**PIPELINE REPORT**  
Specialty Drugs  
July 2017

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<tr>
<th>PIPELINE DRUG</th>
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| abemaciclib Eli Lilly | Phase 3 | 2018 | CDK4/6 inhibitor for the treatment of hormone-receptor-positive (HR+) metastatic breast cancer; oral (PO).  
Breakthrough Therapy |
| ataluren Translarna – PTC Therapeutics | NDA Filed | 2017 10/24/2017 | Gene transcription modulator for the treatment of nonsense mutation Duchenne muscular dystrophy (DMD); oral (PO)  
Orphan Drug |
| axicabtagene ciloleucel Kite Pharma | BLA Filed | 2017 12/01/2017 | Chimeric antigen receptor T-cell therapy (CAR-T therapy) for the treatment of patients with relapsed or refractory aggressive B- cell non-Hodgkin lymphoma (NHL); intravenous (IV).  
Breakthrough Therapy  
Orphan Drug |
| baricitinib Olumiant - Lilly / Incyte | Complete Response | 2018 | Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis (RA); PO.  
Orphan Drug |
| benralizumab AstraZeneca | BLA Filed | 2017 12/02/2017 | IL-5Ra inhibitor for the treatment of severe asthma; subcutaneous (SQ).  
Orphan Drug |
| binimetinib Array BioPharma | Phase 3 | 2018 | MEK inhibitor for the treatment of advanced and unresectable or metastatic malignant cutaneous melanoma harboring NRAS mutations; PO.  
Orphan Drug  
PGx |
| durvalumab Imfinzi - AstraZeneca | Approved | 2017 05/01/2017 | Programmed cell death ligand 1 (PD-L1) inhibitor for the treatment of patients with locally advanced or metastatic urothelial carcinoma whose disease has progressed during or after one line of platinum-based chemotherapy; IV.  
Breakthrough Therapy |
| edaravone Radicava - Mitsubishi Tanabe Pharma | Approved | 2017 05/05/2017 | Free radical scavenger for the treatment of amyotrophic lateral sclerosis (ALS); IV.  
Orphan Drug |
| enasidenib Agios Pharmaceuticals/Celgene | NDA Filed | 2017 08/30/2017 | IDH2 mutant inhibitor for the treatment of acute myelogenous leukemia (AML) in patients with advanced hematologic malignancies that carry an IDH2 mutation; PO.  
Orphan Drug  
PGx |

**PGx** = Pharmacogenetic test in development
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| entinostat Syndax Pharmaceuticals | Phase 3        | 2018                 | Histone deacetylase inhibitor for the second-line treatment postmenopausal women with advanced ER+ breast cancer with exemestane; PO.  
**Breakthrough Therapy**  
**PGx**                                                                 |
| glecaprevir/pibrentasvir AbbVie | NDA Filed       | 2017 08/19/2017      | Next generation NS3/4 protease inhibitor / NS5a inhibitor for the pan-genotypic treatment of hepatitis C; PO.  
**Breakthrough Therapy**                                                                 |
| guselkumab Janssen            | BLA Filed       | 2017 07/14/2017      | Monoclonal antibody targeting interleukin-23 (IL-23) for treatment of adults with moderate to severe plaque psoriasis; SQ.  
**PGx**                                                                 |
| nonacog beta pegol Refixia – Novo Nordisk | BLA Filed       | 2017 05/16/2017      | Long-acting factor IX (FIX) derivative for the treatment of hemophilia B; IV.  
**PGx**                                                                 |
| romosozumab Evenity - Amgen /UCB | BLA Filed       | 2017 07/19/2017      | Humanized antibody that targets and inhibits sclerostin for the treatment of postmenopausal osteoporosis; SQ.  
**PGx**                                                                 |
| sarilumab Kevzara - Sanofi / Regeneron | BLA Filed       | 2017 05/22/2017      | Interleukin-6 receptor (IL-6R) inhibitor for the treatment of rheumatoid arthritis (RA), in combination with methotrexate (MTX); SQ.  
**PGx**                                                                 |
| sirukumab Janssen / GlaxoSmithKline | BLA Filed       | 2017 09/23/2017      | Interleukin-6 (IL-6) inhibitor for the treatment of RA, as monotherapy or in combination with MTX; SQ.  
**PGx**                                                                 |
| tildrakizumab Sun Pharmaceuticals | Phase 3        | 2018                 | Anti-IL-23 antibody for the treatment of moderate to severe plaque psoriasis; SQ.  
**PGx**                                                                 |
| tisagenlecleucel-T CTL019 - Novartis | NDA Filed       | 2017 09/29/2017      | CAR-T therapy for the treatment of patients with relapsed/refractory acute lymphoblastic leukemia (r/r ALL); IV.  
**Breakthrough Therapy**                                                                 |
| velpatasvir/voxilaprevir/ sofosbuvir Gilead | NDA Filed       | 2017 08/08/2017      | Three-drug single-tablet regimen for the pan-genotypic treatment of hepatitis C; PO.  
**Breakthrough Therapy**                                                                 |
**Breakthrough Therapy**  
**Orphan Drug**                                                                 |

**PGx = Pharmacogenetic test in development**

Route of Administration/Dosing: Oral (PO) [200 mg every 12 hours until disease progression].

Proposed Indication(s): As monotherapy for the treatment of refractory patients with hormone-receptor positive (HR+), human epidermal growth factor 2-negative (HER2-) metastatic breast cancer who have failed multiple prior treatments.

Mechanism of Action: Abemaciclib is designed to selectively inhibit cyclin-dependent kinase (CDK) 4 and CDK 6. Uncontrolled cell growth is characterized by a loss of cell cycle regulation associated with increased signaling from CDK 4 and CDK 6.

Patient Impact: Breast cancer is the most common cancer in women worldwide, with over 40,000 deaths in the U.S. annually. An estimated 240,000 new cases of invasive breast cancer are diagnosed each year in the U.S., with over 70% of those cases ER+/HER2-. The overall 5-year survival rate for patients with breast cancer is on average 90%; however, patients with advanced metastatic disease have an estimated 5-year survival rate of 22%. Breast cancer has a high recurrence rate up to 40% in patients, with varying subtypes. Metastatic HR+/HER2- breast cancer accounts for the majority of metastatic disease and has a poor prognosis. Despite breakthrough in oncology therapies available, the overall 5-year survival rate has remained relatively unchanged over the past decade. Historically, metastatic breast cancer has been regarded as incurable but treatable.

Cost Estimate: $145,000/yr.

Current Therapies: Pfizer’s Ibrance® (palbociclib), a CDK 4/6 inhibitor, approved in February 2015 in combination with letrozole for the treatment of HR+/HER2- breast cancer in women with disease progression following endocrine therapy. In February 2016, Ibrance received an expanded approval for use in combination with fulvestrant, for treating women of any age who have HR+/HER2- metastatic breast cancer that has progressed despite prior treatment with an endocrine therapy. On Mar. 13, 2017, Novartis’ Kisqali® (ribociclib), a CDK 4/6 inhibitor, was approved for ER+/HER2-breast cancer.

Pipeline Product(s): Syndax Pharmaceuticals’ entinostat is a histone deacetylase inhibitor (HDAC) in Phase III trials for metastatic ER+ breast cancer. Puma Biotechnology’s neratinib is an irreversible pan-ErbB tyrosine kinase inhibitor in Phase III development for advanced breast cancer. Entinostat and neratinib are all oral drugs that would be used in combination with other breast cancer agents. They could reach the market in 2018.

Comments: FDA granted abemaciclib, a breakthrough designation for patients with refractory HR+ advanced or metastatic breast cancer on October 3, 2015. The designation was assigned based upon results of the Phase I study, JPBA, which looked at the safety and efficacy of abemaciclib in women with advanced or metastatic breast cancer. In the Phase I study, patients were placed into two arms: 1) abemaciclib monotherapy and 2) abemaciclib and fulvestrant. Patients receiving single-agent abemaciclib demonstrated an objective response rate (ORR) of 33.3% in heavily treated HR+ breast cancer patients. The median duration of response was 13.4 months, with a median progression-free survival (PFS) of 8.8 months. On June 3, 2016, Eli Lilly released topline results from its Phase II study, Monarch I, which enrolled 132 patients in a single-arm study, designed to evaluate safety and efficacy of monotherapy oral 200mg abemaciclib administered every 12 hours until disease progression. After 12 months of follow-up, patients achieved an ORR of 19.7%, a median time to response of 3.7 months, and a median duration of response of 8.6 months. The PFS was six months. Eli Lilly’s Phase III study, MONARCH II, is currently evaluating abemaciclib in combination with fulvestrant in HR+, HER2- advanced or metastatic breast cancer in postmenopausal women with advanced breast cancer who have relapsed or progressed after endocrine therapy. Additionally, the company has a second Phase III study, Monarch III, examining the combination of abemaciclib and a nonsteroidal aromatase inhibitor in HR+, HER2- locoregionally recurrent or metastatic breast cancer in postmenopausal women. The company also has a Phase III trial, JUNIPER, studying the abemaciclib in NSCLC. In Oct. 2016, Lilly announced that at the pre-specified 9-month interim analysis, abemaciclib as either single agent or add-on to anastrozole statistically significantly improved Ki67 (a biomarker of cancer cell proliferation) vs anastrozole alone in a Phase II neoadjuvant study (NeoMONARCH) of women with untreated HR+/HER2- early-stage invasive breast cancer. The study also showed a statistically significant reduction in complete cell cycle arrest. Importantly, loperamide was administered prophylactically for the first 28 days and continued at the discretion of the investigators. On Mar. 20, 2017, Eli Lilly announced that its MONARCH II trial of abemaciclib met the primary endpoint of PFS. The results demonstrated the addition of abemaciclib to fulvestrant resulted in a statistically significant improvement in
PFS, when compared to the control arm of placebo plus fulvestrant. On Apr. 24, 2017, Lilly announced that following a pre-planned interim analysis for MONARCH II, the trial met its primary endpoint of demonstrating statistically significant improvement in PFS. In addition, improvement was shown in a key secondary endpoint of ORR. Filing for first-line use in combination with an aromatase inhibitor is expected in 3Q:2017.

ataluren (Translarna™ - PTC Therapeutics)


Route of Administration/Dosing: PO powder for suspension (10mg/kg in the morning, 10mg/kg midday and 20mg/kg in the evening).

Proposed Indication(s): Treatment of patients with nonsense mutation Duchenne muscular dystrophy (nmDMD).

Mechanism of Action: Protein restoration therapy designed to enable the formation of a functioning protein in patients with genetic disorders caused by a nonsense mutation. A nonsense mutation is an alteration in the genetic code that prematurely halts the synthesis of an essential protein. The resulting disorder is determined by which protein cannot be expressed in its entirety and is no longer functional (dystrophin in DMD).

Patient Impact: DMD is a severely debilitating childhood neuromuscular disease that affects up to 1 in 3,500 live male births. There are approximately 20,000 boys in the U.S. with DMD. This rare disease is caused by mutations in the dystrophin gene, resulting in the absence or defect of the dystrophin protein. Patients suffer from progressive loss of muscle function, often making them wheelchair bound before the age of 12. Respiratory and cardiac muscle can also be affected by the disease. Few patients survive past the age of 30. A nonsense mutation is the cause of dystrophinopathy in approximately 10-15% of boys with the disease.

Cost Estimate: $300,000/yr

Current Therapies: There is no cure for DMD. Current treatment aims to control symptoms and improve quality of life. Steroids can slow the loss of muscle strength. Drugs to help heart function are often used. Patients with reflux often use proton pump inhibitors.

Pipeline Product(s): BioMarin’s Kyndrisa (drisapersen) is an antisense oligonucleotide that may be approved in 2017 for the treatment of patients with DMD with mutations amenable to exon 51 skipping. Sarepta’s eteplirsen works similar to drisapersen in patients with DMD. Eteplirsen may be approved by May 26, 2016.

Comments: On Oct. 15, 2015, PTC Therapeutics announced results from the Phase III, double-blind, placebo-controlled, 48-week ACT DMD trial of Translarna™ for the treatment of nmDMD. The trial included 228 patients between the ages of 7 and 16 with nmDMD who were randomized to receive either Translarna 40mg/kg per day (n=114) or placebo (n=114) over 48 weeks. The trial results showed clinically meaningful benefits for Translarna-treated patients. In the overall intent-to-treat study population, the primary endpoint of change from baseline in the 6-minute walk test (6MWT) demonstrated a 15 meter benefit (p=0.213), which was not statistically significant. A highly significant benefit of 47 meters (p=0.007) was demonstrated in the pre-specified patient population of 300-400 meters at baseline as measured by the 6MWT, which is in line with the Company's prior experience in its Phase Ib trial and consistent with the evolving understanding of the 6MWT. No patients in this group lost ambulation (0/47) versus four patients in the placebo group (4/52). Translarna showed a benefit over placebo across key secondary and tertiary endpoints, including timed function tests (10 meter run/walk, 4 stair climb, 4 stair descend) and the North Star Ambulatory Assessment test. In addition, a pre-specified meta-analysis of the combined placebo-controlled ACT DMD and Phase Ib trials demonstrated a statistically significant benefit of Translarna across the primary and key secondary endpoints. The ACT DMD study confirmed the favorable safety profile of Translarna, which was generally well-tolerated, consistent with results from previous studies. On Feb. 23, 2016, PTC Therapeutics announced that it received a refuse to file letter from FDA regarding its application for approval of Translarna. FDA indicated that both the Phase Ib and ACT DMD trials were negative and do not provide substantial evidence of effectiveness. The FDA also characterized certain of the company's adjustments to the ACT DMD study as post hoc and therefore not supportive of effectiveness. In addition, the FDA noted that the NDA did not contain adequate information regarding the abuse potential of Translarna, a requirement for new molecules that cross the blood-brain barrier. PTC is working with FDA to resolve these issues. On March 6, 2017, PTC Therapeutics announced that the FDA has acknowledged the filing over protest of PTC’s NDA for Translarna. The Company is seeking approval to market the drug for the treatment of nmDMD patients in the U.S. The FDA has granted standard review and assigned a PDUFA date of October 24, 2017.
axicabtagene ciloleucel (Kite Pharma)


Route of Administration/Dosing: One intravenous (IV) infusion of 2 × 106 CAR-T cells/kg of body weight.

Proposed Indication(s): Treatment of patients who have relapsed (recurring) and/or refractory aggressive B-cell non-Hodgkin lymphoma ([NHL; including chemorefractory diffuse large B-cell lymphoma (DLBCL)], primary mediastinal B-cell lymphoma (PMBCL) and transformed follicular lymphoma (TFL)] who are not candidates for stem-cell transplant. It is also in early phase development for several other blood cancers, such as acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL) and mantle-cell lymphoma (MCL).

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 U.S., with around 90% involving B-cells. Between 25-35% 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 30-50%.

Cost Estimate: $300,000+ per treatment

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.

Pipeline Product(s): Novartis' tisagenlecleucel-T is a CAR-T therapy that is expected to be approved in Sep. 2017 for ALL. Filing for the treatment of adult patients with relapsed and refractory DLBCL, who have failed two or more prior therapies expected in 2017. It is also a breakthrough therapy for this indication. Juno’s JCAR017 is another CAR-T therapy. Juno expects to begin JCAR017 pivotal trials in r/r NHL(DLBCL) in 2H:17 and expects to gain FDA approval in 2H:18.

Comments: In clinical trials, patients were treated with a low-dose chemotherapy regimen (cyclophosphamide at 500 mg/m2 along with fludarabine 30 mg/m2) for three days followed by one infusion of axicabtagene ciloleucel at a target dose of 2 × 106 CAR T cells/kg of body weight. Among 101 patients with DLBCL, PMBCL or TFL in the Phase II ZUMA-1 clinical trial, interim results show that 82% had an overall response (OR) and 54% had complete response (CR) after axicabtagene ciloleucel was infused. Nearly nine months after treatment, 44% of patients maintained OR, with 39% still in CR. Comparatively, the rates for OR and CR from current therapies are about 26% and 8%, respectively; and median survival time is around six months. With a median follow-up of 8.7 months, the median overall survival (OS) has not yet been reached. The overall duration of response (DOR) was 8.2 months and has not yet been reached for patients with a CR. In the SCHOLAR-1 pooled analysis, a retrospective study to evaluate the response rate and overall survival in patients with refractory DLBCL to serve as a benchmark for other trials, the median OS was estimated to be 6.6 months with only 8% achieving CR with currently available therapies. On Mar. 31, 2017, Kite Pharma announced that it has completed the rolling submission with the FDA of the BLA for axicabtagene ciloleucel as a treatment for patients with relapsed or refractory aggressive NHL who are ineligible for autologous stem cell transplant (ASCT). Approval is expected by Dec. 1, 2017.

baricitinib (Olumiant - Lilly / Incyte)


Route of Administration/Dosing: PO (4mg once daily).

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

Mechanism of Action: Janus kinase (JAK) 1 and JAK2 inhibitor.
Patient Impact: RA 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 affected with RA.

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 (NSAIDs), oral disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate (MTX), 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 Feb. 2016.

Pipeline Product(s): Can-Fite Biopharma’s CF-101 is an oral A3 adenosine receptor agonist in Phase III development that may be approved for RA in 2017. The following are oral drugs in Phase II development that may compete in the RA market in 2019: Vertex’s decernotinib (JAK3 inhibitor), Galapagos’ filgotinib (JAK1 inhibitor), and AbbVie’s ABT-494 (JAK1 inhibitor).

Comments: On Nov. 7, 2015, Lilly and Incyte announced positive results from its phase III RA-BEAM study. RA-BEAM evaluated the safety and efficacy of baricitinib (4 mg once daily) in patients with active disease despite treatment with MTX, compared to placebo for 24 weeks or adalimumab ([Humira®] 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 American College of Rheumatology score 20% improvement (ACR20) response – a standard clinical measure that represents at least a 20% 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. On Nov. 7, 2015, Lilly and Incyte also announced positive results from its pivotal phase III RA-BEGIN study. In the RA-BEGIN trial, 584 patients who had limited or no prior treatment with MTX and who had never received other conventional or biologic DMARDs were randomized to MTX once weekly (n=210), baricitinib 4 mg once daily (n=159) or baricitinib daily in combination with MTX weekly (n=215) for up to 52 weeks. The weekly MTX dose was increased from 10 mg to 20 mg over 8 weeks. Improvements compared to MTX were seen for baricitinib alone or in combination with MTX as early as week 1 for all components of the ACR response. These improvements were maintained at weeks 24 and 52. On Mar. 31, 2016, Eli Lilly and Incyte announced that results from the Phase III RA-BEACON study were published in the New England Journal of Medicine. The RA-BEACON study enrolled 527 patients with moderate-to-severe 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: 55% for baricitinib 4 mg, 49% for baricitinib 2 mg, and 27% for placebo. On Jun. 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. On Jun. 9, 2016, Lilly and Incyte announced that in two phase III trials with RA treated with baricitinib reported significant improvements in quality of life symptoms and other patient-reported outcomes compared to MTX or adalimumab. 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 Nov. 2, 2016, Lilly and Incyte announced that new data from RA-BEACON 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 DMARDs, including 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. On Nov. 7, 2016, Lilly and Incyte announced that that in two phase III trials, RA-BEAM and RA-BUILD, patients with 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. 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 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. 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 DMARD 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 Jan. 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. On Apr. 14, 2017, Lilly and Incyte announced that FDA issued a 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. Approval is likely delayed until late 2018 at the earliest.

**benralizumab (AstraZeneca)**

**Current Status:** FDA accepted the BLA for benralizumab on Feb. 2, 2017. Approval is expected by Dec. 2, 2017.

**Route of Administration/Dosing:** Subcutaneous [SQ] (30mg every 4 weeks or 30mg every 4 weeks X 3, then every 8 weeks).

**Proposed Indication(s):** As an add-on therapy for the treatment of severe uncontrolled asthma with eosinophilic inflammation in patients 12 years of age and older. Benralizumab is also in Phase III development for the treatment of moderate-to-very-severe chronic obstructive pulmonary disease (COPD) with exacerbation history. AstraZeneca may file for this expanded indication in 2018.

**Mechanism of Action:** Fully humanized anti-interleukin-5 receptor alpha (IL-5RA) chain monoclonal antibody; anti-eosinophil monoclonal antibody that depletes eosinophils via antibody-dependent cell-mediate cytotoxicity (ADCC), the process by which natural killer cells are activated to target eosinophils. Benralizumab induces direct, rapid, and near complete depletion of eosinophils in the bone marrow, blood and target tissue.

**Patient Impact:** There are 18.7 million adults and 6.8 million children in U.S. with asthma. Approximately 5-10% of patients with asthma have severe disease and approximately 30-66% of patients with severe asthma have eosinophilic asthma. Eosinophils are the biological effector cells that drive inflammation and airways hyper-responsiveness in approximately 50% of asthma patients, leading to frequent exacerbations, impaired lung function and reduced quality of life. According to the CDC, more than 22 Americans have asthma and there are more than 400,000 asthma-related hospitalizations each year in the U.S.

**Cost Estimate:** $30,000/yr

**Current Therapies:** There are two IL-5 inhibitors currently on the market. GlaxoSmithKline’s Nucala® (mepolizumab; SQ) was approved Nov. 4, 2015, for use as an add-on maintenance treatment of severe eosinophilic asthma in patients at least 12 years of age. Teva’s CinquaIR® (reslizumab; IV) was approved Mar. 23, 2016, for add-on maintenance treatment of adults with severe asthma with an eosinophilic phenotype. They are both administered by a healthcare professional every 4 weeks.

**Pipeline Product(s):** Regeneron and Sanofi’s dupilumab (SQ), which blocks interleukin-4 and interleukin-13, is in Phase III development for the treatment of severe asthma. Dupilumab may be approved for asthma in 2018.

**Comments:** On May 17, 2016, AstraZeneca announced that benralizumab was well tolerated and achieved the primary endpoint in two pivotal Phase III trials (SIROCCO and CALIMA), demonstrating significant reductions in the annual asthma exacerbation rate compared to placebo. SIROCCO and CALIMA are randomized, double-blind, parallel group, placebo-controlled trials designed to evaluate the efficacy and safety of a fixed 30 mg dose of benralizumab administered SQ in patients with a history of asthma exacerbations and uncontrolled asthma receiving inhaled corticosteroids (ICS) and long acting beta agonist (LABA) with or without oral corticosteroids (OCS) and additional asthma controllers. A total of 2,511 patients were randomized globally and received benralizumab 30mg every 4 weeks; 30mg every 4 weeks for the first three doses followed by 30mg every 8 weeks; or placebo. In SIROCCO and CALIMA, the primary analysis population included patients on high-dose ICS plus LABA with a baseline blood eosinophil count ≥ 300 cells/microliter. Patients were randomized to receive benralizumab 30mg every 4 weeks for the first three
doses followed by 30mg every 8 weeks; or placebo. On Sep. 6, 2016, AstraZeneca announced results from the SIROCCO and CALIMA trials that demonstrated that adding benralizumab to standard-of-care medicine significantly reduced exacerbations and improved lung function and asthma symptoms in severe asthma patients with an eosinophilic phenotype. Results showed: reductions in the annual rate of asthma exacerbations (up to 51%); improvement in lung function (change in FEV1 of up to 159 mL), which was seen at 4 weeks after the first benralizumab dose and sustained throughout the treatment period; improvement in asthma symptoms, such as wheeze, cough, chest tightness and shortness of breath. The outcomes were demonstrated for the 8-week dosing regimen, with no additional benefit observed with 4-week dosing, which may support less-frequent dosing. In addition, post-hoc analysis showed greater improvements in exacerbation rate reduction, FEV1 and total asthma symptom scores in patients with a history of more frequent asthma exacerbations (≥ 3 in the previous year). According to AstraZeneca, the FDA accepted the BLA for benralizumab on Feb. 2, 2017. Approval is expected by Dec. 2, 2017. While self-administration studies are ongoing, they are expecting a requirement for administration by a healthcare professional at approval.

**binimetinib (Array BioPharma)**

**Current Status:** Will file for combo use combination with encorafenib, for the treatment of BRAF-mutant melanoma, in mid-2017 with approval possible in early 2018.

**Route of Administration/Dosing:** PO (45 mg twice daily).

**Proposed Indication(s):** Use in combination with encorafenib, Array’s oral BRAF inhibitor, to treat patients with BRAF-mutant melanoma.

**Mechanism of Action:** MEK inhibitor.

**Patient Impact:** Melanoma is a rare, but aggressive and deadly form of skin cancer. Each year in the U.S., 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:** $110,000/yr.

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

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

**Comments:** On Jun. 30, 2016, Array BioPharma announced the submission of a NDA for binimetinib in patients with advanced NRAS-mutant melanoma to the FDA. The submission is based on results of the pivotal Phase III NEMO (NRAS MELANOMA AND MEK INHIBITOR) study, which found binimetinib significantly extended median PFS, the study’s primary endpoint, as compared with dacarbazine: binimetinib’s mean PFS was 2.8 months, as compared with 1.5 months observed with dacarbazine. 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, compared with 1.6 months for those receiving treatment with dacarbazine. Binimetinib also demonstrated significant improvement in ORR: 15% in patients receiving binimetinib vs. 7% in patients receiving dacarbazine. It also demonstrated significant improvement in disease control rate (DCR): binimetinib was 58% vs. 25% for patients receiving dacarbazine. There was no statistically significant difference demonstrated in overall survival, the median overall survival (mOS) favored the binimetinib arm. On Mar. 19, 2017, Array announced that it has withdrawn from the FDA Division of Oncology Products 2 its NDA for binimetinib monotherapy for the treatment of NRAS-mutant melanoma. Based on feedback from the agency, Array concluded that the clinical benefit demonstrated in the Phase III 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 III COLUMBUS trial NDA of binimetinib, in combination with encorafenib, for the treatment of BRAF-mutant melanoma, which remains on track for mid-2017.
**Current Status:** Breakthrough therapy. BLA filed and granted priority review. Approved May 1, 2017

**Route of Administration/Dosing:** IV infusion (10mg/kg or 20mg/kg every 4 weeks).

**Proposed Indication(s):** Treatment of patients with locally advanced or metastatic urothelial carcinoma in patients who have progressed after one standard platinum-based regimen. It is also in Phase III development for the treatment of bladder cancer (1st-line) and NSCLC, both in combination with tremelimumab, an anti-CTLA-4 biologic immunotherapy.

**Mechanism of Action:** Programmed death receptor-ligand 1 (PD-L1) inhibitor; human monoclonal antibody that binds to PD-L1 which is expressed by some tumors to evade detection by the immune system by binding to PD-1 on cytotoxic T lymphocytes. Blocking the interaction between PD-L1 and PD-1 enhances the immune system's ability to detect and kill cancer cells.

**Patient Impact:** Urothelial carcinoma accounts for 90% of all bladder cancers. According to the ACS, it is estimated that more than 74,000 Americans will be diagnosed with bladder cancer in 2015, and approximately 15,000 of new diagnoses are made when bladder cancer is in advanced stages. There is a dramatic difference in survival rates between early and advanced bladder cancer. The ACS estimates that approximately 15% of people with advanced bladder cancer (stage IV) will live for five years, compared to 88% when diagnosed during stage I. Men are about three to four times more likely to get bladder cancer during their lifetime than women. Lung cancer is the most common cause of death due to cancer in both men and women throughout the world. Statistics from the ACS estimated that about 221,000 new cases of lung cancer in the U.S. will be diagnosed in 2015. NSCLC is one of the most common types of the disease and accounts for approximately 85% of cases.

**Cost Estimate:** $172,000/yr

**Current Therapies:** Currently available PD-1/PD-L1 inhibitors include Merck’s Keytruda® (pembrolizumab; approved for melanoma, NSCLC, head or neck squamous cell carcinoma), Bristol-Myers Squibb’s Opdivo® (nivolumab; approved for melanoma, NSCLC, renal cell carcinoma, Hodgkin lymphoma, head or neck squamous cell carcinoma), and Genentech’s Tecentriq® (atezolizumab; approved for locally advanced or metastatic urothelial carcinoma, NSCLC). Opdivo was approved for urothelial carcinoma in Feb 2017.

**Pipeline Product(s):** EMD Serono and Pfizer’s Bavencio® (avelumab) was approved in March 2017 for the second-line treatment of metastatic Merkel cell carcinoma. An expanded metastatic urothelial carcinoma indication is expected in Aug. 2017. Keytruda® is expected to get an expanded urothelial carcinoma indication in June 2017.

**Comments:** On Jun. 5, 2016, preliminary results of the Phase I/II trial, presented at the American Society of Clinical Oncology (ASCO) Annual Meeting, showed an ORR of 31% in all evaluable patients and 46% in patients with PD-L1-high expressing tumors. DCR, defined as confirmed complete or partial response or stable disease for 12 or more weeks, was 48% in all evaluable patients, and 57% in patients with PD-L1-high expressing tumors. On Feb. 17, 2016, AstraZeneca announced that FDA granted Breakthrough Therapy Designation for durvalumab for the treatment of patients with PD-L1 positive inoperable or metastatic urothelial bladder cancer whose tumor has progressed during or after one standard platinum-based regimen. The Breakthrough Therapy Designation for durvalumab was granted by the FDA on the basis of early clinical data from a Phase I trial (Study 1108) in patients with advanced metastatic urothelial bladder cancer whose tumors had progressed during or after one standard platinum-based regimen. On Dec. 9, 2016, AstraZeneca announced that FDA accepted the BLA for durvalumab and granted priority review status with a PDUFA set for the second quarter of 2017. As part of a broad development program, durvalumab is being tested as monotherapy and in combination with tremelimumab in the Phase III DANUBE trial as 1st-line treatment for patients with urothelial carcinoma, regardless of eligibility for cisplatin-based chemotherapy. The combination of durvalumab and tremelimumab is also being studied in Phase III trials in NSCLC, head and neck squamous cell carcinoma (HNSCC) and in Phase II and earlier trials in gastric cancer, pancreatic cancer, hepatocellular carcinoma (HCC) and blood cancers.
edaravone (Radicava - Mitsubishi Tanabe Pharma)


Route of Administration/Dosing: IV (60mg once daily for 14 days followed by 14 days observation, then 5 cycles of 10 days of treatment followed by 14 days observation).

Proposed Indication(s): Treatment of patients with amyotrophic lateral sclerosis (ALS).

Mechanism of Action: Edaravone is a free-radical scavenger that inhibits the activity of lipoperoxide 15-HPETE, which increases with age. Activity of lipoperoxide 15-HPETE has been associated with neurodegeneration due to oxidative stress. Oxidative stress is thought to be an imbalance between the production of free radicals and the ability of the body to counteract or detoxify their harmful effects. In patients with ALS, there are consistent increases in oxidative stress biomarkers.

Patient Impact: ALS, sometimes called Lou Gehrig’s disease, attacks the nerve cells in the brain and the spinal cord responsible for controlling voluntary muscles, such as those needed to move, speak, eat and breathe. It is estimated that as many as 30,000 people in the U.S. suffer from ALS, with approximately 5,600 individuals newly diagnosed each year. In 5-10% of cases, the disease is believed to be inherited, with the exact cause of the disease largely unknown. Current literature supports the notion that the cause is likely a combination of genetic and environmental factors. Treatment of ALS remains symptom based, with only one drug approved by the FDA for treatment of ALS. The average life expectancy for an individual newly diagnosed with ALS is between 3 and 5 years. Respiratory failure is the major cause of death in this patient population.

Cost Estimate: $145,500/yr

Current Therapies: There is no cure for ALS, but there are treatments available to relieve symptoms associated with the disease. Rilutek® (riluzole – Clovis Oncology, generics) has remained the only FDA approved drug for ALS since 1995, which is a treatment aimed at minimizing the neuronal damage caused by glutamate signaling. Nuedexta® (dextromethorphan hydrobromide and quinidine sulfate – Avanir Pharmaceuticals) was approved for the treatment of pseudobulbar affect (PBA) in 2010. PBA is characterized by frequent and involuntary episodes of laughing and/or crying that occurs secondary to neurological conditions such ALS or multiple sclerosis (MS).

Pipeline Product(s): Other ALS drugs in development are not expected to be approved for at least 2 years, pending trial results. Tirasemtiv (PO; Cytokinetics) – Phase III, ibudilast (PO; MediciNova) – Phase II, VM 202 (IM; ViroMed) – Phase II.

Comments: In May 2015, Mitsubishi received orphan drug designation from the FDA for its product edaravone, intended for the treatment of ALS. In a Phase II open-label study, patients on edaravone showed a significantly less 6-month decline in functional loss as measured the amyotrophic lateral sclerosis functional rating scale (ALSFRS-R) as compared to their decline assessed prior to edaravone therapy. Patients were randomized to six-cycles (24 weeks) of edaravone 60mg or matching placebo followed by a drug-free period of two weeks between each cycle. The primary endpoint of the study was change in the ALSFRS-R at week 24. A Phase III double-blind, parallel group, study (NCT01492686) of edaravone over 24 weeks was conducted in patients with ALS. Treatment consisted of 6 cycles of 60mg edaravone/matching placebo treatment, with ALSFRS-R serving as the primary efficacy endpoint. Analysis indicated the reduction of ALSFRS-R was lower in the edaravone group, however, did not reach statistical significance. Based upon subgroup analysis of the NCT01492686 trial, the investigators are in the process of conducting a second Phase III study, enrolling patients with a more rapidly progressive form of the disease, who showed more benefit from the drug in the sub-analysis. On Aug. 30, 2016, Mitsubishi Tanabe Pharma Corporation (MTPC) announced that the FDA has accepted the company’s NDA for edaravone (MCI-186) an IV treatment for ALS. A decision on the application is anticipated on June 16, 2017 based on the PDUFA. If approved, the medicine will be commercialized, under the brand name Radicava™, through the newly-formed MT Pharma America, Inc. On May 5, 2017, FDA approved Radicava for the treatment of ALS. It will be launched in August.
### Enasidenib (Agios Pharmaceuticals/Celgene)


**Route of Administration/Dosing:** PO (one 100mg tablet per day).

**Proposed Indication(s):** Treatment of relapsed (recurring) and/or refractory (resistant to treatment) acute myeloid (also called myelogenous) leukemia (AML) that has isocitrate dehydrogenase-2 (IDH2) mutations.

**Mechanism of Action:** Enasidenib is the first in a new class, IDH2 inhibitors. It blocks the activity of an enzyme located in mitochondria, cell structures responsible for changing nutrients into energy. Normal IDH2 assists in the energy transition process, but mutated forms produce high levels of a chemical (2-hydroxyglutarate or 2-HG) that may contribute to cancer formation and growth.

**Patient Impact:** According to the ACS, approximately 21,000 patients – mostly adults over 45 – are diagnosed with AML in the U.S. each year. AML is a cancer that 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 treated early and aggressively. Only about one-quarter of patients survive for five years or longer after diagnosis. Up to 19% of AML patients also have IDH2 mutations.

**Cost Estimate:** $100,000 - $150,000/yr

**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.

**Pipeline Product(s):** A number of drugs are in late-stage development to treat AML including Vyxeos™ (cytarabine/daunorubicin - Jazz Pharmaceuticals), which is expected to be approved Oct.3, 2017. Agios’ ivosidenib is an isocitrate dehydrogenase inhibitor, but ivosidenib interferes with IDH1. It is being developed for AML patients who are newly diagnosed, who have an IDH1 mutation, and who are not candidates for intensive chemotherapy. NDA submission is expected by the end of 2017. Boehringer Ingelheim’s volasertib (polo-like kinsase 1 (PLK1) inhibitor, IV) is a breakthrough therapy that is in Phase III development for use in combination with low-dose cytarabine for treatment-naive AML patients who are at least 65 years old and who are not eligible for intensive induction therapy. Volasertib may be approved in late 2017 or early 2018.

**Comments:** In the phase I/II AG221-C-001 study, which began in 2013, 181 patients – including 128 with relapsed (recurring) or refractory (resistant to treatment) AML – were assessed after treatment with enasidenib. Among all evaluated patients, CR was attained by 18% and 41% had an objective response (OR). AML patients had a median response duration of six months. By May 2015, some AML patients had been on therapy for 15 months. A two-year long phase III study is comparing enasidenib monotherapy with common current treatments (azacitidine or cytarabine) for patients over age 60 whose late stage IDH2+ AML has returned even after being treated two or three times. All participants also receive supportive care, which could include blood transfusions, nutritional assistance and drugs for fever, infections, nausea and pain. Celgene is also evaluating enasidenib compared with conventional therapy in older patients with an IDH2 mutation and relapsed or refractory AML in the ongoing phase III IDHENTIFY trial. Enasidenib was well tolerated at 60mg to 450mg in 177 patients with AML during a phase I study (NCT01915498). A companion diagnostic blood test for IDH2 mutations, developed by Abbott, also has been filed for FDA approval. A positive result proving an IDH4 mutation will be required before patients can begin enasidenib. On Mar. 1, 2017, Celgene Corporation and Agios Pharmaceuticals announced that the FDA has accepted Celgene’s NDA for enasidenib for the treatment of patients with relapsed or refractory AML with an IDH2 mutation. The NDA was granted Priority Review and has been given a PDUFA action date of Aug. 30, 2017.

### Entinostat (Syndax Pharmaceuticals)

**Current Status:** Phase III for breast cancer. Breakthrough therapy for breast cancer indication. Phase II for NSCLC, non-Hodgkin’s lymphoma and ovarian cancer.

**Route of Administration/Dosing:** PO (5mg once weekly) in combination with exemestane (Aromasin® - Pfizer) PO 25 mg 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: Histone deacetylase inhibitor (HDAC). It 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/yr

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® (everolimus) or Ibrance® (palbociclib) + letrozole. Novartis’ Kisqali® (ribociclib) is a CDK 4/6 inhibitor that was approved Mar. 13, 2017, for ER+/HER2- breast cancer.

Pipeline Product(s): Puma Biotechnology’s neratinib is an oral, irreversible pan-ErbB receptor tyrosine kinase inhibitor 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. Lilly’s abemaciclib is an oral CDK 4/6 inhibitors that may be approved in 2018 for ER+/HER2- breast cancer.

Comment(s): Entinostat is currently being evaluated in a Phase III clinical trial in advanced HR+ breast cancer in collaboration with the National Cancer Institute. The Phase III clinical trial is designed to determine whether the addition of entinostat to Aromasin improves PFS, overall survival (OS), 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 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 U.S., 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 PFS in patients who received entinostat and exemestane, compared with exemestane alone. Treatment with entinostat, in combination with exemestane, improved PFS 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 PFS was over six months in the subset of entinostat patients who exhibited lysine hyperacetylation. Compared with exemestane alone, entinostat plus exemestane treatment also improved OS by 8.3 months, corresponding to a 41% reduction in risk of dying. Results from the phase II ENCORE 303 study in post-menopausal women with advanced, ER+ 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%, the ORR was 3.9% and PFS was 4.8 months. Further results presented at the 48th Annual Meeting of the ASCO, also showed an improvement in overall survival. Based on data from this trial, the 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.

glecaprevir/pibrentasvir (AbbVie)


Route of Administration/Dosing: PO (three tablets, each containing 100mg of glecaprevir and 40mg of pibrentasvir) once daily for 8 or 12 weeks.

Proposed Indication(s): Treatment of genotypes 1 through 6 chronic hepatitis C virus (HCV) infections.

Mechanism of Action: Glecaprevir is an NS3/4A protease inhibitor. Pibrentasvir is an NS5A inhibitor.

Patient Impact: Hepatitis C, a virus that infects the liver, is transmitted through direct contact with infected blood and blood products. The World Health Organization (WHO) estimates that between 130 million and 150 million people are infected with hepatitis C worldwide. As many as 85% of those acutely infected with hepatitis C will become chronically infected. Approximately 2.7 million to 3.9 million individual have chronic hepatitis C in the U.S., according to the CDC. Up to 30% of people who have chronic hepatitis C will develop cirrhosis, and up to 25% of cirrhosis patients may progress to liver cancer. Because cirrhosis develops so slowly, however, symptoms do not usually appear until liver damage is severe. Many
hepatitis C cases are discovered after routine blood testing during checkups. At least six separate genotypes of hepatitis C virus currently are known, and they have over 50 subtypes. Designated as genotypes 1 through 6, the main types are distributed differently around the world. In the U.S., about 70% of chronic hepatitis C patients have type 1, which is the most common. Around 55% of them have type 1a and around 35% have 1b. Genotype 2 accounts for approximately 15% to 20% of American patients, type 3 for about 12% and types 4 through 6 for 1% or less, each.

Cost Estimate: Approximately $75,000 for the treatment course.

Current Therapies: It will primarily compete with Gilead’s Epclusa® (sofosbuvir/velpatasvir), which was approved Jun. 28, 2016, for adults with genotypes 1 through 6 and chronic HCV infections. It is taken once daily for 12 weeks. Other DAAs include: Harvoni® (sofosbuvir/ledipasvir – Gilead), Zepatier® (elbasvir/grazoprevir - Merck), Technivie™ (ombitasvir/paritaprevir/ritonavir - AbbVie), Viekira Pak® (ombitasvir/paritaprevir/ritonavir with dasabuvir - AbbVie), Viekira XR™ (ombitasvir/paritaprevir/ritonavir with dasabuvir – AbbVie) Daklinza™ (daclatasvir – Bristol-Myers Squibb), Olysio® (simeprevir – Janssen), and Sovaldi® (sofosbuvir – Gilead).

Pipeline Product(s): Gilead’s triple-therapy, sofosbuvir/velpatasvir/voxilaprevir, also an oral pan-genotypic DAA therapy, has an FDA-action date of August 8, 2017. It combines an already approved nucleotide analog NS5B polymerase inhibitor (sofosbuvir) and pan-genotypic NS5A inhibitor (velpatasvir) with a new pan-genotypic NS3/4A protease inhibitor (voxilaprevir). In clinical trials, it was effective for patients with any type of hepatitis C that did not respond to previous DAA therapy, as well as for patients new to drug treatment. Several other DAA single-agents and combinations, including additional protease, polymerase and NS5A inhibitors, are in phase II trials, but none is likely to be approved until 2020 or later. All are oral and most are pan-genotypic.

Comments: Patients with all six types of hepatitis C participated in phase III trials of glecaprevir/pibrentasvir (G/P). Newly diagnosed patients were treated, as were patients with more advanced disease and those with comorbidities, such as HIV or chronic kidney disease (CKD). In the ENDURANCE-1 trial, 351 participants who had type 1 hepatitis C that had not been treated previously and who did not have cirrhosis took G/P for eight weeks. Sustained virologic response at 12 weeks (SVR12) was attained by 99% of treatment-naïve, non-cirrhotic patients with genotypes 2, 4, 5 and 6 accomplishing SVR12 following eight weeks of G/P therapy. Hepatitis C type 3 patients enrolled in ENDURANCE-3 were new to treatment and they did not have cirrhosis. Eight weeks of therapy with G/P produced SVR12 for 149 of the 157 (95%) patients. Among 104 patients with serious CKD and any of the six hepatitis C types treated in the EXPEDIITION-3 study, 102 (98%) achieved SVR12, but treatment was extended to 12 weeks instead of eight. Although some trial participants also used interferon or ribavirin, neither of those drugs increased response rates achieved by G/P alone. On Apr. 20, 2017, AbbVie announced that in its Phase III EXPEDIITION-1 study, 99% (n=145/146) of chronic hepatitis C infected patients with genotype 1, 2, 4, 5 or 6 and compensated cirrhosis (Child-Pugh A) achieved SVR12 post-treatment with G/P. This high SVR12 rate was seen following 12 weeks of G/P treatment without ribavirin. Patients with specific virus strains associated with resistance or with a high quantity of the virus in their bloodstream before treatment initiation were not excluded from the study. On Apr. 21, 2017, AbbVie announced results from its Phase III ENDURANCE-3 study. The study found high SVR12 rates were achieved with 8 weeks of G/P in patients with challenging to treat genotype 3 (GT3) chronic HCV infection. In results from the 95% (n=149/157) of GT3 chronic HCV infected patients without cirrhosis and who are new to treatment achieved G/P treatment following 8 weeks of treatment with G/P. The ENDURANCE-3 study was designed to evaluate whether 12 weeks of G/P is non-inferior to 12 weeks of sofosbuvir plus daclatasvir (SOF+DCV), a current standard of care for GT3 chronic HCV infected patients. SVR12 rates of 95% were seen in both 8 weeks (n=149/157) and 12 weeks (n=222/233) of treatment with G/P. Additionally, 12 weeks of treatment with G/P was demonstrated to be non-inferior to 12 weeks of treatment with SOF+DCV (97%, n=111/115). Glecaprevir/pibrentasvir is not recommended to treat patients with decompensated (advanced) cirrhosis because protease inhibitors are not as active for patients whose liver function is inadequate to break them down effectively. Across all clinical trials, side effects generally were mild and temporary, with fatigue, headaches and nausea being reported the most.
guselkumab (Janssen)


Route of Administration/Dosing: SQ injection (100mg at weeks 0, 4, 12 and every 8 weeks thereafter).


Mechanism of Action: IL-23 inhibitor.

Patient Impact: Psoriasis is a chronic, autoimmune inflammatory disorder that results in the overproduction of skin cells, characterized by raised, inflamed, scaly, red lesions, or plaques, which can cause physical pain and itch. It is estimated that as many as 125 million people worldwide have psoriasis, including 7.5 million Americans, and nearly one-quarter of people affected have cases that are considered moderate-to-severe.

Cost Estimate: $55,000/yr

Current Therapies: Biologics for psoriasis include Enbrel®, Humira®, Stelara®, Remicade®, Cosentyx® and Taltz® (IL-17A inhibitors). Valeant’s Siliq® (brodalumab) is an IL-17 inhibitor approved Feb. 15, 2017 for moderate-to-severe plaque psoriasis.

Pipeline Product(s): Sun’s tildrakizumab and Boehringer Ingelheim and AbbVie’s risankizumab are SC IL-23 inhibitors that are in Phase III development for moderate-to-severe plaque psoriasis.

Comments: On Oct. 1, 2016, Janssen announced findings from the Phase III VOYAGE 1 study in adults with moderate-to-severe plaque psoriasis. Data from the VOYAGE 1 trial showed significantly higher proportions of patients receiving guselkumab achieved cleared/minimal disease compared with patients receiving placebo, as defined by at least a 90% improvement in the Psoriasis Area Severity Index (PASI) 90, near complete skin clearance (73.3% with guselkumab vs. 2.9% with placebo) and an Investigator’s Global Assessment (IGA) score of cleared (0) or minimal disease (1) at week 16, the study co-primary endpoints (85.1% with guselkumab vs. 6.9% with placebo). The VOYAGE 1 trial also included an active comparator arm evaluating guselkumab versus Humira® (adalimumab), and showed the superiority of guselkumab across major study endpoints and through 48 weeks of treatment. All major secondary endpoints in VOYAGE 1 achieved statistical significance in comparisons of guselkumab versus adalimumab administered SQ at weeks 0 (80 mg), 1 (40 mg) and then 40 mg every other week (P < 0.001 for all measures). At week 16, following three injections of guselkumab and ten injections of adalimumab, significantly higher proportions of patients receiving guselkumab achieved IGA 0/1 and PASI 90 (85.1% with guselkumab vs. 6.9% with placebo). At week 24, the proportion of patients who achieved a PASI 90 response was significantly higher in the guselkumab group compared with the adalimumab group (80.2% vs. 53.3%, respectively). Higher levels of skin clearance among the guselkumab group continued through weeks 24 and 48, with significantly more patients receiving guselkumab achieving IGA 0/1 and PASI 90, as well as measures of full skin clearance, as indicated by a 100% improvement in PASI score (PASI 100) or an IGA score of 0, compared with adalimumab. On Nov. 17, 2016, Janssen announced the submission of its BLA to the FDA seeking approval of guselkumab for the treatment of adults living with moderate-to-severe plaque psoriasis. According to Janssen, the FDA action date is July 14, 2017. On Mar. 3, 2017, Janssen announced new findings from two pivotal Phase III studies reporting the efficacy and safety of guselkumab in the treatment of adults with moderate-to-severe plaque psoriasis. Data from the VOYAGE 2 study showed that patients treated with guselkumab experienced significant improvements in skin clearance and other measures of disease activity compared with placebo, and significantly greater improvements compared with the anti-TNF-alpha treatment Humira® (adalimumab). Data from the Phase III study (NAVIGATE) showed that patients who had an inadequate response following treatment with the IL-12/23 monoclonal antibody (mAb) Stelara® (ustekinumab) and who then switched to guselkumab, showed significantly greater improvements in skin clearance compared with patients who continued to receive Stelara. In the VOYAGE 2 study, the co-primary endpoints were met at week 16, with 84.1% of patients receiving guselkumab 100 mg at weeks 0 and 4 and then every 8 weeks achieving an IGA score of 0/1 disease compared with 8.5% of patients receiving placebo (P < 0.001). In addition, 70.0% of patients receiving guselkumab achieved a PASI 90 score (near complete skin clearance) compared with 2.4% of patients receiving placebo (P < 0.001). Major secondary endpoints in VOYAGE 2 achieved statistical significance in comparisons of guselkumab versus adalimumab administered SQ at weeks 0 (80 mg), 1 (40 mg) and then 40 mg every other week (all P < 0.001). At week 16, following three injections of guselkumab and ten injections of adalimumab, significantly higher proportions of patients receiving guselkumab versus adalimumab...
achieved IGA 0/1 (84.1% versus 67.7%, respectively) and PASI 90 (70.0% versus 46.8%, respectively). Guselkumab continued to demonstrate superiority versus adalimumab at week 24 for both the IGA 0/1 and PASI 90 scores. Among other secondary endpoints, significantly higher proportions of patients receiving guselkumab compared with adalimumab achieved Dermatology Life Quality Index (DLQI) scores of 0/1 (indicating no impact of psoriasis on health-related quality of life) and PASI 100 scores (complete skin clearance) at week 24. Additionally, at week 16 and 24, 34.1% and 44.2% of patients receiving guselkumab achieved PASI 100 responses, respectively. The NAVIGATE study evaluated the efficacy and safety of guselkumab in patients who continued to experience mild-to-severe skin symptoms (IGA of 2 or more) following 16 weeks of treatment with Stelara. Patients who switched to guselkumab consistently showed greater improvement in their psoriasis between weeks 28 and 40, compared with patients who continued to receive Stelara, having twice as many office visits with at least a 2 point improvement in IGA from week 16, the study’s primary endpoint, and an IGA score of 0 or 1 (1.5 and 0.7 respectively; P < 0.001). Guselkumab also demonstrated superiority across major secondary endpoints in comparisons with Stelara. Major secondary endpoints included the number of visits that patients achieved a PASI 90 response or IGA score of 0 between weeks 28 and 40, and the proportions of patients that achieved an IGA score of 0 or 1 with at least a 2 point improvement from week 16 at week 28 (all P ≤ 0.001). In addition, a significantly higher proportion of patients in the guselkumab group achieved an IGA score of 0 or 1 and at least a 2 point improvement from week 16 at week 52, and a PASI 90 response at weeks 28 and 52, compared with Stelara (all P < 0.001).

### nonacog beta pegol (Refixia - Novo Nordisk)

**Current Status:** BLA filed May 16, 2016. FDA approval expected May 16, 2017.

**Route of Administration/Dosing:** Once weekly, single 40 U/kg IV dose (or 80 U/kg for severe bleeding).

**Proposed Indication(s):** Prophylaxis and treatment of hemophilia B.

**Mechanism of Action:** PEGylated, long-acting factor IX (FIX) derivative which has a 5x longer half-life than standard FIX products which enables once-weekly dosing.

**Patient Impact:** Hemophilia B, also called FIX deficiency, is a genetic disorder caused by missing or defective FIX, a clotting protein. Although it is passed down from parents to children, about 1/3 of cases are caused by a spontaneous mutation. According to the CDC, hemophilia occurs in approximately 1 in 5,000 live births. There are about 20,000 people with hemophilia in the U.S. All races and ethnic groups are affected. Hemophilia B is four times less common than hemophilia A.

**Cost Estimate:** $500,000/yr

**Current Therapies:** It will compete with Alprolix® and Idelvion®, which are other long-acting FIX products. Other FIX products, like BeneFIX®, Ixinity® and Rixubis need to be given 2 or more times per week.

**Comments:** Paradigm 1 phase III, a total of 16 subjects treated showed two fold increase in recovery, higher activity levels and a fivefold prolongation of half-life compared to existing treatment. The single-dose escalation trial evaluated the safety and pharmacokinetics (PK) of nonacog beta pegol in comparison with marketed recombinant and plasma-derived FIX products. In May 2011, Novo Nordisk initiated a single-blind phase III trial to evaluate the safety, efficacy and PK of nonacog beta pegol in patients with hemophilia B (Paradigm™ 2; NCT01333111). Patients were randomized to receive nonacog beta pegol as prophylaxis at dose 40 IU/kg once-weekly for 52 weeks, or as an on-demand treatment for 28 weeks. The trial enrolled of 74 male patients aged 13 to 70 years and was completed in April 2013. The Paradigm 2 phase III pivotal trial showed nonacog beta pegol to be safe and well-tolerated with a median annualized spontaneous bleeding rate of 0.0. The trial further demonstrated that 97% of breakthrough bleeds were treated successfully and 90% of target joints no longer classified as such. Once-weekly 10 and 40 U/kg doses as prophylaxis for 12 months reduced median annualized bleeding rates compared to on-demand treatment for six months (2.9 and 1 episode per year, respectively, vs. 15.6 episodes per year). Novo Nordisk completed an open-label, uncontrolled phase III trial in December 2013, which confirmed the safety and efficacy of the nonacog beta pegol during and after major surgical procedures in patients with hemophilia B (Paradigm™ 3; NCT01386528). In the 13 treated patients (males aged 13 to 70 years), a single preoperative dose provided effective hemostatic coverage with no patient requiring any additional doses on the day of surgery. In addition, three doses proved sufficient in maintaining hemostasis during the first two
weeks following the procedure. Novo Nordisk initiated an open-label, phase III extension trial in April 2012, to assess the safety and efficacy of nonacog beta pegol after long-term exposure in patients with hemophilia B (Paradigm™ 4; NCT01395810). The trial enrolled 71 patients who have participated in the Paradigm 2 or 3 trials, and was completed in March 2014. The 71 patients treated, reported an improvement in quality of life during the trial. Novo Nordisk initiated an open-label, controlled phase III trial in May 2012, to assess the safety, efficacy and PK of once-weekly prophylaxis and treatment of bleeding of nonacog beta pegol in previously treated children with hemophilia B (Paradigm™ 5). Enrollment of 24 boys aged up to 13 years was completed in April 2013. The Paradigm 5 phase III pediatric single-arm 52 week trial showed that all the patients maintained mean factor activity levels above 15% one week after dosing of 40 IU/kg and a median ABR ratio of 0.0 and 2.0 for children aged 0-6 and 7-12 years old respectively. A multinational phase III trial of nonacog beta pegol was initiated in July 2014 in approximately 50 previously untreated patients aged under 6 years who have hemophilia B. Patients will receive single 40 U/kg IV doses of nonacog beta pegol (or 80 U/kg for severe bleeding) for prophylaxis or treatment of bleeding episodes. The primary aim of the trial is to evaluate the incidence of inhibitory antibodies against FIX up to 72 months from study start.

romosozumab (Evenity - Amgen / UCB)


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

Proposed Indication(s): 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% of all fractures.

Cost Estimate: $17,000/yr

Current Therapies: Lilly’s Forteo® (teriparatide) is a once-daily SQ injection parathyroid hormone (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 SQ (once daily) is a synthetic analog of the PTH-related protein that was approved Apr. 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 II study showing the efficacy and safety of a second course of treatment with Evenity™ (romosozumab), an investigational agent for postmenopausal women with osteoporosis. 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%), total hip (5.8%) and femoral neck (6.3%) during months 36 to 48. In those patients who received a second course of Evenity after denosumab, Evenity further increased BMD by 2.8 % at the lumbar spine, while maintaining BMD at the total hip and femoral neck. Romosozumab is currently under FDA review with a PDUFA date of July 19, 2017.
sarilumab (Kevzara - Sanofi / Regeneron)


Route of Administration/Dosing: SQ every other week.

Proposed Indication(s): Treatment of RA.

Mechanism of Action: Fully human monoclonal antibody targeting the IL-6 receptor. IL-6 is a signaling protein widely involved in the regulation of immune and inflammatory responses and has been shown to be a key mediator of inflammation in RA.

Patient Impact: RA is chronic systemic autoimmune disease affecting approximately 0.5-1% of the global adult population. An estimated 1.5 million adult Americans have been diagnosed with RA. RA affects women 2.5 times as often as men and can start at any age, although the peak age of onset is between 30 and 55 years. Approximately 294,000 children <18 are affected by pediatric arthritis and rheumatologic conditions. RA can be very painful and affects a person’s ability to carry out everyday tasks.

Cost Estimate: $25,000/yr

Current Therapies: Biologic DMARDs used to manage RA include: Enbrel® (etanercept – Amgen), a SQ TNF blocker; Kineret® (anakinra – Amgen), a SQ IL-1 receptor antagonist; Humira® (adalimumab - AbbVie) a SQ TNF blocker, Cimzia® (certolizumab pegol – UCB) a SQ TNF blocker, Simponi® (golimumab – Janssen) a SQ TNF blocker, Simponi Aria® (golimumab – Janssen) IV TNF blocker, Remicade® (infliximab – Janssen) – an IV TNF blocker; Rituxan® (rituximab - Biogen) an IV CD20-directed cytolytic antibody, Ocrevus® (aenzacept - BMS) an IV/SQ selective T cell costimulation modulator; Actemra® (tocilizumab – Genentech) an IV/SQ IL-6 receptor antagonist; and Xeljanz® (tofacitinib - Pfizer) an PO JAK inhibitor.

Pipeline Products(s): Additional IL-6 inhibitors in the pipeline include: sirukumab (Janssen/GlaxoSmithKline) is expected to be approved by Sep. 23, 2017; clazakizumab (BMS); okolizumab (UCB-R-Pharm); ALX-0061 (Ablynca/Abbvie); and MEDI5117 (AstraZeneca).

Comments: The SARIL-RA-MOBILITY trial, a Phase III trial, enrolled 1,197 patients with active moderate-to-severe RA who were inadequate responders to MTX. All patients were on background MTX and were randomized to 200mg sarilumab, 150mg sarilumab or placebo, all given every other week. The trial had three co-primary endpoints, improvements in signs and symptoms as measured by the ACR20 score at week 24, improvement in physical function at week 16 as measured by the HAQ-DI, and inhibition of progression of structure damage at week 52, as measured by change in the van der Heijde modified total Sharp score (mTSS). Both sarilumab groups showed statistically significant improvements compared to placebo in all three co-primary endpoints. ACR20 scores were 58%, 66% and 33% in the sarilumab 150mg, sarilumab 200mg and placebo groups respectively; HAQ-DI results were -0.53, -0.55, and -0.29, respectively and, mTSS score results were 0.90, 0.25 and 2.78 respectively. On May 21, 2015, Regeneron and Sanofi announced results of the Phase III trial, SARIL-RA-TARGET, evaluating the efficacy and safety of two SQ sarilumab doses versus placebo, added to non-biologic DMARD therapy in RA patients who were inadequate responders to or intolerant of TNF-alpha inhibitors. The trial enrolled 546 patients who were randomized to one of three treatment groups: 200mg sarilumab administered SQ every other week (Q2W), 150mg sarilumab administered SQ Q2W, or placebo, plus DMARD therapy. Both treatment groups showed statistically significant improvements compared to placebo in both co-primary endpoints. Improvements in signs and symptoms of RA at 24 weeks, as measured by the ACR20, were 61% in the sarilumab 200 mg Q2W group, 56% in the sarilumab 150mg Q2W group, and 34% in the placebo group (all in combination with DMARD therapy). On Mar. 11, 2016, Regeneron and Sanofi announced that a Phase III monotherapy study met its primary endpoint demonstrating that sarilumab was superior to adalimumab in improving signs and symptoms in patients with active RA at Week 24. The SARIL-RA-MONARCH study enrolled 369 adult patients with active RA who were inadequate responders to, intolerant of, or inappropriate candidates for MTX. Patients were randomized to receive either SQ sarilumab monotherapy (200 mg Q2W) or adalimumab monotherapy (40 mg Q2W); patients who did not respond adequately to adalimumab could increase to weekly dosing. The primary endpoint was change from baseline in DAS28-ESR at 24 weeks, which demonstrated a statistically significant difference in favor of sarilumab (-3.25 for sarilumab compared to -2.22 for adalimumab, p<0.0001). The study also met clinically important secondary endpoints including improvements in signs and symptoms of RA as measured by patients achieving an ACR20 criteria (72% for sarilumab vs. 58% for adalimumab, p<0.01). Additional positive
secondary endpoints included ACR50 and ACR70 response, and improvement in physical function, as measured by the HAQ-DI as compared to adalimumab (p<0.01 for all of these measures). DAS28-ESR is a measure of disease activity in RA, which includes the evaluation of 28 joints in the body for tenderness and swelling, a general health assessment, and ESR, a laboratory measure for inflammation. On April 28, 2017, Regeneron Pharmaceuticals, Inc. and Sanofi today announced that the FDA has accepted the resubmission of the BLA for Kevzara® (sarilumab) as a Class I response with a two month review timeline. Per the PDUFA, the new target action date is May 22, 2017.


Route of Administration/Dosing: SQ every other week or every 4 weeks (50mg or 100mg).

Proposed Indication(s): Treatment of adults with moderately-to-severely active RA.

Mechanism of Action: Human monoclonal IgG1 kappa antibody targeting the IL-6 receptor. IL-6 is a signaling protein widely involved in the regulation of immune and inflammatory responses and has been shown to be a key mediator of inflammation in RA.

Patient Impact: RA is chronic systemic autoimmune disease affecting approximately 0.5-1% of the global adult population. An estimated 1.5 million adult Americans have been diagnosed with RA. RA affects women 2.5 times as often as men and can start at any age, although the peak age of onset is between 30 and 55 years. Approximately 294,000 children <18 are affected by pediatric arthritis and rheumatologic conditions. RA is characterized by an abnormal immune response that causes inflamed, thickened synovium, the membrane that lines the joints and can damage the bone and cartilage of the joint and the surrounding tissues. RA-related inflammation can involve the heart and lungs; in 10% of patients, the liver is affected. Complications of RA include anemia and leukopenia. RA can be very painful and affects a person’s ability to carry out everyday tasks.

Cost Estimate: $25,000/yr

Current Therapies: Biologic DMARDs used to manage RA include: Enbrel® (etanercept – Amgen), a SQ TNF blocker; Kinetrel® (anakinra – Amgen), a SQ IL-1 receptor antagonist; Humira® (adalimumab - AbbVie) a SQ TNF blocker, Cimzia® (certolizumab pegol – UCB) a SQ TNF blocker, Simponi® (golimumab – Janssen) a SQ TNF blocker, Simponi Aria® (golimumab – Janssen) IV TNF blocker, Remicade® (infliximab – Janssen) – an IV TNF blocker; Rituxan® (rituximab - Biogen) an IV CD20-directed cytolytic antibody, Orencia® (abatacept - BMS) an IV/SQ selective T cell costimulation modulator; Actemra® (tocilizumab – Genentech) an IV/SQ IL-6 receptor antagonist; and Xeljanz™ (tofacitinib - Pfizer) an PO JAK inhibitor.

Pipeline Product(s): Additional IL-6 inhibitors in the pipeline include: sarilumab (Saraca – Regeneron /Sanofi) is expected to be approved in 2017; clazakizumab (BMS); olokizumab (UCB-R-Pharm); ALX-0061 (Ablync/Abbvie); and MEDI5117 (AstraZeneca).

Comments: On Jun. 8, 2016, Janssen announced results from SIRROUND-D, a pivotal Phase III study. In SIRROUND-D, a total of 1,670 patients were randomized evenly to receive sirukumab 50 mg every four weeks or sirukumab 100 mg every two weeks or placebo. The study met both co-primary endpoints evaluating treatment with sirukumab in adult patients with active RA who had an inadequate response to treatment with DMARDs. Inhibition of radiographic progression, or joint destruction, was significantly greater among sirukumab-treated patients, with a mean change from baseline to week 52 in the van der Heijde-Sharp score of 0.50 among patients receiving sirukumab 50 mg every four weeks (n=557) and 0.46 for patients receiving sirukumab 100 mg every two weeks (n=557) compared with 3.69 among the placebo group (n=556) (both P < 0.001). Significant inhibition of radiographic progression was demonstrated in both patients naïve to biologic therapy and those treated with biologics in the past, and was seen as early as week 24. At least a 20% improvement in RA signs and symptoms as measured by the ACR20 at week 16 was achieved by 54.8% and 53.5% of patients receiving sirukumab 50 mg and sirukumab 100 mg, respectively, compared with 26.4% of the placebo group (both P < 0.001). All major secondary endpoints were also met with statistical significance for both doses of sirukumab versus placebo (P < 0.001 for all measures across both doses). These included the change from baseline in the HAQ-DI, percentage of patients achieving at least a 50% improvement in RA symptoms (ACR50), percentage of patients with improved disease activity score in 28 joints. The Phase III clinical program in patients with active RA also includes four other studies investigating sirukumab 50 mg and 100 mg administered SQ, in combination with conventional DMARDs or as monotherapy every four or two weeks, respectively. On Sep. 23, 2016, Janssen Biotech, Inc. announced today the submission of a BLA to the FDA seeking approval of sirukumab for the treatment of adult patients with moderately to severely active RA. Approval is...
expected by Sep. 23, 2017. On Nov. 16, 2016, Janssen announced results from two pivotal Phase III studies evaluating sirukumab in adults with moderately-to-severely active RA. In SIRROUND-H, a comparator study of sirukumab monotherapy versus adalimumab monotherapy, patients receiving sirukumab 50 mg every Q4W and patients receiving sirukumab 100 mg Q2W experienced significant mean changes from baseline in DAS28 at week 24 of -2.58 and -2.96, respectively, one of two co-primary endpoints of the study, compared with a mean change of -2.19 in patients receiving adalimumab 40 mg Q2W (P = 0.013 and P < 0.001, respectively). All treatment groups showed clinically relevant improvements in achieving the other co-primary endpoint, at least 50% improvement in signs and symptoms (ACR50) of disease at week 24, although the proportions of patients in ACR50 response were not significantly different between sirukumab 50 mg Q4W, sirukumab 100 mg Q2W and adalimumab 40 mg Q2W (27%, 35% and 32%, respectively [P > 0.05]). In SIRROUND-T, among patients refractory/intolerant to anti-TNF treatments, 40% of patients receiving sirukumab 50 mg Q4W and 45% of patients receiving sirukumab 100 mg Q2W achieved the study’s primary endpoint, at least a 20% improvement in signs and symptoms (ACR20) at week 16, compared with 24% of patients receiving placebo (P ≤ 0.001). Approximately 40% of patients in the study had prior exposure to non-TNF biologic therapies.

**Current Status:** Phase III. Approval expected in the first half of 2018.

**Route of Administration/Dosing:** SQ injection (100mg or 200mg at weeks 0 and 4, then every 12 weeks thereafter.

**Proposed Indication(s):** Treatment of adults living with moderate-to-severe plaque psoriasis.

**Mechanism of Action:** IL-23 inhibitor; the antibody specifically targets IL-23p19 subunit.

**Patient Impact:** Psoriasis is a chronic, autoimmune inflammatory disorder that results in the overproduction of skin cells, characterized by raised, inflamed, scaly, red lesions, or plaques, which can cause physical pain and itch. It is estimated that as many as 125 million people worldwide have psoriasis, including 7.5 million Americans, and nearly one-quarter of people affected have cases that are considered moderate to severe.

**Cost Estimate:** $55,000/yr

**Current Therapies:** Biologics for psoriasis include Enbrel®, Humira®, Stelara®, Remicade®, Cosentyx® and Taltz® (IL-17A inhibitors). Valeant’s Siliq™ (brodalumab) is an IL-17 inhibitor approved Feb. 15, 2017, for moderate-to-severe plaque psoriasis.

**Pipeline Product(s):** Janssen’s guselkumab is a SC IL-23 inhibitor that is expected to be approved by Jul. 14, 2017, for the treatment of moderate-to-severe plaque psoriasis. Boehringer Ingelheim and AbbVie’s risankizumab is a SC IL-23 inhibitor that is in Phase III development for moderate-to-severe plaque psoriasis.

**Comments:** On May 4, 2016, Sun Pharmaceutical Industries Ltd. announced that antibody tildrakizumab met the co-primary endpoints in two Phase III trials to treat moderate-to-severe plaque psoriasis. In both studies, 100 and 200 mg doses of tildrakizumab significantly improved PASI 75 response rates and the proportion of patients with a score of 0 or 1 on the Physician’s Global Assessment (PGA) of psoriasis at week 12 vs. placebo. On the latter endpoint, patients also had to have at least a two-point reduction from baseline on the seven-point scale, where 0 indicates clear skin. One of the studies also included an active-control arm comparing tildrakizumab to etanercept. In that study, Sun said high-dose tildrakizumab was superior to etanercept on both PASI 75 response rates and PGA scores at week 12; the low dose was superior to etanercept on PASI 75. In a part I of the phase II study, administration of tildrakizumab in patients with moderate-to-severe chronic plaque psoriasis resulted in 33.3%, 64.4%, 66.3%, 74.4% and 4.4% PASI 75 responses at week 16 in the 5 mg, 25 mg, 100 mg, 200 mg tildrakizumab and placebo groups, respectively (p ≤ 0.001 versus placebo). Clinically important changes (> 4 points) including mean changes from baseline in DLQI, improvement in symptoms/feelings and daily activities leisure, work/school, personal relationships were correlated with improvements in PASI scores. The results were reported from 355 patients enrolled in double-blind randomized study. The co-primary endpoints of the proportion of patients with PASI 75 response at week 12, and the proportion of patients with a PGA score of clear or minimal with at least a 2 grade reduction from baseline at week 12, versus placebo, were met in two phase III trials (Studies MK-3222-010 and MK-3222-011) that evaluated tildrakizumab in patients with moderate-to-severe plaque psoriasis. In the reSURFACE 1 and reSURFACE 2 studies, an average of 63% patients achieved PASI 75 response by week 12 and two injections and 77% achieved PASI 75 response, after 28 weeks and three injections of 100mg dose of tildrakizumab. Patients receiving 100mg dose saw an average of
57% and 66% of patients achieving PGA score of ‘clear’ or ‘minimal’ at weeks 12 and 28 respectively, while these values were 59% and 69% for the 200mg dose. PASI 75 score at weeks 12 and 28 were indicated in 64% and 78% of patients. Additionally, in Study MK-3222-011, tildrakizumab 200 mg demonstrated superiority to etanercept on both primary endpoints, whereas the 100 mg dose was superior on the PASI 75 endpoint only. Higher number of patients on tildrakizumab achieved PASI 90 and 100 compared to placebo and etanercept. An average of 37% and 36% of patients receiving tildrakizumab reached PASI 90 at week 12 with the 100mg and 200mg doses respectively. These values increased to 54% and 59% respectively at week 28. Thirteen percent of patients on tildrakizumab reached PASI 100 at week 12 irrespective of dose with an increase to 24% for the 100 mg dose and 30% for the 200 mg dose at week 28.

**Current Status:** Breakthrough therapy. BLA filed. Priority review granted. Approval expected by Sep. 29, 2017.

**Route of Administration/Dosing:** One IV infusion at a median dose of 2.9x106 transduced cells/kg.

**Proposed Indication(s):** Treatment of relapsed (recurring) and refractory (unresponsive to earlier treatment) B-cell acute lymphoblastic (also called lymphocytic) leukemia (B-cell ALL) in pediatric and young adult patients. Filing for the treatment of adult patients with relapsed and refractory DLBCL, who have failed two or more prior therapies expected in 2017. It is also a breakthrough therapy for this indication. Tisagenlecleucel-T is in additional phase II trials for CLL, multiple myeloma (MM) and non-Hodgkin’s lymphoma (NHL). Phase I studies are underway for other cancers, such as mantle-cell lymphoma (MCL).

**Mechanism of Action:** 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:** In ALL and DLBCL, lymphocytes cannot develop properly in the bone marrow. Underdeveloped cells continue to replicate and build up, however, eventually displacing bone marrow, overwhelming normal blood cells and interfering with organ function. Two different types of lymphocytes, B-cells or T-cells, may be affected. According to the ACS, approximately 6,000 new cases of ALL are diagnosed in the U.S. per year. Most often, it is diagnosed among children five years old or younger, with around 60% of newly diagnosed patients younger than 21. The risk for having ALL tapers off during the teens and early twenties; but then increases, again, after the age of about 50. Among ALL patients, up to 85% of children and 80% of adults have B-cell ALL. An estimated 85% of children treated for ALL survive for at least five years, which essentially is considered a cure because pediatric ALL usually does not return after that long. Approximately 25% of adults who have ALL also have an abnormal Philadelphia chromosome (Ph+), which results in lower response rates. Presently, only about 20% of adults survive ALL. The ACS estimates that about 60,000 NHL cases are diagnosed each year in the U.S., with around 90% involving B-cells. About one-half of newly diagnosed DLBCL patients are 60 years old or older. 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 30-50%.

**Cost Estimate:** $300,000+ per treatment

**Current Therapies:** Treatment of ALL is typically treated with induction, consolidation and maintenance therapy that includes chemotherapy, steroids, MTX, targeted therapy, radiation and/or stem cell transplant. 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.

**Pipeline Product(s):** Several other CAR-T products are in development for treating ALL, but most are in early trials phase. After a series of setbacks with other CAR-T inhibitors, Juno is beginning a phase II study of JCAR015 for adult B- ALL patients. Kite Pharma is developing KTE-C19 (axicabtagene ciloleucel), which is in phase III trials for treating ALL, NHL, MCL and other cancers. Other types of phase III drugs in the ALL pipeline include an enzyme, calaspargase pegol (Sigma-Tau Pharmaceuticals), herpes simplex virus thymidine kinase (HSV-tk - MolMed) and inotuzumab ozogamicin, an antineoplastic antibody/calicheamicin conjugate (Pfizer). For DLBCL, Juno’s JCAR017 is in phase II studies and Seattle Genetics has a conjugate of a C-19 inhibitor (denintuzumab mafodotin) with the microtubule disruptor, (monomethyl auristatin F) in phase I trials.
Comments: Interim results from the phase II ELIANA clinical trial were released in December 2016. The study evaluated the efficacy and safety of tisagenlecleucel-T for children and young adult patients who have B-cell ALL that either relapsed after or was refractory to treatment. Among 50 patients from three years old to 23 years old, who were treated in the study, 41 went into complete remission (CR) or remission with incomplete blood count recovery (CRi) within three months of treatment. In the earlier phase IIIa ENSIGN study, 29 patients with refractory or relapsing B-cell ALL were treated with one dose of tisagenlecleucel-T based on their weight. All were between the ages of three and 25. When followed up between two weeks and 14 months after receiving treatment, twenty of the treated patients had achieved CR or CRi, but eight of them had a relapse between about two months to about eight months. The JULIET study is investigating the effectiveness of tisagenlecleucel-T – eventually for approximately 130 adult patients with relapsing or refractory DLBCL. In very preliminary results from the phase II trial, which began in February 2014, five of the 13 DLBCL patients who were treated with tisagenlecleucel-T achieved CR within three months after treatment. By mid-2016, 11 patients were in CR. On March 29, 2017, Novartis announced that the FDA has accepted the company's BLA filing and granted priority review for tisagenlecleucel-T in relapsed and refractory (r/r) pediatric and young adult patients with B-cell ALL. Approval is expected by Sep. 29, 2017.

**velpatasvir/voxilaprevir/sofosbuvir (Gilead)**

**Current Status:** FDA accepted Gilead's NDA for sofosbuvir / velpatasvir / voxilaprevir in December 2016. Approval is expected by August 8, 2017.

**Route of Administration/Dosing:** PO (once tablet, sofosbuvir 400mg/velpatasvir 100mg/voxilaprevir 100mg) once daily for 12 weeks.

**Proposed Indication(s):** Treatment of DAA-experienced chronic hepatitis C patients.

**Mechanism of Action:** Triple-combination therapy that adds a protease inhibitor (voxilaprevir) to its Epclusa® components (velpatasvir: NS5A inhibitor; sofosbuvir: nucleotide analog polymerase inhibitor).

**Patient Impact:** Hepatitis C, a virus that infects the liver, is transmitted through direct contact with infected blood and blood products. The WHO estimates that between 130 million and 150 million people are infected with hepatitis C worldwide. As many as 85% of those acutely infected with hepatitis C will become chronically infected. Approximately 2.7 million to 3.9 million individuals have chronic hepatitis C in the U.S., according to the CDC. Up to 30% of people who have chronic hepatitis C will develop cirrhosis — commonly over 20 years or longer, and up to 25% of cirrhosis patients may progress to liver cancer. Because cirrhosis develops so slowly, however, symptoms do not usually appear until liver damage is severe. Many hepatitis C cases are discovered after routine blood testing during checkups. At least six separate genotypes of hepatitis C virus currently are known, and they have over 50 subtypes. Designated as genotypes 1 through 6, the main types are distributed differently around the world. In the U.S., about 70% of chronic hepatitis C patients have type 1, which is the most common. Around 55% of them have type 1a and around 35% have 1b. Genotype 2 accounts for approximately 15% to 20% of American patients, type 3 for about 12% and types 4 through 6 for 1% or less, each.

**Cost Estimate:** Approximately $75,000 for the treatment course.

**Current Therapies:** Gilead’s Epclusa® (sofosbuvir/velpatasvir) is a DAA that was approved Jun. 28, 2016, for adults with genotypes 1 through 6 chronic HCV infections. It is taken once daily for 12 weeks. Other DAA include: Harvoni® (sofosbuvir/ledipasvir – Gilead), Zepatier® (elbasvir/grazoprevir - Merck), Technivie™ (ombitasvir/paritaprevir/ritonavir - AbbVie), Viekira Pak® (ombitasvir/paritaprevir/ritonavir with dasabuvir - AbbVie), Viekira XR™ (ombitasvir/paritaprevir/ritonavir with dasabuvir – AbbVie), Daklinza™ (daclatasvir – Bristol-Myers Squibb), Olysio® (simeprevir - Janssen), and Sovaldi® (sofosbuvir – Gilead).

**Pipeline Product(s):** AbbVie submitted its NDA for a fixed combination of two new protease inhibitors, glecaprevir and pibrentasvir, on December 19, 2016. Under priority review, its FDA-action date is Aug. 19, 2017. It also is an oral, once daily DAA that treats all genotypes in as little as eight weeks for treatment-naïve, non-cirrhotic patients. Gilead’s Epclusa® (sofosbuvir/velpatasvir), which was approved Jun. 28, 2016, for adults with genotypes 1 through 6 chronic HCV infections. It is taken once daily for 12 weeks.

**Comments:** The NDA for SOF/VEL/VOX is based on data from two Phase III studies (POLARIS-1 and POLARIS-4), which evaluated 12 weeks of the fixed-dose combination in DAA-experienced patients with hepatitis C genotypes 1-6, including those who failed prior treatment with an NS5A-containing regimen. Of the 445 patients treated with SOF/VEL/VOX, 430 (97%) achieved the primary efficacy endpoint of SVR12.
voretigene neparvovec (SPK-RPE65 - Spark Therapeutics)

**Current Status:** Orphan drug. Breakthrough therapy. Phase III. Rolling submission of the BLA has been initiated. Approval expected in 2018.

**Route of Administration/Dosing:** Intraocular injection (single injection).

**Proposed Indication(s):** Treat an inherited retinal disease caused by non-sex-linked or autosomal recessive, mutations in the RPE65 gene.

**Mechanism of Action:** Adeno-associated virus (AAV) capsid is used to deliver a functional copy of the RPE65 gene to the retina for treating blindness caused by RPE65 mutations.

**Patient Impact:** Patients suffering from RPE65-mediated inherited retinal disease are affected by a range of severe visual impairments, notably night blindness, or nyctopia, that make independent activities of daily living challenging and ultimately lead to blindness. For example, affected children often depend on visual aids to carry out classroom activities while adults with these diseases may face diminished employment opportunities and may be stripped of some of the rewards of parenting, such as watching a child play his or her favorite sport. The company estimates that there are approximately 3,500 individuals with RPE65-mediated inherited retinal disease in the U.S., France, Germany, Italy, Spain and the U.K.

**Cost Estimate:** $1 to $1.5 million (gene therapy: single dose/eye).

**Comments:** Spark Therapeutics gene therapy, voretigene neparvovec, has been granted breakthrough status by FDA for the treatment of inherited blindness caused by mutations of the RPE65 gene. In October 2015, Spark announced positive top-line results from our pivotal Phase III clinical trial of voretigene neparvovec, the first successfully completed randomized controlled Phase III trial of a gene therapy for genetic disease in the U.S. The trial of 31 subjects met with statistical significance its primary endpoint, the bilateral mobility test change score (p = 0.001), as well as the first two of three secondary endpoints, specifically full-field light sensitivity threshold testing, or FST, (p<0.001) and the assigned first eye mobility test change score (p = 0.001). Statistical significance was not achieved for the third secondary endpoint, visual acuity (p = 0.17). In April 2016, the company submitted the non-clinical modules of the BLA to FDA which are the first components of a rolling BLA submission. The company anticipates that additional modules of the BLA will occur in early 2017. The Phase III trial demonstrated a statistically significant restoration of vision in subjects that were progressing toward complete blindness. On average, subjects that received voretigene neparvovec demonstrated an improvement of 1.9 light levels one year post-administration. Specifically, nearly two-thirds of the subjects in the intervention group achieved the maximum improvement measurable on the mobility test. Similarly, on average, intervention group subjects achieved a 100-fold improvement in light sensitivity as measured by FST. In August 2016, the company announced positive one-year follow-up data from the Phase III trial on the nine control subjects that crossed over after one year and received voretigene neparvovec. Eight of the nine subjects improved as measured by the bilateral mobility test, with all eight responders achieving the maximum improvement measurable. The average improvement among all nine subjects was 2.1 light levels. As measured by FST, eight of the nine crossover subjects improved, with the average improvement of all nine subjects being nearly 200-fold. Spark is on track to complete voretigene neparvovec's BLA submission in 2017.