was 12.7 versus 9.0 months, respectively (HR, 0.41; P = .0011). In the overall population, the ORR with duvelisib was 73.8% versus 45.3% with ofatumumab (P <.0001) and lymph-node burden was reduced by more than half in 85% versus 16% of patients, respectively. Among patients with del (17p), the ORR was 70.0% versus 43.0% with duvelisib versus ofatumumab, respectively (P = .0182). In the intent to- treat population, overall survival (OS) between the 2 arms was similar (HR, 0.99; P = .4807). The median time on treatment was 50.3 weeks (range, 0.9-160.0) versus 23.1 weeks (range, 0.1-26.1) in the duvelisib and ofatumumab arms, respectively. The most common grade ≥3 adverse events (AEs) in the duvelisib group were neutropenia (30%) and anemia (13%). The most frequent nonhematologic grade ≥3 AEs were diarrhea (15%), pneumonia (14%), and colitis (12%). There were 4 patient deaths associated with duvelisib treatment-related AEs: general physical health deterioration (n = 1), pneumonia staphylococcal (n = 2), and sepsis (n = 1). The open-label phase II DYNAMO study, which began enrolling in May 2013, included patients with iNHL who were refractory to rituximab (Rituxan) and either chemotherapy or radio immunotherapy. Among the 129 enrolled patients, the disease types included follicular lymphoma (n = 83), SLL (n = 28), and marginal zone lymphoma (n = 18). Continuous duvelisib was administered at 25 mg twice daily. The ORRs in the follicular lymphoma, SLL, and marginal zone lymphoma groups were 41%, 68%, and 33%, respectively. The median duration of response was 9.9 months. At a median follow-up of 11.5 months, the median OS in the entire iNHL population was 18.4 months and the

median PFS was 8.4 months. The most common grade ≥3 AEs were neutropenia (23%), anemia (12%), thrombocytopenia (10%), and diarrhea (15%). Seventeen percent of patients discontinued duvelisib due to an AE. There were 6 patient deaths related to AEs. On April. 9, 2018, Verastem announced that FDA granted priority review. Approval expected by October 5, 2018.

entinostat (Syndax Pharmaceuticals)

Current Status: Phase III for breast cancer. Breakthrough therapy for breast cancer indication. Phase II for non-small cell lung cancer, non-Hodgkin's lymphoma and ovarian cancer

Route of Administration/Dosing: Oral [5mg once weekly in combination with exemestane (Aromasin® - Pfizer) orally 25mg once daily]

Proposed Indication(s): Treatment of postmenopausal women with advanced estrogen receptor-positive (ER+) breast cancer who have progressed on a non-steroidal aromatase inhibitor.

Mechanism of Action: This histone deacetylase inhibitor (HDACi) works by blocking some of the enzymes needed for tumor cell growth. Entinostat also acts on immune regulatory cells, potentially enhancing the body's immune response to tumors.

Patient Impact: Each year in the U.S., approximately 232,000 women are diagnosed with invasive breast cancer. ER+/HER2- breast cancer is the most common type of this tumor, accounting for about 70% of all breast cancers.

Cost Estimate: $120,000/year

Current Therapies: Patients with advanced, postmenopausal breast cancer may be treated with a non-steroidal aromatase inhibitor [Arimidex (anastrozole), Femara (letrozole)], a steroidal aromatase inactivator Aromasin (exemestane) + Afinitor (everoliumus) or Ibrance (palbociclib) + letrozole. Novartis' Kisqali (ribociclib) is a CDK 4/6 inhibitor that was approved March 13, 2017, for ER+/HER2- breast cancer. Lilly's Verzenio (abemaciclib) is an oral CDK 4/6 inhibitor that was approved September 28, 2017 for ER+/HER2- breast cancer.

Pipeline Product(s): Puma Biotechnology's neratinib is an oral, irreversible pan-HER receptor tyrosine kinase inhibitor (TKI) in Phase III development for the treatment of advanced breast cancer (including HER2+), as monotherapy and in combination with chemotherapy. Approval of neratinib is expected in 2017.

Comments: Entinostat is currently being evaluated in a Phase 3 clinical trial in advanced HR+ breast cancer in collaboration with the National Cancer Institute. The Phase 3 clinical trial is designed to determine whether the addition of entinostat to Aromasin improves progression-free survival, overall survival, or both in patients with advanced HR+ breast cancer who have previously progressed after treatment with standard-of-care hormonal agents. Syndax plans on using this trial, if the results are positive, as a basis for its submission for FDA approval. Syndax has completed a phase II clinical trial that evaluated the safety and efficacy of entinostat in combination with exemestane in postmenopausal women with estrogen receptor-positive (ER+) metastatic breast cancer with disease progression after treatment with a non-steroidal aromatase inhibitor (NCT00676663; ENCORE 301). The study included 130 patients in the US, Canada, the Czech Republic, Hungary and Russia. They received exemestane 25 mg/day with placebo or with entinostat 5 mg/week. The trial met its primary endpoint of improvement in progression-free survival in patients who received entinostat and exemestane, compared with exemestane alone. Treatment with entinostat, in combination with exemestane, improved progression-free survival (primary endpoint) compared with placebo (4.28 vs 2.27 months; p = 0.06) during a randomized, double-blind, phase II study in patients (n = 130) with metastatic breast cancer (ENCORE 301). Median progression-free survival was over six months in the subset of entinostat patients who exhibited lysine hyperacetylation. Compared with exemestane alone, entinostat plus exemestane treatment also improved overall survival by 8.3 months, corresponding to a 41% reduction in risk of dying (p = 0.04; median follow up 25 months). Results from the phase II ENCORE 303 study in post-menopausal women with advanced, estrogen receptor (ER) positive breast cancer who were progressing on aromatase inhibitor therapy showed that of 26 evaluable patients, one achieved a partial response and three achieved stable disease (>6 months). The clinical benefit rate was 15.4%. Objective response rate was 3.9% and progression-free survival was 4.8 months. Further results presented at the 48th Annual Meeting of the American

Society of Clinical Oncology, also showed an improvement in overall survival. Based on data from this trial, the US FDA granted entinostat breakthrough therapy designation in September 2013, for the treatment of locally recurrent or metastatic ER+ breast cancer, in combination with exemestane in postmenopausal women whose disease has progressed following non-steroidal aromatase inhibitor therapy. Treatment with entinostat in combination with exemestane did not significantly increase the incidence of serious adverse events, compared with exemestane plus placebo (13% vs 12%), in the phase II ENCORE 301 trial. The most frequently reported adverse events in the entinostat group were gastrointestinal events, hematological abnormalities and fatigue.

erenumab (Aimovig - Amgen/Novartis)

Current Status: BLA filed. PDUFA date: May 17, 2018. FDA APPROVED May 17, 2018.

Route of Administration/Dosing: subcutaneous (SC) therapy (once monthly)

Proposed Indication(s): For the prevention of migraine in patients experiencing at least four migraine days per month

Mechanism of Action: Erenumab is a fully human monoclonal antibody under investigation for the prevention of migraine. Erenumab specifically targets the Calcitonin-Gene-Related-Peptide (CGRP) receptor, which is believed to transmit signals that can cause incapacitating pain.

Patient Impact: Migraine impacts approximately 12% of the US population – approximately 18% of women and 6% of men. In clinical practice, experts suggest considering preventative therapies in patients who have four or more migraine attacks per month, or are overusing acute medication, or who experience significant disability for migraine. It is estimated that approximately 3.5 million patients in the U.S. use medications that prevent/reduce migraine frequency/severity. Amgen estimates that the majority of patient on preventative therapy are receiving first-line therapy (55%) and would not be the target population for erenumab. Up to 1.6 million Americans may be candidates for CGRPs.

Cost Estimate: $6,000 to $14,000 per year

Current Therapies: Oral, injectable and intranasal "triptans", injectable dihydroergotamine, intranasal dihydroergotamine (Migranal – Valeant), Botox

Pipeline Product(s): fremanezumab (TEV-48125 - Teva) - October 17, 2018; galcanezumab (LY2951742 - Lilly) - 2018; eptinezumab (ALD403 - Adler) - 2019; ubrogepant (MK-1602 - Allergan) - 2020

Comments: Erenumab is a novel migraine treatment that targets the calcitonin-gene-related-peptide (CGRP) pathway. Migraines are currently thought to begin with dilation of cranial blood vessels, which activates perivascular trigeminal sensory nerve fibers. These in turn release the neuropeptide CGRP, which contributes to vasodilation, neurogenic inflammation, and subsequently the transmission of pain impulses. Amgen's erenumab (developed with Novartis, NVS, and [MP]) targets the CGRP receptor whereas Alder's ALD403, Teva's TEV-48125, and Eli Lilly's (LLY, [OP]) galcanezumab bind CGRP itself (the ligand). Amgen's product is slightly different as it targets the CGRP receptor, whereas the other three products directly target circulating CGRP. All four compounds have initiated phase 3 development in what is becoming an increasingly crowded market. On July 20, 2017, Amgen announced that the U.S. FDA has accepted for review the Biologics License Application for Aimovig (erenumab) for the prevention of migraine in patients experiencing four or more migraine days per month. The FDA has set a Prescription Drug User Fee Act target action date of May 17, 2018. Aimovig will be jointly commercialized in the U.S. by Amgen and Novartis. On September 7, 2017, Amgen announced data from a pre-planned sub-analysis from the pivotal Phase 2 chronic migraine study, demonstrating that Aimovig reduced the number of monthly migraine days (MMDs) in patients who have failed previous preventive therapies. Additionally, results from a study in patients with stable angina adds further support to the safety profile of Aimovig. Studies have shown that up to 80 percent of people with migraine discontinue preventive treatment within one year. In a pre-specified sub-analysis from the Phase 2 study, Aimovig showed benefits for people with chronic migraine who have previously tried and failed preventive treatments. At the end of the 12-week study,

patients who had failed two or more prior preventive treatments experienced a reduction of 7.0 days and 5.4 days in the Aimovig 140 mg and 70 mg, respectively, compared to placebo reduction of 2.7 days (p<0.001). Furthermore, in the Aimovig treated arms, the odds of cutting migraine days in at least half was three-to-four fold higher than in the placebo arm (140 mg: 41.3 percent, 70 mg: 35.6 percent, placebo: 14.2 percent (p<0.001 for both doses versus placebo). The safety profile of Aimovig was similar to placebo across both treatment arms in the Phase 2 study. No adverse event was reported in greater than five percent of patients treated with Aimovig; the most common adverse events were injection site pain, upper respiratory tract infection and nausea. Aimovig was tested in a group of patients with stable angina due to coronary artery disease. A treadmill "stress test" is often used to gauge how well a patient's heart can handle exercise. The study met it primary endpoint of noninferiority, showing no difference in exercise time among participants receiving Aimovig or placebo. The treatment difference in mean change from baseline in exercise time was –11.0 seconds (90 percent confidence interval –44.9, 22.9). In addition, no significant differences were seen between the two groups in time to onset of angina or time to onset of electrocardiogram change consistent with onset of myocardial ischemia. Adverse events were reported in 27 percent of patients receiving Aimovig and in 32 percent of patients receiving placebo. The most frequent treatment-emergent adverse events (reported in >2 percent of patients) were headache (4.5 percent) and viral upper respiratory infection (4.5 percent) in the Aimovig group, and were hypotension (4.5 percent), influenza (4.5 percent) and viral infection (4.5 percent) in the placebo group. On November 29, 2017, Novartis announced that the New England Journal of Medicine (NEJM) published positive results from the six-month Phase III STRIVE study evaluating erenumab in the prevention of episodic migraine (defined in STRIVE as 4 to 14 migraine days per month). STRIVE enrolled 955 patients, who were randomized to receive either placebo or subcutaneous erenumab 70mg or 140mg once a month, for six months. Patients taking erenumab at the higher dose experienced a significant 3.7-day reduction in monthly migraine days from the baseline of 8.3 days (3.2-day reduction with 70mg, 1.8-day reduction with placebo, both p<0.001). Fifty percent of patients taking erenumab 140mg had their migraine days cut by at least half, representing a significantly higher likelihood of achieving this response compared to placebo (43.3% with 70mg; 26.6% with placebo, both p<0.001; odds ratios of 2.8 and 2.1 respectively for 140mg and 70mg). STRIVE endpoints were assessed from baseline to the average of the last three months (months 4, 5, 6). Other secondary endpoint results from the study include: Patients taking erenumab had significant reductions in the number of days per month using an acute or "rescue" migraine-specific medication (1.6 days for 140mg group and 1.1 days for 70mg compared to 0.2-day reduction with placebo; both p<0.001). Results from the MPFID showed erenumab delivered meaningful benefits by reducing the impact of migraine on patients' everyday activities, such as getting ready for the day, doing household chores or activities requiring concentration (5.9 points, 140mg; 5.5 points, 70 mg; 3.3 points, placebo; both p<0.001). MPFID scores in physical impairment, such as getting out of bed or activities requiring physical effort, were also significantly reduced with erenumab (4.8 points, 140mg; 4.2 points, 70 mg; 2.4 points, placebo; both p<0.001). In STRIVE, more than 90% of patients taking erenumab completed the study. Adverse reactions leading to discontinuation of treatment occurred in 2.2% of erenumab-treated patients and in 2.5% of patients receiving placebo. On January 22, 2018, Amgen announced positive results from the Phase 3b LIBERTY study assessing the efficacy and safety of Aimovig (erenumab) 140 mg in patients with episodic migraine who had experienced two to four previous preventive treatment failures, due to lack of efficacy or intolerable side effects. The study met its primary endpoint, with significantly more patients taking Aimovig experiencing at least a 50 percent reduction from baseline in their monthly migraine days as compared to placebo. LIBERTY also met all secondary endpoints, including reduction of monthly migraine days, reduction in days needing acute (rescue) medication, improvement in scores on the Migraine Physical Function Impact Diary (MPFID) tool, and 75 percent and 100 percent responder rates (number of patients experiencing at least a 75 percent or 100 percent reduction in monthly migraine days compared to placebo). The safety data are consistent with previous studies of Aimovig to date. On April 17, 2018, Amgen announced full results from the Phase 3b LIBERTY trial of Aimovig in episodic migraine patients. In LIBERTY, 246 patients who had experienced two to four previous preventive treatment failures (due to lack of efficacy or to intolerable side effects) were randomized to receive monthly subcutaneous injections of either Aimovig 140 mg or placebo for 12 weeks. Patients taking Aimovig had nearly three-fold higher odds of having their migraine days cut by at least 50 percent, with more than twice as many patients taking Aimovig achieving this reduction compared to placebo (weeks 9-12: 30.3 percent with Aimovig, 13.7 percent with placebo, p<0.002, odds ratio 2.73). Over 97 percent of Aimovig patients completed the double-blind phase of the LIBERTY study. There were no adverse events leading to discontinuation of treatment in the Aimovig group, while 0.8 percent of those in the placebo group experienced adverse events leading to discontinuation of treatment. FDA APPROVED May 17, 2018.

fremanezumab (Teva)

Current Status: This product is currently under FDA review with an action date of June 16, 2018. Teva expects a complete response with approval by the end of 2018.

PIPELINE REPORT

Specialty Drug Detail - July 2018

Route of Administration/Dosing: SC injection (225 mg once monthly or 675 mg quarterly); formulation may be too viscous to use an autoinjector which may require dosing in clinicians' offices.

Proposed Indication(s): Prevention of chronic and high frequency episodic migraines

Mechanism of Action: Fully human monoclonal antibody under investigation for the prevention of migraine. Fremanezumab specifically targets the Calcitonin-Gene-Related-Peptide (CGRP), which is believed to transmit signals that can cause incapacitating pain.

Patient Impact: Migraine impacts approximately 12% of the US population – approximately 18% of women and 6% of men. In clinical practice, experts suggest considering preventative therapies in patients who have four or more migraine attacks per month, or are overusing acute medication, or who experience significant disability for migraine. It is estimated that approximately 3.5 million patients in the U.S. use medications that prevent/reduce migraine frequency/severity. Amgen estimates that the majority of patient on preventative therapy are receiving first-line therapy (55%) and would not be the target population for erenumab. Up to 1.6 million Americans may be candidates for CGRPs.

Cost Estimate: $6,000 to $14,000 per year

Current Therapies: Oral, injectable and intranasal "triptans", injectable dihydroergotamine, intranasal dihydroergotamine (Migranal – Valeant), Botox

Pipeline Product(s): Amgen's erenumab is a monthly SC CGRP inhibitor that is expected to be approved May 17, 2018. Galcanezumab (LY2951742 - Lilly) - 2018; eptinezumab (ALD403 - Adler) - 2019; ubrogepant (MK-1602 - Allergan) – 2020

Comments: Fremanezumab is a novel migraine treatment that targets the calcitonin-gene-related-peptide (CGRP) pathway. Migraines are currently thought to begin with dilation of cranial blood vessels, which activates perivascular trigeminal sensory nerve fibers. These in turn release the neuropeptide CGRP, which contributes to vasodilation, neurogenic inflammation, and subsequently the transmission of pain impulses. The majority of pipeline drugs, including Teva's fremanezumab, bind to CGRP inhibiting its action. Amgen's product, which is slightly different as it targets the CGRP receptor, is the lead product. Lilly's galcanezumab and Teva's fremanezumab are close behind. All of these products are administered via subcutaneous injection. Fremanezumab has a longer half-life than other near-term pipeline agents allowing for possible quarterly administration. The BLA includes data from the HALO clinical trial program, which enrolled more than 2,000 patients with episodic migraine (EM) and chronic migraine (CM), evaluating both monthly and quarterly dose regimens of fremanezumab. Results from these trials were recently presented at the Congress of the International Headache Society (IHC) in September and will be published in future peer-reviewed publications. Across the Phase III HALO studies in chronic and episodic migraine, fremanezumab achieved statistically significant and clinically meaningful results for all 25 primary and secondary analyses in both monthly and quarterly dosing regimens. In the chronic migraine study, endpoint analyses presented at IHC include: Significant reduction in the number of monthly headache days of at least moderate severity during the 12-week period after 1st dose for both dosing regimens [monthly (-4.6 days) and quarterly (-4.3 days) versus placebo (-2.5 days); $p<0.0001$]; Statistically significant reduction in the number of monthly migraine days during the 12-week period after the 1st dose, for both dosing regimens [monthly (-5.0 days from a baseline of 16.0 days) and quarterly (-4.9 days from a baseline of 16.2 days) versus placebo (-3.2 days from a baseline of 16.3 days); $p<0.0001$], and during the 4-week period after 1st dose, for both dosing regimens ($p<0.0001$); Improvement in Migraine-Specific Quality of Life scores for both dosing regimens [least-squares mean ± standard error differences versus placebo: monthly (6.3±1.4) and quarterly (5.6±1.4); $p<0.0001$]; Improvement in overall health status as measured by the EuroQol 5-dimension 5 response level (EQ-5D-5L) questionnaire for both dosing regimens [quarterly (4.6±1.1; $p=0.0402$) and monthly (4.8±1.1; $p=0.0291$) versus placebo (2.2±1.1)]; Significant reduction in the weekly number of headache days of at least moderate severity at week 1 (-1.1 days; $p<0.0001$) versus placebo (-0.5 days).In episodic migraine, endpoint analyses presented at IHC include: Reduction in the number of monthly migraine days during the 12-week period for both dosing regimens [monthly (-3.7 days from a baseline of 9.2 days) and quarterly (-3.4 days from a baseline of 8.9 days) versus placebo (-2.2 days from a baseline of 9.1 days); $p<0.0001$] and during the 4-week period after 1st dose, for both dosing regimens; Reduction in the number of monthly

headache days of at least moderate severity during the 12- week period for both dosing regimens [monthly (-2.9 days) and quarterly (-3.0 days); vs placebo (-1.5 days); p<0.0001)] and during the 4-week period after 1st dose, for both dosing regimens (p<0.0001); Significant reduction in the number of monthly days of acute headache medication use for both [monthly (-3.0 days) and quarterly (-2.9 days versus placebo (-1.6 days)); p<0.0001]; A ≥50% reduction in monthly average number of migraine days of least moderate severity for both dosing regimens [monthly (47.7%) and quarterly (44.4%) versus placebo (27.9%); p<0.0001]; Improvement in disability as measured by the Migraine Disability Assessment (MIDAS) for both dosing regimens [monthly (-24.6; p=0.0021) and quarterly (-23.0; p=0.0023) versus placebo (-17.5)]. The most common adverse events reported in clinical trials include injection site induration, erythema, and pruritus. On October 17, 2017, Teva announced the submission of the biologics license application (BLA) for fremanezumab to the FDA. On December 18, 2018, Teva announced that FDA accepted the application for fremanezumab. According to Teva, it was granted priority review. Approval is expected by June 15, 2018. On February 8, 2018, Teva announced its sole API manufacturer for fremanezumab – Celltrion's facility in Incheon, South Korea – received an FDA warning letter. As the warning letter was not related to API part of the site, Teva is hopeful that it will be able to work with the FDA on having the API part of the plant inspected and its product approved on time (June PDUFA). However, it could delay the fremanezumab launch. On May 3, 2018, Teva announced that it does not expect to receive FDA approval of fremanezumab on the mid-June PDUFA date. Teva expects an FDA pre-approval inspection to take place in the coming months and to receive FDA approval and launch before the end of 2018.

inotersen (Tegsedi - Ionis Pharmaceuticals/Akcea)

Current Status: Orphan drug. NDA filed. FDA extended review by three months to October 6, 2018

Route of Administration/Dosing: Subcutaneous injection (300mg three times on alternating days the first week, then once-weekly)

Proposed Indication(s): Hereditary amyloid transthyretin-mediated (hATTR) amyloidosis

Mechanism of Action: Antisense drug designed to reduce the production of transthyretin (TTR)

Patient Impact: The proteins that cause hATTR amyloidosis are folded and bent in ways the body cannot use, so they also build up – but mostly in the heart and nerve fibers in the body's periphery (the hands, arms, legs and feet). Known as amyloid fibrils, they interfere with organ function, eventually causing death. Early symptoms include eye problems and peripheral neuropathy. If the nerves that control body systems are affected, patients may experience problems with blood pressure, digestion, urination and other body functions. Amyloid deposits in the heart cause cardiomyopathy (enlargement and thickening of the heart) that may result in dizziness, fatigue, shortness of breath and swelling in the ankles and legs. Atrial fibrillation and heart failure often follow. Most ATTR amyloidosis is inherited, but some cases are spontaneous or "wild". Symptoms of both are general and they develop slowly, making diagnosis difficult. Even if the patient has a family history of the disease, most cases are not recognized until the patient is an adult. Although hATTR amyloidosis is more common in certain parts of the world (areas of Brazil, Japan, Portugal and Sweden), only about one in 100,000 Americans – approximately 3,000 individuals -- are believed to have it and most have not yet been diagnosed. Once it is symptomatic, hATTR amyloidosis limits life expectancy significantly, with survival estimates ranging from just a couple of years up to around 20 years. Polyneuropathy from hATTR affects about 3,000 -7,000 patients in the U.S. About 45,000 to 50,000 patients in the US have cardiomyopathy from hATTR. There is also overlap, in which patients have polyneuropathy and cardiomyopathy. The current diagnoses rate of hATTR is 10-30%. Average age of diagnosis is 60-65 years. Once diagnosed, which usually takes many years/specialists, the survival rate is 2-15 years.

Cost Estimate: $300,000/year

Current Therapies: No drugs are currently FDA-approved for hATTR amyloidosis. Because the liver produces most amyloid, a liver transplant can stop or slow down additional amyloid deposits. Some patients require heart transplants, as well. Not all patients are candidates for transplant, however; and damage to the heart and nerves generally cannot be reversed.

Pipeline Product(s): Alnylam's patisiran is an RNAi therapeutic targeting transthyretin in development for the treatment of

polyneuropathy caused by hATTR amyloidosis. The rolling NDA started in November 2017 with completion expected by the end of 2017. Approval expected in mid-2018. It's administered as an IV infusion every 3 weeks. Analysts project patisiran to capture about 75% of the FAP market (inotersen 25% market share) due to potential superior safety profile. Pfizer's tafamidis is an oral TTR stabilizer in Phase III development to treat hATTR amyloidosis associated cardiomyopathy (hATTR-CM). Tafamidis keeps certain types of amyloid fibrils from forming, so deposits are decreased or prevented. Approval is possible in the second half of 2018 or in 2019.

Comments: On November 2, 2017, Ionis Pharmaceuticals, Inc. announced new data from the Phase 3 NEURO-TTR study, evaluating inotersen in patients with hereditary TTR amyloidosis (hATTR). The NEURO-TTR study met both co-primary endpoints, the Norfolk QoL-DN, a validated instrument for physician-assessed quality of life, and mNIS+7, a validated instrument for evaluating hATTR disease severity. Consistent and significant benefit compared to placebo was observed in both co-primary endpoints at both eight months and 15 months. In addition, consistent and significant benefit was observed in both endpoints independent of disease stage, types of mutation, previous use of TTR stabilizers or presence of cardiomyopathy. Compared to placebo-treated patients, inotersen-treated patients experienced substantial and statistically including: A mean 11.68-point and a mean 6.14-point benefit compared to placebo in Norfolk QoL-DN at 15 months and eight months respectively (p=0.0006, p=0.032). A mean 3.59-point clinically meaningful benefit compared to placebo in the SF-36 Health Survey at 15 months (p=0.006). SF-36 is a commonly used and validated QoL instrument for assessing general health status across eight domains of health. A mean 19.73-point and a mean 8.69-point benefit compared to placebo in mNIS+7 at 15 months and eight months respectively (p=0.00000004, p=0.0005). Encouraging benefit compared to placebo in multiple cardiac measures in patients with significant cardiac disease at baseline (interventricular septum thickness, IVS ≥ 1.5 cm), including left ventricle mass (p=0.0288), IVS (p=0.0150), posterior wall thickness (p=0.0425), and trends in favor of inotersen treatment vs. placebo treatment in global longitudinal strain. Significant benefit compared to placebo in patients with cardiac disease at baseline in both primary endpoints (Norfolk QoL-DN, p=0.036 and mNIS+7, p<0.001) and in the SF-36 Health Survey endpoint (p=0.025) at 15 months. Two key safety issues were identified during the study: thrombocytopenia and safety signals related to renal function. Enhanced monitoring was implemented during the study to support early detection and management of these issues. Serious platelet and renal events were infrequent and easily managed with routine monitoring, which has proven effective since implementation. Other serious adverse events were observed in 24.1% of inotersen-treated patients and 21.7% of placebo-treated patients. No cumulative toxicities have been identified with long-term exposure. Adverse events occurring in ≥10% of patients and twice as frequently in inotersen-treated patients compared with placebo-treated patients, included thrombocytopenia/ platelet count decreases, nausea, pyrexia, chills, vomiting and anemia. Injection site reactions accounted for less than 1% of all injections and were mild or moderate in severity. There were no discontinuations due to injection site reactions. The overall mortality rate in the NEURO-TTR study was 2.9% and was lower than mortality rates reported in other studies in hATTR patients. There was a total of five deaths in the study, five (4.7%) in the inotersen arm and zero in the placebo arm. Four deaths in the inotersen arm were associated with disease progression and considered unrelated to treatment. As previously reported, there was one fatal intracranial hemorrhage in conjunction with serious thrombocytopenia. No serious thrombocytopenia was observed following implementation of more frequent monitoring. On November 6, 2017, Ionis Pharmaceuticals announced that the company submitted a new drug application (NDA) to the FDA for inotersen for the treatment of patients with hereditary TTR amyloidosis (hATTR). Priority review was granted; approval is expected by July 6, 2018. On March 26, 2018, Ionis Pharmaceuticals and Akcea Therapeutics announced Phase 3 data showing that inotersen-treated patients with hereditary ATTR (hATTR) amyloidosis who were treated for up to 27 months in the NEURO-TTR and open-label extension (OLE) studies continued to demonstrate sustained benefit in measures of quality of life and neuropathy. The NEURO-TTR significant benefits, study was a Phase 3 randomized (2:1), double-blind, placebo-controlled, international study in 172 patients with polyneuropathy due to hATTR. The 15-month study measured the effects of inotersen on neurological dysfunction and on quality-of-life by measuring the change from baseline in the modified Neuropathy Impairment Score +7 (mNIS+7) and in the Norfolk Quality of Life Questionnaire-Diabetic Neuropathy (Norfolk QOL-DN) total score. The NEURO-TTR OLE is an ongoing study for patients who completed the NEURO-TTR study and is intended to evaluate the long-term efficacy and safety profile of inotersen. OLE results showed the benefit observed with inotersen treatment in the NEURO-TTR study, as measured by Norfolk QOL-DN and mNIS+7, continued in the OLE, with up to 27 months of total treatment (15 months in NEURO-TTR and up to 12 months in OLE). In addition, the OLE results demonstrate that patients who initiated inotersen treatment 15 months earlier (at initiation of NEURO-TTR) experienced greater benefit in Norfolk QOL-DN and mNIS+7 than those who received placebo treatment in the NEUROTTR study and progressed in their disease, and then initiated inotersen treatment in the OLE. Patients receiving placebo in the NEURO-TTR study experienced a rapid onset of effect following inotersen treatment that was sustained for up to 12 months in the OLE, including: improvements in quality of life and activities of daily living as measured by Norfolk QOL-DN, decreased rate of disease

progression as measured by mNIS+7 compared to their rate of progression in NEURO-TTR. No new safety concerns were identified in the OLE. Total drug exposure, including NEUROTTR and OLE, as of September 15, 2017 was 307 patient years. The median exposure was 692 days (n=161) and the longest exposure was 4.5 years. Serious adverse events occurred in 22 patients (26%) and 11 patients (22%) in the inotersen-inotersen and placebo-inotersen groups, respectively, and were considered related to treatment in 2 patients (2%) and 1 patient (2%), respectively. Five fatal adverse events occurred during the OLE; none were considered related to treatment. NEURO-TTR results showed a significant benefit was observed in inotersen-treated patients with cardiac disease at baseline in both primary endpoints (Norfolk QoL-DN, p=0.036 and mNIS+7, p<0.001) and in the way they felt and functioned in the SF-36 Health Survey endpoint (p=0.025) at 15 months, compared to placebo. Most inotersen treated patient's experienced substantial reductions in TTR. Nearly 90% of patients achieved >50% TTR reduction and nearly 50% achieved over 75% TTR reduction at 15 months. Median TTR reduction was 75-79% between weeks 13-65. Encouraging benefit was observed in inotersen-treated patients with significant cardiac disease at baseline (interventricular septum thickness, IVS ≥ 1.5 cm) in multiple cardiac measures, including mean decreases in left ventricle mass (p=0.0288), IVS (p=0.0150) and posterior wall thickness (p=0.0425), which increased, on average, in placebo-treated patients. Results from an ongoing investigator-sponsored Phase 2 study in cardiomyopathy patients with hATTR amyloidosis and wild-type ATTR (wtATTR) amyloidosis treated with inotersen further support cardiac benefit observed in NEURO-TTR study: Reduction of 8.5% in left ventricular mass (LVM) at 24 months in both hATTR and wtATTR amyloidosis patients (n=10) treated with inotersen, compared to an increase of 8% at 12 months in hATTR amyloidosis patients (n=9) with similar disease characteristics in a prior natural history study1. Mean improvement from baseline in 6-minute walk test (6-MWT) of 29 meters and 41 meters at 12 and 24 months, respectively, in hATTR amyloidosis patients (n=8) treated with inotersen, compared to a decrease of 117.5 meters over 18 months in hATTR amyloidosis patients (n=3) in a prior natural history study1. No drug-related occurred. There were no severe thrombocytopenia or renal adverse events. On May 4, 2018, Ionis and Akcea announced that the FDA decided they needed additional time to review some of our responses to their standard serious adverse events were observed in 24.1% of inotersen-treated patients and 21.7% of placebo-treated information requests and, therefore, has extended the review period for Tegsedi to October 6, 2018.

Ivosidenib (Tibsovo - Agios Pharmaceuticals)

Current Status: Priority review granted. Approval expected by August 21, 2018

Route of Administration/Dosing: Oral (500mg once daily)

Proposed Indication(s): Relapsed or refractory (R/R) acute myeloid leukemia (AML) that has an isocitrate dehydrogenase 1 (IDH1) mutation

Mechanism of Action: First-in-class inhibitor of mutant isocitrate dehydrogenase 1 (IDH1). Ivosidenib interferes with IDH1, an enzyme found mostly in liver cells and mainly in cell parts called peroxisomes and cytosol (the watery material that surrounds most cell structures). Normally, IDH1 helps to break down fats from food, recognize glucose levels and protect against oxidative stress. Mutated IDH1 converts normal substances into 2 hydroxyglutarate (2-HG), which is involved in multiple cancers.

Patient Impact: According to the National Cancer Institute (NCI), approximately 21,000 patients – mostly adults over 45 – are diagnosed with AML in the U.S. each year. AML begins in immature bone-marrow cells that usually develop into a type of white blood cells known as myeloid cells. Because myeloids divide very fast, myeloid cancer can spread into the blood quickly, unless it is treated early and aggressively. Chemotherapy (chemo) is not successful for many AML patients and fewer than one-third of patients survive for five years or longer after diagnosis. Approximately 6% to 10% of AML patients also have IDH1 mutations.

Cost Estimate: $300,000/year

Current Therapies: Because AML usually worsens very rapidly, treatment starts as soon as possible after diagnosis. AML is generally treated with induction and consolidation chemotherapy. A new combination chemo drug, Vyxeos™ (cytarabine/daunorubicin - Jazz Pharmaceuticals) was FDA approved in August 2017 for treating certain aggressive types of AML. Although not specifically indicated for AML with IDH mutations, it could be used for general treatment of AML patients.

Pipeline Product(s): There are no drugs in late-phase development for the treatment of patients with AML with IDH1 mutations.

Comments: The phase I clinical trial that is under review for FDA approval, included 125 patients who had relapsed or failed previous treatment. After an average of 2.7 months of ivosidenib treatment, complete response (CR) was achieved by 21.6% of participants, with another 8.8% recovering somewhat. The most common Grade 3-4 adverse events were anemia, febrile neutropenia, neutropenia, thrombocytopenia and pneumonia, according to the press release. One patient also experienced IDH differentiation syndrome. Although data for the study was submitted in May 2017, numerous patients continue to be treated through an expanded access program. A phase III trial is underway to compare the use of the chemo drug, azacitidine, in combination with ivosidenib versus azacitidine and a placebo. Patients receive 500mg of ivosidenib every day along with subcutaneous or intravenous azacitidine that is given for only the first week of each 28-day treatment period. Results are not expected until mid-2022. Ivosidenib is also being developed for AML patients who are newly diagnosed, whose AML has IDH1 mutations and who are not candidates for intense chemo. On Feb. 15, 2018, Agios announced that the FDA accepted the NDA for ivosidenib for the treatment of patients with relapsed or refractory (R/R) acute myeloid leukemia (AML) with an isocitrate dehydrogenase 1 (IDH1) mutation. The NDA was granted Priority Review and has been given a Prescription Drug User Fee Act (PDUFA) action date of August 21, 2018.

lanadelumab (Shire)

Current Status: Orphan drug. Breakthrough therapy. Approval expected by August. 26, 2018

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

Proposed Indication(s): Prevention of Hereditary Angioedema (HAE) attacks in patients 12 years of age or older

Mechanism of Action: Fully human monoclonal antibody that specifically binds and inhibits plasma kallikrein

Patient Impact: HAE is a rare, genetic disorder caused by a deficiency of C1 inhibitor. Approximately 6,500 Americans have HAE. Patients with the disease experience recurrent, unpredictable inflammatory attacks affecting the larynx, abdomen, face, extremities and urogenital tract. These episodes can be life-threatening, particularly those affecting the larynx.

Cost Estimate: $300,000/year

Current Therapies: Infused C1 esterase inhibitors approved for HAE include Shire's Cinryze and CSL Behring's Berinert and Salix and Pharming's Ruconest. Dyax's Kalbitor (ecallantide) is a SC plasma kallikrein inhibitor to treat HAE attacks and Shire's Firazyr (icatibant) is a selective bradykinin B2 receptor antagonist that can be self-administered by SC injection to treat HAE attacks. CSL Behring's Haegarda is a self-administered subcutaneously injected (twice weekly) C1 esterase inhibitor that was approved on June 22, 2017, for the prevention of HAE attacks.

Pipeline Product(s): N/A

Comments: On May 18, 2017, Shire announced positive topline Phase 3 results for the HELP™ study. The global, multicenter, randomized, parallel group, double-blind, placebo-controlled, evaluating 125 patients 12 years of age or older with type I/II HAE. Patients were randomized into four arms to receive repeated subcutaneous administrations of lanadelumab 300 mg every two weeks, 300 mg every four weeks, 150 mg every four weeks or placebo over 26 weeks. Lanadelumab is an investigational treatment being evaluated for the prevention of angioedema attacks in patients with HAE. This study met its primary endpoint and all secondary endpoints with highly statistically significant and clinically meaningful results for all three lanadelumab treatment arms compared to placebo. The 300 mg dose administered once every two weeks resulted in a statistically significant reduction in mean HAE attack frequency of 87% compared to placebo ($p < 0.001$). 300mg every 4 weeks produced a 73% reduction in attacks vs placebo, and 150mg every 4 weeks produced a 76% reduction in attacks vs placebo (both $p<0.001$). Overall, 52% of patients experienced three or more attacks per month at baseline, 65% of patients reported a history of laryngeal attacks and 56% were on long-term prophylaxis

(LTP). Ninety percent of patients completed the study. Ninety-six percent of those who completed the study chose to roll-over into the ongoing long-term safety study (HELP™ Study Extension). Lanadelumab was generally well tolerated over the 26-week treatment period. No treatment-related serious adverse events or deaths were reported. The most common adverse event was injection site pain (29.3% placebo vs. 42.9 % combined lanadelumab arms). On February 26, 2018, Shire announced that FDA granted priority review for lanadelumab, a biologic kallikrein inhibitor prevention in angioedema attacks in patients 12 years and older that have hereditary angioedema (HAE). Approval is expected by August 26, 2018.

larotrectinib (Bayer/Loxo Oncology)

Current Status: Orphan drug. Breakthrough therapy. Rolling NDA completed March 26, 2018. Approval expected by November 26, 2018

Route of Administration/Dosing: Oral (capsules or liquid; 50mg or 100mg once daily)

Proposed Indication(s): To treat tropomyosin receptor kinase (TRK) fusion cancers; unresectable or metastatic solid tumors with neurotrophic tyrosine receptor kinase (NTRK)-fusion proteins in adult and pediatric patients who require systemic therapy and who either have progressed following prior treatment or who have no acceptable alternative treatments.

Mechanism of Action: Tropomyosin receptor kinase (TRK) inhibitor, resulting in reduced growth and increased apoptosis among cells with TRK fusions.

Patient Impact: Diagnostic tests already are available to identify TRK fusions, which are extremely uncommon in normal tissues. Generally, they are not found in most types of cancer, either; present in less than 3% of cases. However, they often are associated with certain malignancies, including rare, hard-to-treat cancers of the appendix, gall bladder, pancreas, salivary glands and thyroid.

Cost Estimate: $50,000 - $150,000/year

Current Therapies: There are no currently-available therapies that target TRK mutations.

Pipeline Product(s): Entrectinib (RXDX-101, CEP-32496 - Ignyta) currently is in a phase II basket trial (STARTRK-2) of patients with solid tumors that have fusions not only among NTRK genes, but also with two others, the anaplastic lymphoma kinase (ALK) gene and the c-ros oncogene 1 (ROS1). FDA has designated entrectinib as a breakthrough therapy for metastatic solid tumors that are NTRK fusion–positive. Acquired resistance affected some patients, but which mutations were involved is not clear. Loxo' second-generation TRK inhibitor, LOXO-195, is intended to counteract acquired resistance. Started in July 2017, a phase I/II trial is enrolling confirmed TRK-fusion patients with acquired resistance or intolerance to a previously administered TRK inhibitor.

Comments: The phase I trial for larotrectinib included eight adults, its phase II basket trial (NAVIGATE) had 35 adults and the phase I/II pediatric basket trial (SCOUT) enrolled 12 patients age 21 or younger. Although seventeen different types of cancers were represented among the participants, all had TRK fusion mutations. Slightly more than two-thirds of all the patients had at least some response to treatment. Roughly 12% each achieved a complete response and had their cancers stabilize. However, disease progressed for another 12% and acquired resistance developed for 6% of patients. Their cancers responded initially, but then treatment lost its effectiveness as the cancer cells adapted to evade the drug's effects. Investigators reported that they did not find correlations between response rates and patient age, cancer type or specific NTRK gene involvement. However, the numbers of patients treated may be too small to reveal associations. On October 18, 2017, Loxo Oncology announced top-line overall response rate (ORR) results from the independent review committee (IRC) assessment of the larotrectinib dataset. The NDA dataset includes adult and pediatric tropomyosin receptor kinase (TRK) fusion patients enrolled in Loxo Oncology's Phase 1 adult trial, Phase 2 trial (NAVIGATE), and Phase 1/2 pediatric trial (SCOUT). The dataset is based on the intent to treat (ITT) principle, using the first 55 TRK fusion patients with RECIST-evaluable disease enrolled to the three clinical trials, regardless of prior therapy or tumor tissue diagnostic method. The primary endpoint for the integrated analysis of efficacy is overall response rate (ORR) according to the independent review committee assessment, as measured by RECIST v1.1. A key secondary endpoint is ORR according to local

investigator assessment, as measured by RECIST v1.1. The IRC ORR was 75%, comprised of a 62% partial response (PR) rate and a 13% complete response (CR) rate. The larotrectinib adverse event (AE) profile is consistent with data previously presented publicly. At ASCO the most common AEs were fatigue (43%, 5% Grade 3), dizziness (28%, 2% Grade 3), nausea (27%, 2% Grade 3), and anemia (26%, 9% Grade 3). Thirteen percent of patients required a dose reduction due to AEs and no patients discontinued due to an AE. On December 4, 2017, Bayer and Loxo Oncology announced updated clinical data from the pediatric Phase I SCOUT trial. As of the July 17, 2017 data cut-off date, 24 pediatric patients were enrolled in the dose escalation portion of the Phase I trial, including 17 patients with TRK fusion cancers. TRK fusion patients carried primary diagnoses of infantile fibrosarcoma, thyroid cancer, and various soft tissue sarcomas. Among the 17 patients with TRK fusion cancers, 94 percent either remain on drug or received surgery with curative intent; four patients have been followed greater than one year and 12 have been followed greater than six months. The Overall Response Rate (ORR = PR + CR, Partial Response + Complete Response) in the TRK fusion patients was 93 percent as assessed by both the investigators and an independent review committee. The larotrectinib adverse event profile is consistent with data previously presented publicly. The most common treatment-related adverse events at the Phase II dose included increased liver function tests, nausea, and neutropenia. On December 20, 2017, Loxo Oncology announced that it has initiated submission of a rolling New Drug Application (NDA) to the FDA for larotrectinib for the treatment of unresectable or metastatic solid tumors with NTRK-fusion proteins in adult and pediatric patients who require systemic therapy and who have either progressed following prior treatment or who have no acceptable alternative treatments. The company expects to complete the NDA submission in early 2018. On February 21, 2018, Bayer and Loxo Oncology announced the publication in The New England Journal of Medicine (NEJM) of larotrectinib data for pediatric and adult patients whose tumors harbor Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusions. These data include an additional three months of patient follow-up to data presented at the 2017 ASCO Meeting. In data from 55 patients across the Phase I adult trial, Phase II trial (NAVIGATE), and Phase I/II pediatric trial (SCOUT), larotrectinib demonstrated an overall response rate (ORR) of 75% (95% CI 61, 85) by central assessment and 80% (95% CI 67, 90) by investigator assessment. At the time of analysis, 86% of responding patients remained on larotrectinib or underwent surgery with curative intent. The median duration of response (DOR) and progression-free survival (PFS) had not been reached. Treatment related adverse events of any grade observed in more than 15% of patients in the clinical trials included increased alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level (38%), dizziness (25%), fatigue (16%), nausea (16%) and constipation (16%). On March. 26, 2018, Loxo announced the completion of its rolling NDA submission. Approval is expected by November 26, 2018.

lisocabtagene maraleucel (JCAR017 - Celgene)

Current Status: Breakthrough therapy, Phase III- Approval expected in second half of 2018

Route of Administration/Dosing: One or two intravenous (IV) infusions totaling 5X10^7, 1X10^8 or 1.5X10^8 CAR T cells.

Proposed Indication(s): Second-line treatment of relapsed or refractory diffuse large B-cell lymphoma (DLBCL), a type of non-Hodgkin lymphoma (NHL). It also is in a phase I study for treating children, teens and young adults who have relapsed/refractory CD19-positive acute lymphoblastic (also called lymphocytic or lymphoid) leukemia (ALL).

Mechanism of Action: Chimeric antigen receptor T (CAR-T) cell targeting the CD19 antigen expressed by many B-cell malignancies. In CAR-T therapy, some of the patient's T cells are removed, modified to target antigens produced by the cancer and then infused back into the patient.

Patient Impact: The American Cancer Society (ACS) estimates that about 60,000 NHL cases are diagnosed each year in the United States, with around 90% involving B-cells. Between 25% and 35% of NHL patients have DLBCL and about one-half of DLBCL patients respond to the first line of treatment. However, approximately one-tenth have cancers that persist even after repeated treatment cycles using different drug regimens. Without treatment, such refractory DLBCL patients live an average of only three to four months. Overall five-year survival rates for DLBCL range from about 30% to around 50%.

Cost Estimate: $300,000+ per treatment

PIPELINE REPORT

Specialty Drug Detail - July 2018

Current Therapies: DLBCL that recurs or resists standard therapy usually is treated with high-dose chemo and a transplant of the patient's own stem cells, which were removed before the cancer drugs were started. Kite/Gilead's Yescarta (axicabtagene ciloleucel) is a CAR-T therapy that was approved on October 18, 2017, for the treatment of adult patients with relapsed or refractory forms of non-Hodgkin lymphoma (NHL), which include diffuse large-B cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL) or transformed follicular lymphoma (TFL) that already has been treated at least twice with other drugs.

Pipeline Product(s): Filing of Novartis' Kymriah for the treatment of adult patients with relapsed and refractory diffuse large B-cell lymphoma (DLBCL), who have failed two or more prior therapies expected in 2017. It is also a breakthrough therapy for this indication.

Comments: On June 5, 2017, Juno presented an update from the Phase I TRANSCEND study of JCAR017 in non-Hodgkin's lymphoma (NHL) at the American Society of Clinical Oncology (ASCO) today. The updated diffuse large B-cell lymphoma (DLBCL) data were presented for two groups. The core analysis includes 44 DLBCL patients with ECOG performance status 0-1 that will be evaluated in the planned pivotal study (to initiate in 2H17) and are similar to patients studied by KITE and Novartis. The full analysis includes all 54 treated patients in the DLBCL cohort including those with poor performance status or niche subtypes of NHL (e.g. Richter's transformation). For the core group, an overall (best) response rate (ORR) of 86% (38/44) and complete response (CR) rate of 59% (26/44) was reported. The 3-month ORR was 66% (21/32) and 3-month CR rate was 50% (16/32). In the full group, the ORR was 76% and the CR rate was 52% were achieved, with a 3 month ORR of 51% and 3-month CR rate of 39%. In the core subgroup (n=44), Grade 3 CRS was observed in only one patient (2%). 68% of patients were completely fever-free and 28% of patients had Grade 1/2 CRS (35% in all 54 patients). Neurotoxicity was observed in 23% of patients (22% in all 54 patients), with 18% being G3/4 (16% in all patients). These safety data are largely comparable to data presented previously at ASH 2016 where a CRS rate of 36% was observed (no G3/4) and neurotoxicity rate of 18% was observed (14% G3/4). Of note, there was one death reported in TRANSCEND which was classified as treatment-related due to diffuse alveolar damage, which was deemed to be related to fludarabine, cyclophosphamide, and JCAR017 treatment on day 23 in an 82 year old subject who refused supportive care (mechanical ventilation for progressive respiratory failure). According to Juno, the turnaround time (vein-to-vein) with the current process is 24 days although with the new manufacturing process to be used in the pivotal study management expects to get the turnaround time to under 3 weeks. Initiation of a pivotal clinical trial in DLBCL with JCAR017 continues to be expected in 2H17 following dose selection. On November 1, 2017, an ASH abstract includes updated data from the core analysis group (N=49 vs. 44 at ASCO). Top-line data from the abstract for both dose levels for the core group as of a data cut-off date of July 7, 2017 included (1) a 73% 3-month CR rate in n=15 patients treated at dose-level 2 (studied in the pivotal cohort), as well as a 3 month CR-rate of 33% in n=21 patients at dose-level 1. Across both doses, the best CR rate was 61% (n=49), the 3-mo CR rate was 53% (n=40) and the 6-mo CR rate was 52% (n-23). This compares to data presented previously at ASCO, indicating a 3-month CR rate of 50% in 32 patients at both dose-levels combined. There was no increase in cytokine release syndrome (CRS) and neurotoxicity (NT) rates associated with the higher dose or between the full and core groups. Across doses in the full group, 1% (1/69) experienced severe CRS and 14% (10/69) experienced severe NT. 30% (21/69) had any grade CRS and 20% (14/69) had any grade NT. 64% (44/69) had no CRS or NT. At ASCO (LINK, LINK), Grade 3 CRS was observed in only one patient (2%). 68% of patients were completely fever-free and 28% of patients had Grade 1/2 CRS (35% in all 54 patients). Neurotoxicity was observed in 23% of patients (22% in all 54 patients), with 18% being G3/4 (16% in all patients). Juno is exploring outpatient infusion of JCAR017.

lorlatinib (Pfizer)

Current Status: NDA filed. Orphan drug. Breakthrough therapy. Priority review. Approval expected by August 12, 2018

Route of Administration/Dosing: Oral (100 mg once daily)

Proposed Indication(s): Treatment of patients with ALK-positive metastatic non-small cell lung cancer (NSCLC), previously treated with one or more ALK TKIs.

Mechanism of Action: Anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor (TKI)

Patient Impact: Lung cancer is the most common cancer worldwide with 1.7 million new cases annually; with NSCLC accounting for

almost 85 percent of all lung cancers. There are about 224,210 new cases of lung cancer diagnosed each year in the U.S.; therefore, there are approximately 190,600 cases of NSCLC diagnosed each year in the U.S. NSCLC progresses rapidly with a five-year survival rate in advanced NSCLC patients of less than five percent. It is estimated that approximately 60 percent of lung cancer diagnoses in the U.S. are made when the disease is in the advanced stages. Approximately 3-5% of people with NSCLC in the U.S. are ALK-positive. Approximately 10,000 patients are diagnosed with ALK-positive NSCLC each year in the U.S. ALK-positive NSCLC is often found in younger people who have a light or non-smoking history. Cancer spreads to the brain in about half of people with ALK-positive lung cancer.

Cost Estimate: $170,000/year

Current Therapies: Pfizer's Xalkori® (crizotinib) is a kinase inhibitor indicated in the U.S. for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test. Novartis' Zykadia® (ceritinib) is another kinase inhibitor indicated for the treatment of patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib. Genentech's Alecensa® (alectinib) was approved December 11, 2015, for the treatment of ALK+ metastatic NSCLC who have progressed on or are intolerant to crizotinib. Takeda Oncology's Alunbrig™ (brigatinib) was approved on April 28, 2017. An oral tyrosine kinase inhibitor (TKI), Alunbrig is an oral TKI indicated for treating patients who have metastatic ALK+ non-small cell lung cancer (NSCLC) and who have progressed on or are intolerant to Xalkori.

Pipeline Product(s): Several manufacturers are developing ALK inhibitors, including Astellas, Ignyta, Tesaro, Teva and Xcovery.

Comments: On October 16, 2017, Pfizer announced full results from the Phase 2 clinical trial of lorlatinib that exhibited clinically meaningful activity against lung tumors and brain metastases in a range of patients with ALK-positive and ROS1-positive advanced non-small cell lung cancer (NSCLC), including those who were heavily pretreated. Further, side effects were generally manageable and primarily mild to moderate in severity. The Phase 2 study examined the antitumor activity and safety of lorlatinib in 275 patients with or without asymptomatic, untreated or treated brain metastases. Patients were enrolled in six cohorts based on biomarker (ALK-positive or ROS1-positive) and prior therapy. The primary endpoints were objective response rate (ORR) and intracranial ORR (IC-ORR) confirmed by independent central review (ICR). Results by clinically relevant groups showed: ALK-positive treatment-naïve: ORR was 90% (27/30; 95% CI: 74, 98) and IC-ORR was 75% (6/8; 95% CI: 35, 97). ALK-positive previously treated with crizotinib with or without chemotherapy: ORR was 69% (41/59; 95% CI: 56, 81) and IC-ORR was 68 %(25/37; 95% CI: 50, 82). ALK-positive previously treated with a non-crizotinib ALK inhibitor with or without chemotherapy: ORR was 33% (9/27; 95% CI: 16, 54) and IC-ORR was 42% (5/12; 95% CI: 15, 72). ALK-positive previously treated with two or three prior ALK inhibitors with or without chemotherapy: ORR was 39% (43/111; 95% CI: 30, 49) and IC-ORR 48% (40/83; 95% CI: 37, 59). ROS1-positive regardless of prior treatment: ORR was 36% (17/47; 95% CI: 23, 52) and ICORR was 56% (14/25; 95% CI: 35, 76). Lorlatinib was generally tolerable. Most adverse events were mild to moderate and were managed by dose reductions or delay or with standard medical therapy. There were no treatment-related deaths and a low (3%) rate of discontinuation due to drug-related adverse events. The most common adverse events were: hypercholesterolemia (81%), hypertriglyceridemia (60%), edema (43%), peripheral neuropathy (30%), weight increase (18%), cognitive effects (18%), mood effects (15%), fatigue (13%), diarrhea (11%), arthralgia (10%), and increased AST (10%). On February 12, 2018, Pfizer announced that the FDA accepted and granted Priority Review to the company's New Drug Application for lorlatinib. The submissions are based on Phase 2 data from a Phase 1/2 clinical trial of lorlatinib, evaluating patients treated in distinct cohorts based on prior therapy. Approval is expected by August 12, 2018. The Phase 3 CROWN study of lorlatinib began enrolling patients earlier this year. CROWN is an ongoing, open label, randomized, two-arm study comparing lorlatinib to crizotinib for treatment-naïve patients with metastatic ALK-positive NSCLC.

migalastat (Galafold - Amicus)

Current Status: Orphan drug. NDA filed. Priority review granted. Approval expected by August 13, 2018

Route of Administration/Dosing: Oral capsule (150mg every other day)

Proposed Indication(s): Treatment of Fabry disease, as monotherapy or in combination with enzyme replacement therapy.

PIPELINE REPORT

Specialty Drug Detail - July 2018

Mechanism of Action: Galafold selectively binds to and stabilizes alpha galactosidase (a-GAL), the enzyme deficient in Fabry disease. Galafold uses pharmacological chaperone technology, which involves the use of small molecules that selectively bind to and stabilize proteins in cells, leading to improved protein folding and trafficking and increased activity.

Patient Impact: Fabry disease, a rare, inherited lysosomal storage disorder (LSD). Fabry disease is an X-linked lysosomal storage disease that is caused by deficient activity of lysosomal enzyme α -galactosidase A (α -Gal A). Most males with no α -Gal A activity develop the classic phenotype of Fabry disease, which affects multiple organ systems. The first clinical manifestations of the disease, which consist of episodes of severe pain in the extremities (acroparesthesias), hypohidrosis, corneal and lenticular changes, and skin lesions (angiokeratoma) develop in childhood. Glycosphingolipids, predominantly globotriaosylceramide (GL-3) and galabiosylceramide, accumulate in the lysosomes of various cells (eg, in the vascular endothelium of multiple organs) owing to α -Gal A deficiency. The accumulation of GL-3 in the lysosomes causes lysosomal and cellular dysfunction; this, in turn, triggers the cascade of cells and tissue ischemia and fibrosis. Prior to the availability of renal transplant, dialysis, and, more recently, enzyme replacement therapy (ERT), the average age at death in men with classic Fabry disease was 41 years. Renal failure, heart failure and/or myocardial infarction, and stroke were among the most likely causes of death. Most currently untreated and undiagnosed patients with primarily CV involvement have more residual enzyme activity, as opposed to the classical phenotype which is characterized by zero residual enzyme and makes up the ERT market today. In addition, most patients currently on ERT are men that suffer primarily kidney complications, whereas two thirds of disease prevalence is women who have less severe kidney disease but significant cardio/neurovascular morbidity. In Fabry, heart disease is more common than kidney issues but ERT can't reach the heart, thus there has been more focus on the kidney historically. Fabry disease affects every 1:40,000 to 60,000 males; therefore, approximately 3,000 males in the US have Fabry disease.

Cost Estimate: ~ $325,000/year

Current Therapies: Fabrazyme: enzyme replacement therapy

Pipeline Product(s): N/A

Comments: Amicus has commercial rights to Amigal (and other Fabry products) in the US and GSK has commercial rights in the rest of the world. On April 29, 2014, Amicus announced positive 12- and 24-month data from its first Phase 3 study (Study 011) of the oral small molecule chaperone migalastat HCl monotherapy in Fabry patients with amenable mutations. As previously reported, patients on migalastat experienced greater reductions in GL-3 as compared to placebo during the initial 6-month period; however, this difference was not statistically significant under the original study primary endpoint (responder analysis with a 50% reduction threshold at month 6). Globotriaosylceramide (GL-3) is the lipid substrate that accumulates in tissues of patients with Fabry disease, most notably in the kidney. GL-3 clearance from the kidney interstitial capillaries has been used as a marker of treatment effect in Fabry disease. Following a Type C Meeting with the U.S. Food and Drug Administration (FDA) in the second quarter of 2013, and based on feedback from the agency at that meeting, Amicus revised the Statistical Analysis Plan to pre-specify the primary analysis at month 12 as the mean change in GL-3 in patients with amenable mutations in a GLP-validated human embryonic kidney (HEK) cell-based in vitro assay ("GLP HEK amenable"). Approximately 30-50% of patients with Fabry disease have these amenable mutations. Subjects who switched from placebo to migalastat after month 6 demonstrated a statistically significant reduction in kidney interstitial capillary GL-3 at month 12 ($p=0.013$). Subjects who remained on migalastat for 12 months demonstrated a durable reduction in kidney interstitial capillary GL-3. Reduction in disease substrate was also observed in plasma lyso-Gb3, another important biomarker of disease, in subjects who switched from placebo to migalastat ($p<0.0001$). Subjects who remained on migalastat demonstrated a durable reduction in lyso-Gb3. Kidney function (estimated glomerular filtration rate (eGFR), iohexol mGFR) remained stable over 18-24 months. Migalastat was generally safe and well-tolerated. On August 20, 2014, Amicus Therapeutics announced positive 18-month data from its second Phase 3 study (Study 012) of the oral small molecule chaperone migalastat in Fabry patients with amenable mutations. Study 012 compared oral migalastat to standard-of-care enzyme replacement therapies (ERTs) for Fabry disease (Fabrazyme and Replagal). The co-primary outcome measures were the mean annualized changes in estimated glomerular filtration rate (eGFR) and measured (iohexol) GFR (mGFR) assessed by descriptive comparisons of migalastat and ERT over 18 months. The study enrolled 60 patients (26 males and 34 females) with Fabry disease with amenable mutations in a clinical trial

assay who had been treated with ERT for a minimum of 12 months prior to study entry. Study results showed that: migalastat had a comparable effect to ERT on patients' kidney function as measured by the change in eGFR and mGFR. Levels of plasma lyso-Gb3, an important biomarker of disease, remained low and stable in patients with amenable mutations who switched from ERT to migalastat. Migalastat was generally safe and well-tolerated. Of 48 patients with GLP HEK-amenable mutations who completed Study 012, 46 (96%) elected to continue with the 12- month treatment extension and 45 remain on migalastat today as their only treatment for Fabry disease. On March 2, 2016, Amicus presented 30-month follow-up data from the EU '012 trial of Galafold in Fabry disease; 30-month Renal Data Suggests Galafold is Just As Good as ERT In Preserving Renal Function in Fabry Patients. Data presented at WORLD showed eGFR declined 1.718 mL/min/1.73m2 from baseline at 30 month. The mGFR measure declined 2.746 1.718 mL/min/1.73m2. The annualized rates of change in eGFR and mGFR were comparable to those previously reported in the 18-month '012 following up data: -1.0 (-3.6, 1.6) and -3.2 (-7.8, 1.3), respectively. A KOL interprets these data to mean that Galfold is equal to ERT in preserving renal function and better at improving cardiac markers than ERT. 30-month data showed '012 extension patients showed a mean change from baseline of a mean 7.772 g/m2 in the overall population and a 9.959 g/m2 (representing LVMi) in those patients with pre-existing left ventricular hypertrophy (LVH). Safety data as reported today remains very clear. One patient developed proteinuria. On November 29, 2016, Amicus announced that FDA requested a new 12-month study using diarrhea as a primary endpoint and file for full approval. Top-line results are expected in 2019. On July 11, 2017, Amicus announced that FDA indicated that it okay for Amicus to file for accelerated approval based on existing data, including reduction in disease causing substrate (GL-3), as well as the totality of data from completed clinical studies. Amicus has submitted new safety analyses and also provided updated post-marketing experience from Europe. On December 14, 2017, Amicus Therapeutics submitted a new drug application (NDA) to the FDA for the treatment of migalastat HCl in patients 16 years and older with Fabry disease who have amenable mutations. The NDA submission is based on existing clinical data, including reduction in disease-causing substrate (GL-3), as well as the totality of data from two Phase 3 pivotal studies in treatment-naïve (Study 011, or FACETS) and enzyme replacement therapy (ERT) switch patients (Study 012, or ATTRACT), as well as other completed clinical studies. On February 12, 2018, the FDA accepted the NDA for filing under priority review for migalastat HCl for the treatment of patients 16 years and older with Fabry disease who have amenable mutations. The Prescription Drug User Fee Act (PDUFA) goal date for the FDA decision is August 13, 2018.

ozanimod (Celgene)

Current Status: NDA filed in December 2017. Refuse-to-file letter from FDA in February 2018. Re-filing expected in 1Q:2019 with approval in the 2H:2019

Route of Administration/Dosing: Oral (0.5mg or 1mg capsule once daily)

Proposed Indication(s): Relapsing multiple sclerosis (RMS); also in Phase III development for ulcerative colitis and Phase II development for Crohn's disease

Mechanism of Action: Sphingosine-1-phosphate (S1P) receptor agonist; similar to but more selective than Gilenya® (fingolimod – Novartis). S1P is an intercellular signaler with multiple effects, including the regulation of immune cell transit through the body. It is known to have five subtypes, labeled as S1P1 through S1P5. Agonists of S1P work by trapping B lymphocytes and T lymphocytes in the lymph nodes, decreasing their numbers in circulation and keeping some of them away from inflammation sites. Preventing white blood cells from reaching the central nervous system (CNS) limits myelin and nerve damage for patients with MS. Ozanimod affects S1P1 and S1P5, the two subtypes most involved with the CNS. It also may promote remyelination.

Patient Impact: In MS, the immune system damages myelin sheathes (the protective coverings for nerves) in the CNS, eventually destroying the nerves and blocking nerve signaling to the brain. Generally, treatment should start as soon as MS is diagnosed because research shows that nerve damage is most severe in the first stages of the disease and that early damage results in worse disability in late stages of MS. Nerve degeneration leads to fatigue, cognitive disabilities and mood disorders and a wide range of other related conditions, as well as physical impairments that can be debilitating. About 400,000 Americans have MS, a chronic autoimmune condition that has no cure. Although nerve function deteriorates steadily for up to 15% of MS patients who have primary progressive MS (PPMS), the majority of patients have alternating periods of decline (relapses) and remissions when symptoms improve. Relapses

occur about every year or two for most RMS patients. Relapses and disease progression are unpredictable, though; and different patients have different symptoms depending on which nerves are affected. Most cases are diagnosed in young adulthood and about two to three times as many women have it as men. MS also is much more common among people who live in far northern or far southern parts of the world than for individuals living closer to the equator. Over two or three decades, RMS gradually transitions to the secondary progressive form of the disease (SPMS) for approximately 75% of patients. In SPMS, neurological function declines continually, with little or no recovery following relapses.

Cost Estimate: $60,000-$80,000year

Current Therapies: Gilenya is the only currently approved drug that is similar to ozanimod. Generics to Gilenya are expected to launch February 18, 2019. Gilenya was approved in 2010 as the first oral disease modifier for MS. Because it blocks all five of the S1P receptors, however, Gilenya is less specific than ozanimod. Additionally, it has some possibly serious cardiovascular, hepatic and ocular side effects that have not occurred in clinical trials for ozanimod. Gilenya also has a longer half-life, meaning its effects last longer. For trial participants using ozanimod, immune function returned to normal levels after only a few days when ozanimod treatment ended, compared to as much as several weeks for Gilenya. Other oral disease-modifying therapies for MS are: Aubagio® (teriflunomide - Sanofi) – a pyrimidine synthesis inhibitor that also decreases immune activity in the CNS. Tecfidera® (dimethyl fumarate – Biogen Idec) – which is believed to activate the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway that protects against inflammation and oxidative stress. Self-injected interferons have been the mainstay of MS treatment for decades. They include: Avonex and Rebif® (interferon beta-1a), Betaseron® and Extavia® (interferon beta-1b) and Plegridy® (peginterferon beta-1a). Interferons are synthetic forms of naturally-occurring anti-inflammatory substances that reduce inflammation in multiple ways. In general, they decrease immune cell production and activation and lessen the ability of inflammatory cells to reach the CNS. Many patients who use them have troublesome side effects, however; primarily a persistent flu-like syndrome. Avonex is injected intramuscularly (IM); the others are subcutaneous (SC). Two non-interferon injectables also are available. Glatiramer (branded as Copaxone® and Glatopa® and also available as generics) is a synthetic peptide that inactivates auto-immune cells. Zinbryta® (daclizumab), an interleukin-2 (IL-2) receptor inhibitor, helps to reduce T-cell overactivity. Zinbryta is dispensed only through a risk evaluation and mitigation strategy (REMS) because it may cause liver damage, immune reactions, or other serious adverse effects. Among intravenous (IV) disease-modifying MS drugs are mitoxantrone (branded as Novantrone®) and three brand-only monoclonal antibodies -- Lemtrada® (alemtuzumab), Ocrevus™ (ocrelizumab) and Tysabri® (natalizumab). Mitoxantrone works in different ways to reduce production of B cells, T cells, IL-2 and other inflammatory substances. It may be associated with cardiotoxicity and an increased risk of acute myelogenous leukemia (AML). Lemtrada, usually held until third-line treatment, blocks a cell protein (CD52) to decrease the numbers and activity of T cells. It also has a REMS due to its potential for causing serious autoimmune conditions, malignancies and life-threatening infusion reactions. Ocrevus was FDA approved in early 2017 as the first drug to treat PPMS, as well as treating RMS. It sticks to CD20-positive B cells, a specific type of immune cells believed to damage myelin and nerves. Tysabri is a selective adhesion molecule (SAM) inhibitor that stops immune cells from reaching the CNS. It is available only through a risk management program to minimize the risk of progressive multifocal leukoencephalopathy (PML), a rare but potentially fatal brain infection associated with its use.

Pipeline Product(s): Siponimod (Novartis) is an oral S1P inhibitor that blocks only S1P1. It is in Phase III development with filing expected in 1H:2018. Ponesimod is being developed by the Actelion division of Janssen. It is in Phase II development with approval possible in 2020 development with approval possible in 2020.

Comments: On September 16, 2016, Celgene Corporation announced results from the 96-week blinded extension period (for a total of up to 120 weeks of exposure on treatment) of the RADIANCE phase 2 trial of ozanimod in patients with relapsing multiple sclerosis (RMS). Reported treatment-emergent adverse events (AEs) were comparable across ozanimod dose groups; the most common reported AEs during the blinded extension (weeks 24 to 96) were minor infections (nasopharyngitis, respiratory tract and urinary tract) and headache. Alanine aminotransferase at least three times the upper limit of normal was reported in 11 patients (4.4 percent) through extension week 96. Consistent with extension week 48 data, no noteworthy occurrences of cardiac, pulmonary, serious opportunistic infections, ophthalmologic, or malignancy-related treatment-emergent adverse events (TEAEs) were observed. No first-dose TEAEs of bradycardia of AV block ≥ 2nd degree were reported from day 1 of the study or day 1 of the extension. On February 17, 2017, Celgene Corporation announced that its phase III SUNBEAM trial, evaluating the efficacy and safety of ozanimod met the

primary endpoint in reducing annualized relapse rate (ARR), compared to weekly interferon (IFN) -1a (Avonex®). SUNBEAM evaluated two orally administered treatment doses (0.5 mg and 1 mg) of ozanimod, with patients treated for at least one year. The randomized phase III trial enrolled 1,346 RMS patients in 20 countries. Top-line data show that both the ozanimod 1 mg and 0.5 mg treatment arms demonstrated statistically significant and clinically meaningful improvements compared to Avonex® for the primary endpoint of ARR and the measured secondary endpoints of the number of gadolinium-enhancing MRI lesions and the number of new or enlarging T2 MRI lesions at month 12. On May 22, 2017, Celgene Corporation announced that its phase III RADIANCE trial, evaluating the efficacy and safety of ozanimod in patients with relapsing multiple sclerosis (RMS), met the primary endpoint in reducing annualized relapse rate (ARR), compared to weekly interferon (IFN) -1a (Avonex®). RADIANCE evaluated two doses (0.5 mg and 1 mg) of oral ozanimod, with patients treated for two years. The trial enrolled 1,313 RMS patients in 21 countries. Both ozanimod 0.5 mg and 1 mg doses demonstrated statistically significant and clinically meaningful reductions in the primary endpoint of ARR and the key secondary endpoints of the number of new or enlarging T2 MRI lesions over 24 months of treatment compared to Avonex and the number of gadolinium-enhancing MRI lesions at 24 months of treatment compared to Avonex. On October 27, 2017, Celgene announced detailed results from the phase III SUNBEAM™ trial evaluating the efficacy and safety of ozanimod versus a first-line treatment, Avonex® (interferon beta-1a) (IFN), in patients with relapsing multiple sclerosis (RMS). A significant reduction in annualized relapse rate (ARR) was demonstrated for ozanimod 1 mg (ARR=0.18, $p < 0.0001$) and for ozanimod 0.5 mg (ARR=0.24, $p=0.0013$) compared with IFN (ARR=0.35) over an average of 13.6 months of treatment. Ozanimod demonstrated a significant reduction in new or enlarging T2 lesions over one year for 1 mg (48 percent, $p < 0.0001$) and 0.5 mg (25 percent, $p=0.0032$) compared with IFN. A significant reduction in gadolinium-enhanced MRI lesions at 1 year was also demonstrated for ozanimod 1 mg (63 percent, $p < 0.0001$) and ozanimod 0.5 mg (34 percent, $p=0.0182$) compared with IFN. In SUNBEAM, a reduction in brain volume loss, a measure associated with MS disease progression, was observed for the ozanimod dose groups compared with the IFN group. Whole brain volume loss was reduced by 33 percent with the 1 mg dose of ozanimod (median percent change from baseline to 1 year: -0.39, nominally significant $p < 0.0001$) and by 12 percent in the 0.5 mg group (-0.50, $p=0.06$) versus IFN (-0.57) at one year. Treatment emergent adverse events (AEs) were experienced by 59.8 percent of patients on ozanimod 1 mg, 57.2 percent on ozanimod 0.5 mg and 75.5 percent on IFN. The most common AEs in ozanimod-treated patients were nasopharyngitis, headache and upper respiratory infection. AEs of alanine aminotransferase increased were low, transient and generally resolved without study drug discontinuation. The overall incidences of serious AEs were similar across treatment arms (ozanimod 1 mg, 2.9 percent; 0.5 mg, 3.5 percent; IFN, 2.5 percent). The percentages of patients who discontinued study drug due to AEs were 2.9 percent for ozanimod 1 mg, 1.5 percent for 0.5 mg and 3.6 percent for IFN. No second degree or higher atrioventricular blocks were reported. Infection rates were similar across treatment arms; serious infection rates were low and similar across treatment arms, with no serious opportunistic infections in ozanimod-treated patients. On October 28, 2017, Celgene announced detailed results from the phase III RADIANCE™ Part B trial evaluating the efficacy and safety of ozanimod versus a first-line treatment, Avonex in patients with RMS. A significant reduction in annualized relapse rate (ARR) was demonstrated for ozanimod 1 mg (ARR=0.17, $p < 0.0001$) and for ozanimod 0.5 mg (ARR=0.22, $p=0.0167$) compared with IFN (ARR=0.28) over two years of treatment. A significant reduction in new or enlarging T2 lesions was demonstrated for ozanimod 1 mg (42 percent, $p < 0.0001$) and 0.5 mg (34 percent, $p=0.0001$) compared with IFN. A significant reduction in gadolinium-enhanced MRI lesions was also demonstrated for ozanimod 1 mg (53 percent, $p=0.0006$) and ozanimod 0.5 mg (47 percent, $p=0.0030$) compared with IFN. In RADIANCE Part B, a reduction in brain volume loss, a measure associated with MS disease progression, was observed for both ozanimod doses compared with IFN. Whole brain volume loss was reduced by 27 percent with the 1 mg dose of ozanimod (median percent change from baseline to 2 years: -0.69, nominally significant $p < 0.0001$) and by 25 percent in the 0.5 mg group (-0.71, nominally significant $p < 0.0001$) versus IFN (-0.94) at two years. Treatment-emergent adverse events (AEs) were experienced by 75 percent of patients on ozanimod 1 mg, 74 percent on ozanimod 0.5 mg and 83 percent on IFN. Most AEs were mild; the most common AEs across all treatment groups were nasopharyngitis, headache, alanine aminotransferase increased, influenza-like illness, hypertension, gamma-glutamyl transferase increased, pharyngitis, and urinary tract infection. AEs of alanine aminotransferase increased were low, transient and generally resolved without study drug discontinuation. The overall incidences of serious AEs were low and similar across treatment arms (ozanimod 1 mg, 6.5 percent; 0.5 mg, 7.1 percent; IFN, 6.4 percent). The percentages of patients who discontinued study drug due to AEs were 3.0 percent for ozanimod 1 mg, 3.2 percent for ozanimod 0.5 mg and 4.1 percent for IFN. In a pre-specified pooled analysis of the SUNBEAM and RADIANCE™ Part B studies, ozanimod did not reach statistical significance compared with IFN in the time to 3-month confirmed disability progression. A very low rate of disability progression was observed across all treatment groups. In SUNBEAM, the number of patients with 3-month confirmed disability progression by the end of the study was 13 (2.9 percent) in the ozanimod 1 mg group and 17 (3.8 percent) in the ozanimod 0.5 mg group compared with 19 (4.2 percent) in the IFN group. A New Drug Application submission to the U.S. Food and Drug Administration, based on the combined SUNBEAM and RADIANCE trials for RMS, was submitted in December

2017. On February 27, 2018, Celgene announced that the FDA has issued a refusal to file (RTF) letter in reference to the NDA for ozanimod. The letter cited inadequacies in the nonclinical and clinical pharmacology sections in the submission. Celgene indicated that the questions came from a supportive clinical pharmacology study that was submitted as a part of the filing and was not due to any new safety issues or related to the results of the Phase III program. The company also expressed its confidence that no new clinical trials will be required. An analyst has indicated that the RTF letter is due to issues related to a major active metabolite CC112273. The metabolite accounts for 90% of ozanimod's activity and has the same selectivity and potency as ozanimod for the S1P1 and S1P5 receptors. FDA is likely requesting greater characterization of the metabolite. On May 4, 2018, Celgene announced that it will resubmit its application in the first quarter of 2019.

patisiran (Alnylam)

Current Status: Orphan drug. Breakthrough therapy. Priority review granted. Approval expected by August 11, 2018

Route of Administration/Dosing: Intravenous (IV) infusion (0.3mg/Kg once every three weeks)

Proposed Indication(s): Hereditary amyloid transthyretin-mediated (hATTR) amyloidosis

Mechanism of Action: RNAi therapeutic targeting transthyretin (TTR). As a normal biological function, pieces of ribonucleic acid (RNA) called messengers (mRNA) transfer specific amino acid sequences from genes into cells that then produce the specified proteins. Because some of the sequences mutate, abnormal disease-causing proteins sometimes are made. A process now known as RNA interference (RNAi) uses short bits of synthetic RNA that block the defective mRNA. By interrupting mRNA that carries damaged sequences for hATTR amyloidosis, patisiran stops (silences) the resulting protein. It is being developed to relieve peripheral neuropathy (nerve damage that causes numbness, pain or tingling in the arms, hands. legs and feet) associated with hATTR amyloidosis. The condition is abbreviated as hATTR-PN.

Patient Impact: The proteins that cause hATTR amyloidosis are folded and bent in ways the body cannot use, so they also build up – but mostly in the heart and nerve fibers in the body's periphery (the hands, arms, legs and feet). Known as amyloid fibrils, they interfere with organ function, eventually causing death. Early symptoms include eye problems and peripheral neuropathy. If the nerves that control body systems are affected, patients may experience problems with blood pressure, digestion, urination and other body functions. Amyloid deposits in the heart cause cardiomyopathy (enlargement and thickening of the heart) that may result in dizziness, fatigue, shortness of breath and swelling in the ankles and legs. Atrial fibrillation and heart failure often follow. Most ATTR amyloidosis is inherited, but some cases are spontaneous or "wild". Symptoms of both are general and they develop slowly, making diagnosis difficult. Even if the patient has a family history of the disease, most cases are not recognized until the patient is an adult. Although hATTR amyloidosis is more common in certain parts of the world (areas of Brazil, Japan, Portugal and Sweden), only about one in 100,000 Americans – approximately 3,000 individuals -- are believed to have it and most have not yet been diagnosed. Once it is symptomatic, hATTR amyloidosis limits life expectancy significantly, with survival estimates ranging from just a couple of years up to around 20 years. Polyneuropathy from hATTR affects about 3,000 -7,000 patients in the U.S. About 45,000 to 50,000 patients in the US have cardiomyopathy from hATTR. There is also overlap, in which patients have polyneuropathy and cardiomyopathy. The current diagnoses rate of hATTR is 10-30%. Average age of diagnosis is 60-65 years. Once diagnosed, which usually takes many years/specialists, the survival rate is 2-15 years.

Cost Estimate: $300,000+/year

Current Therapies: No drugs are currently FDA-approved for hATTR amyloidosis. Because the liver produces most amyloid, a liver transplant can stop or slow down additional amyloid deposits. Some patients require heart transplants, as well. Not all patients are candidates for transplant, however; and damage to the heart and nerves generally cannot be reversed.

Pipeline Product(s): Ionis Pharmaceuticals' antisense drug inotersen is in development to treat polyneuropathy due to hereditary

TTR amyloidosis (hATTR-PN). Antisense technique is similar to but not identical with RNAi. In the phase III NEURO-TTR trial, patients treated with inotersen had improvements in mNIS+7 and also in the scale used to measure neuropathy caused by diabetes. One patient died, though, from a brain bleed related to treatment. Three others had extremely low platelet counts. Four additional patients experienced kidney problems serious enough for them to stop treatment. Inotersen will be manufactured in 300 mg subcutaneous (SC) self-injectors for once-weekly doses. Approval is expected by November 6, 2018. Pfizer's tafamidis is an oral TTR stabilizer in Phase III development to treat hATTR amyloidosis-associated cardiomyopathy (hATTR-CM). Tafamidis keeps certain types of amyloid fibrils from forming, so deposits are decreased or prevented. Approval is possible in the second half of 2018 or in 2019.

Comments: On November 2, 2017, Alnylam Pharmaceuticals and Sanofi Genzyme announced positive complete results from the APOLLO Phase 3 study. The full APOLLO results showed improvement with patisiran relative to placebo in the primary endpoint of modified Neuropathy Impairment Score +7 (mNIS+7) and additional secondary endpoints encompassing sensory, motor, and autonomic neuropathy symptoms, as well as in exploratory cardiac endpoints, at 18 months. Patients exhibited improved quality of life, activities of daily living, nutritional status, motor strength, and ambulatory ability, with reduced disease symptoms and disability. Patisiran treatment (N=148) resulted in a negative 6.0 point mean change (improvement) in mNIS+7 score from baseline at 18 months as compared to a 28.0 point mean increase (worsening) reported for the placebo group (N=77), resulting in a 34.0 point mean difference relative to placebo (p=9.26 x 10-24). The results were found to be consistent across all sub-components of the mNIS+7 scale. Improvement in mNIS+7 from patisiran treatment was also consistently observed across all defined patient subgroups, including age, sex, race, geographic region, baseline neuropathy impairment, genotype, prior TTR stabilizer use, baseline Familial Amyloid Polyneuropathy (FAP) stage, and inclusion in the pre-specified cardiac subpopulation. Patisiran treatment resulted in a negative 6.7 point mean change (improvement) in Norfolk-Quality of Life-Diabetic Neuropathy (Norfolk QOL-DN) score from baseline at 18 months as compared to a 14.4 point mean increase (worsening) reported for the placebo group, resulting in a mean 21.1 point difference relative to placebo (p=1.10 x 10- 10). Improvements in mNIS+7 and Norfolk QOL-DN with patisiran were also seen at nine months, the earliest time point for these measurements in the study, with a mean 16.0 and a mean 15.0 point difference observed, respectively, relative to placebo. In a pre-specified binary analysis of neurological improvement, 56 percent (95 percent CI: 48.1, 64.1) of patisiran patients had an improvement in mNIS+7 (less than 0 point change compared to baseline at 18 months), while 4 percent (95 percent CI: 0.0, 8.2) of placebo patients had an improvement (p=1.82 x 10-15). Similarly, 51 percent (95 percent CI: 43.3, 59.4) of patisiran patients had an improvement in Norfolk QOL-DN (less than 0 point change compared to baseline at 18 months), versus 10 percent (95 percent CI: 3.6, 17.2) for placebo (p=1.95 x 10-10). Favorable and significant changes in several exploratory cardiac measures, including N terminal pro b-type natriuretic peptide (NT-proBNP), certain echocardiographic parameters, and 10-MWT were reported in patisiran-treated patients in the pre-specified cardiac subpopulation. Patisiran treatment resulted in a median decrease (improvement) of 49.9 pg/ml in NT-proBNP levels as compared to a median increase (worsening) of 320 pg/ml reported for the placebo arm at 18 months (nominal p=7.74 x 10-8, based on analysis of log-transformed values). Regarding echocardiographic measures, patisiran treatment resulted in a mean 0.93 mm reduction (improvement) in left ventricular (LV) wall thickness (nominal p=0.0173) and a mean absolute 1.37 percent improvement in longitudinal strain (nominal p=0.0154) relative to placebo. Regarding functional measures in the cardiac subpopulation, patisiran treatment resulted in a 0.35 m/sec increase (improvement) in 10-MWT (nominal p=7.42 x 10-9) relative to placebo at 18 months. The most commonly reported AEs that occurred more frequently in patisiran patients were peripheral edema (29.7 percent versus 22.1 percent in placebo) and infusion-related reations (IRRs) (18.9 percent versus 9.1 percent in placebo). These were generally mild to moderate in severity and only one patient discontinued due to an IRR (0.7 percent). Compared to placebo, patisiran treatment was associated with fewer treatment discontinuations (4.7 versus 14.3 percent) and fewer study withdrawals (4.7 versus 11.7 percent) due to AEs. The incidence of serious adverse events (SAEs) across the patisiran (36.5 percent) and placebo (40.3 percent) groups was similar. SAEs reported in 2 or more patients in the patisiran group included: diarrhea (5.4 percent), cardiac failure, congestive cardiac failure, orthostatic hypotension, pneumonia, and atrioventricular block complete (2 percent each). These were all considered unrelated to patisiran, except for one SAE of diarrhea. SAEs occurred with similar frequency in the placebo group, except for diarrhea (1.3 percent in placebo group). Deaths were recorded with a similar incidence across the patisiran (4.7 percent) and placebo (7.8 percent) treatment groups. No deaths were considered related to study drug. There were no safety signals with regard to hepatic or renal function, or evidence of thrombocytopenia, due to patisiran. Alnylam will commercialize patisiran in the U.S., Canada and Western Europe, with Sanofi Genzyme commercializing the product in the rest of the world. Priority review was granted. Approval expected by August 11, 2018.

PIPELINE REPORT

Specialty Drug Detail - July 2018

pegvaliase (Palynziq - BioMarin)

Current Status: Orphan drug. PDUFA date: May 25, 2018. **FDA APPROVED May 25, 2018**

Route of Administration/Dosing: Subcutaneous (SC) injection (20mg or 40mg once daily); will be supplied in prefilled syringes (2.5mg, 10mg, and 20mg)

Proposed Indication(s): To reduce blood phenylalanine (Phe) levels in adult patients with phenylketonuria (PKU) who have uncontrolled blood Phe levels on existing management.

Mechanism of Action: Pegvaliase is a pegylated synthetic form of phenylalanine ammonia lyase (PAL), a plant and fungus enzyme that is similar to phenylalanine hydroxylase (PAH). PAL also breaks down phenylalanine. Pegylation chemically alters it to decrease the chance it will trigger an immune response and also to increase the amount of time it stays active in circulation.

Patient Impact: PKU is an inborn error of metabolism (IEM) – a genetic deficiency of key enzymes needed to utilize specific nutrients. In the U.S., it affects about one baby in 15,000, so roughly 22,000 Americans are thought to have it to some degree. There are approximately 800-1,000 adult patients on Kuvan in the U.S. and approximately 2,000 to 3,000 adults in the U.S. with PKU, but not currently on pharmaceutical therapy. Approximately 4,000 patients in the U.S. will be candidates for treatment with pegvaliase. Individuals with PKU produce low or no amounts of PAH, the enzyme that breaks down an amino acid, phenylalanine. Found in proteins, phenylalanine also is in many other foods, including products artificially sweetened with aspartame. If not eliminated from the diet, it builds up in the body of PKU patients — causing brain damage that can lead to behavioral and learning disabilities, seizures and eventually death. Treatment is life-long avoidance of products that contain phenylalanine, beginning as soon as the condition is diagnosed. Because phenylalanine is very common in many regular foods, most PKU patients must follow special diets that do not include it. Adhering to the diet is poor – especially among teens and young adults. Some patients with PKU have very light-colored hair and skin; some have a musty smell to their sweat and urine. However, PKU generally has no early symptoms, so new babies are checked for it at one to two days old. Those who show positive reactions receive additional testing to determine the severity of the condition and to begin dietary restrictions. Patients with PKU are advised to maintain blood levels of phenylalanine between 360µmol and 120 µmol/L (2mg to 6mg/dL).

Cost Estimate: $180,000

Current Therapies: Phenylalanine-restricted diet and specially formulated dietary supplements, which is supplemented by low-protein modified foods and Phe-free medical foods. Presently, the only drug FDA approved for treating PKU is BioMarin's Kuvan® (sapropterin dihydrochloride) tablets and powder for oral solution. It is a synthetic oral form of tetrahydrobiopterin (BH4), which boosts the activity of any natural PAH the patient has. It can be used by children as young as one month old, but not all patients respond to treatment with sapropterin. In two clinical trials, less than 75% of pediatric PKU patients improved with 20 mg/kg/day and the 10 mg/kg/day dose was effective for only 20% of adults and children. Additionally, response can be determined only by a month-long therapeutic trial of sapropterin, making it difficult to prescribe. Dietary limitations still need to be maintained, as well.

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

Comments: In the phase III, PRISM-2 (Previously indicated as 165-302 or PRISM-302) study, pegvaliase doses of 20mg and 40mg per day were compared to each other and to placebo for adult PKU patients. After eight weeks, average phenylalanine levels went up slightly for patients treated with pegvaliase (from a base of 503.9 µmol/L to 527.2 µmol/L) compared to a more than doubling among those receiving a placebo (536.0 µmol/L to 1385.7 µmol/L). In the long-term extension phase of the study, 71 of the 90 patients saw phenylalanine levels decrease by 20% or more and 36 maintained blood levels of 120umol/L or less. In addition, treated patients scored better on attention testing than patients using a placebo. Pegvaliase was well-tolerated compared to placebo and no subjects experienced anaphylaxis or discontinued due to adverse events (AEs). Pegvaliase patients had more hypersensitivity AEs (39%) than placebo (14%), and effects included arthralgia (pegvaliase 14%/placebo 10%), headache (pegvaliase 12%/placebo 24%) and fatigue

(pegvaliase 11%/placebo 10%). Further results are expected in 2018. PRISM-1 (also called 165-301 and PRISM-301) was a phase III, open-label study of 261 adult patients whose phenylalanine levels were over 600mmol/L. None had been treated with pegvaliase before and all began on a dose of 2.5mg/day. Doses gradually were increased to 20mg/day for some patients and 40mg/day for the rest. The 215 patients who achieved at least a 20% drop in phenylalanine levels were enrolled into PRISM-2. On August 29, 2017, BioMarin announced that FDA granted priority review for pegvaliase to reduce blood phenylalanine (Phe) levels in adult patients with phenylketonuria (PKU) who have uncontrolled blood Phe levels on existing management. While the PDUFA date is February 28, 2018, a three-month extension is expected to allow time for FDA to review additional manufacturing information submitted by BioMarin. On September 17, 2017, BioMarin announced that FDA will not hold an advisory panel to discuss pegvaliase. FDA Approved May 24, 2018.

romosozumab (Evenity - Amgen / UCB)

Current Status: July 16, 2017: Complete response letter. Approval is possible in 2018

Route of Administration/Dosing: SC (once monthly) for a year, then Prolia every 6 months

Proposed Indication(s): Romosozumab is under FDA review for the treatment of osteoporosis in postmenopausal women at increased risk of fracture.

Mechanism of Action: Humanized antibody that targets and inhibits sclerostin, increasing bone formation and decreasing bone resorption.

Patient Impact: Osteoporosis affects many postmenopausal women since the production of estrogen, a hormone in women that protects bones, decreases sharply when women reach menopause, resulting in bone loss and increasing the risk for a fracture. Osteoporosis is estimated to affect more than 10 million Americans. Approximately one in two women over age 50 will break a bone because of osteoporosis. Each year in the U.S., it is estimated that 1.5 million women suffer from an osteoporotic fracture. The majority of osteoporosis patients remain undiagnosed and undertreated, and there is an unmet medical need for treatment of incident non-vertebral fractures which currently represent 73 percent of all fractures.

Cost Estimate: $17,000/year

Current Therapies: Lilly's Forteo (teriparatide) is a once-daily SC injection PTH analog that has been on the market since 2002. It is indicated to treat men and women with osteoporosis at high risk for fracture. Radius' Tymlos [abaloparatide is a SC (once daily)] is a synthetic analog of the PTH-related protein that was approved April 29, 2017, for the treatment of postmenopausal women with osteoporosis.

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

Comments: In April 2017, Amgen and UCB announced results from the fourth year of a Phase 2 study showing the efficacy and safety of a second course of treatment with EVENITY™ (romosozumab), an investigational agent for postmenopausal women with osteoporosis. The results were presented in an oral session (OR08-1) at ENDO 2017, the Endocrine Society's Annual Meeting in Orlando, Fla. In the study, postmenopausal women with low bone mass (lumbar spine, total hip or femoral neck T score between -2.0 and -3.5) were initially randomized to various doses of EVENITY or placebo for 24 months and then re-randomized to receive denosumab (Prolia®) or placebo for the next 12 months (24 to 36 months), as previously reported. For months 36 to 48, all of these patients were then treated with EVENITY (210 mg) for 12 months. In patients who initially received 210 mg of EVENITY followed by placebo and then a second course of EVENITY (n=19), the second course led to significant increases in bone mineral density (BMD) to an extent similar to the initial EVENITY treatment: lumbar spine (12.7 percent), total hip (5.8 percent) and femoral neck (6.3 percent) during months 36 to 48. In those patients who received a second course of EVENITY after denosumab, EVENITY further increased

BMD by 2.8 percent at the lumbar spine, while maintaining BMD at the total hip and femoral neck. A similar adverse event (AE) profile was observed in the EVENITY groups, regardless of prior treatment group (placebo or denosumab). In patients treated with EVENITY for months 36 to 48, serious AEs were reported for five percent of patients who initially received EVENITY (n=7/140) and four percent who initially received placebo (n=1/27). The AEs reported by these patients for months 36 to 48 include hypersensitivity (7.4 percent, initial placebo; 7.9 percent, initial EVENITY), injection-site reactions (7.4 percent, initial placebo; 7.1 percent, initial EVENITY), malignancies (3.7 percent, initial placebo; 3.6 percent, initial EVENITY) and osteoarthritis (11.1 percent, initial placebo; 2.1 percent, initial EVENITY). There were no reports of osteonecrosis of the jaw or atypical femoral fracture. On May 21, 2017, Amgen and UCB announced that the EVENITY ARCH study met both primary endpoints and the key secondary endpoint. ARCH (Active-contRolled FraCture Study in Postmenopausal Women with Osteoporosis at High Risk of Fracture) is a Phase 3 multicenter, international, randomized, double-blind, alendronate-controlled study of EVENITY in postmenopausal women with osteoporosis at high risk for fracture based on previous fracture history. The study evaluated 12 months of EVENITY treatment followed by at least 12 months of alendronate treatment, compared with alendronate treatment alone. At 24 months, women in the EVENITY treatment group experienced a statistically significant 50 percent reduction in the relative risk of a new vertebral (spine) fracture compared to those receiving alendronate alone. Women in the EVENITY treatment group also experienced a statistically significant 27 percent reduction in the relative risk of clinical fracture (non-vertebral fracture and clinical vertebral fracture) at the primary analysis. Additionally, non-vertebral fractures were statistically significantly reduced by 19 percent in the EVENITY treatment group, including a nominally significant reduction in hip fractures. Overall adverse events and serious adverse events were generally similar between the treatment groups throughout the study and also in the initial 12-month EVENITY treatment period. In the initial 12-month EVENITY treatment period, the three most commonly reported adverse events in both arms were nasopharyngitis, back pain and arthralgia. Injection site reactions were reported in 4.4 percent of patients in the EVENITY treatment group and 2.6 percent in the alendronate group during the initial 12-month period. Most injection site reactions were reported as mild in severity. During the open-label alendronate period, there were two positively adjudicated events of osteonecrosis of the jaw, one in a patient treated with EVENITY followed by alendronate and one treated with alendronate alone. There were six patients with positively adjudicated events of atypical femoral fracture during the open-label alendronate period (two patients treated with EVENITY followed by alendronate and four treated with alendronate alone). The patient incidence of positively adjudicated cardiovascular serious adverse events at 12 months was 2.5 percent in the EVENITY group compared to 1.9 percent in the alendronate group. No imbalance in cardiovascular serious adverse events was seen in the 7,180-patient placebo-controlled FRAME study. Amgen is going to evaluate the cardiovascular safety signal in more detail. Amgen does not expect approval of EVENITY in 2017. On July 16, 2017, Amgen and UCB announced that the FDA has issued a Complete Response Letter for the BLA for Evenity as a treatment for postmenopausal women with osteoporosis. The original submission included data from the pivotal Phase 3 placebo-controlled FRAME study of postmenopausal women with osteoporosis. With the availability of data from the Phase 3 active-comparator ARCH study, the Agency has asked that the efficacy and safety data from the study be integrated into the application. The resubmission will also include the efficacy and safety data from the BRIDGE study, the Phase 3 trial evaluating EVENITY in men with osteoporosis, which has also been requested. This request will be addressed in the form of a resubmission, which is an extension of the current review. Approval is possible in 2018.