Promising New Agents

**Drug Name: Binimetinib/encorafenib**
Manufacturer: Array BioPharma
Indication: BRAF-mutant melanoma
Formulation: Oral tablet/capsule

Binimetinib, a MEK inhibitor, and encorafenib, a BRAF inhibitor, affect key protein kinases in the cellular signaling pathway. The combination is being investigated for the treatment of BRAF-mutant advanced, unresectable, or metastatic melanoma.

The two-part, randomized, open-label Phase III COLUMBUS trial (N=921) compared binimetinib plus encorafenib to monotherapy with vemurafenib or encorafenib. In Part 1 (N=577), the median progression-free survival (mPFS) was 14.9 months in patients treated with binimetinib 45 mg twice daily plus encorafenib 450 mg once daily compared to 7.3 months in patients treated with vemurafenib 960 mg twice daily (hazard ratio [HR] 0.54, 95 percent CI 0.41 to 0.71, P<0.001) and 9.6 months in patients treated with encorafenib 300 mg once daily (HR 0.75, 95 percent CI 0.56 to 1.00, P=0.051). In Part 2 (N=344), the mPFS was 12.9 months in patients treated with binimetinib 45 mg twice daily plus encorafenib 300 mg once daily compared to 9.2 months in patients treated with encorafenib 300 mg once daily (HR 0.77, 95 percent CI 0.61 to 0.97).

If approved, binimetinib plus encorafenib may provide an effective treatment option for BRAF-mutant advanced, unresectable, or metastatic melanoma. These agents are also being investigated in Phase II trials for the treatment of relapsed or refractory multiple myeloma and BRAF V600E-mutant colorectal cancer. New Drug Applications (NDAs) for binimetinib and encorafenib have been accepted for review by the Food and Drug Administration (FDA) and a decision is expected by June 30, 2018.

**Drug Name: Erenumab**
Manufacturer: Amgen
Indication: Prevention of migraine
Formulation: Subcutaneous injection

Erenumab is a monoclonal antibody targeting the calcitonin gene-related peptide (CGRP) receptor. Erenumab is being studied for the prevention of migraine in patients with at least four migraine days per month.

The Phase III STRIVE (N=955) and ARISE (N=577) trials evaluated the safety and efficacy of once-monthly treatment with erenumab compared to placebo in adult patients with a minimum of a one-year history of episodic migraines. In STRIVE, patients in the erenumab 70 mg and 140 mg groups experienced 3.2-day and 3.7-day reductions in monthly migraine days (MMDs), respectively, from baseline to weeks 13 to 24 compared to a 1.8-day reduction in the placebo group (P<0.001 for both). In addition, 43.3 percent of patients in the 70 mg group and 50.0 percent of patients in the 140 mg group experienced a 50 percent or greater reduction in MMDs compared to 27 percent of patients in the placebo group (odds ratio [OR] 2.13 and 2.81, respectively). In ARISE, patients in the erenumab 70 mg group experienced a 2.9-day reduction in MMDs compared to a 1.8-day reduction in the placebo group (P<0.001). In both trials, the frequency of adverse events was similar between all treatment groups.

If approved, erenumab would be the first monoclonal antibody targeting the CGRP receptor and may offer a treatment alternative for the prevention of migraines. The Biologics License Application (BLA) for erenumab has been accepted for review by the FDA and a decision is expected by May 17, 2018.
Promising New Agents

**Drug Name: Lanadelumab**  
**Manufacturer:** Shire  
**Indication:** Hereditary angioedema  
**Formulation:** Subcutaneous injection

Lanadelumab is being investigated for the long-term prophylaxis of angioedema attacks in patients with hereditary angioedema (HAE). Lanadelumab is a long-acting, fully-human monoclonal antibody that binds to plasma kallikrein.

The efficacy and safety of lanadelumab was evaluated in the Phase III HELP™ study (N=125). Patients ages 12 years and older with type I and II HAE were randomized to one of three lanadelumab regimens (300 mg every two weeks, 300 mg every four weeks, or 150 mg every four weeks) or placebo. The primary efficacy endpoint, the number of investigator-confirmed angioedema attacks during the 26-week treatment period, was reduced by 87 percent in the 300 mg every two weeks group, 73 percent in the 300 mg every four weeks group, and 76 percent in the 150 mg every four weeks group compared to placebo (P<0.001). Results were found to be similar regardless of baseline attack frequency. Lanadelumab was generally well-tolerated with the most commonly-reported adverse event being injection site pain. The HELP™ Study Extension is ongoing to evaluate long-term safety.

If approved, lanadelumab may provide an advantage over currently-available long-term HAE prophylactic medications due to less frequent dosing and convenience of administration. A BLA for lanadelumab is anticipated by late 2017 or early 2018. The FDA has granted lanadelumab the Orphan Drug and Breakthrough Therapy designations.

**Drug Name: Lasmiditan**  
**Manufacturer:** Eli Lilly  
**Indication:** Migraine  
**Formulation:** Oral tablet

Lasmiditan is a first-in-class serotonin (5HT) receptor targeting receptors in the trigeminal pathway. It is being investigated for the acute treatment of migraine.

In the randomized, double-blind, placebo-controlled Phase III SPARTAN trial (N=3,007), the safety and efficacy of three lasmiditan doses were compared to placebo for the acute treatment of migraine. At two hours post-first dose, the percentage of patients who were migraine pain-free was greater in the lasmiditan 50 mg, 100 mg, and 200 mg groups compared to the placebo group (28.6 percent, P=0.003; 31.4 percent, P<0.001; 38.8 percent, P<0.001; and 21.3 percent, respectively). More patients treated with lasmiditan 50 mg, 100 mg, and 200 mg were also free of their migraine-associated most bothersome symptom at two hours post-first dose compared to patients treated with placebo (40.8 percent, P=0.009; 44.2 percent, P<0.001; 48.7 percent, P<0.001; and 33.5 percent, respectively). These findings were consistent with the previous Phase III trial, SAMURAI (N=2,232), which compared two doses of lasmiditan (100 mg and 200 mg) to placebo. The ongoing, open-label Phase III GLADIATOR study will evaluate the long-term safety of lasmiditan.

If approved, lasmiditan may provide a therapeutic alternative for the treatment of migraine without the vasoconstrictor activity associated with SHT1B/1D receptor agonists, such as triptans. An NDA submission for lasmiditan is anticipated in the second half of 2018.

**Drug Name: Omadacycline**  
**Manufacturer:** Paratek  
**Indication:** ABSSSI, CABP  
**Formulation:** Oral, intravenous

Omadacycline is a first-in-class aminomethylcyclocline with broad-spectrum activity against gram-positive, gram-negative, and atypical bacteria. It is being studied for the treatment of acute bacterial skin and skin structure infection (ABSSSI) and community-acquired bacterial pneumonia (CABP).

In the Phase III OPTIC trial (N=774), adults with CABP were randomized to omadacycline or moxifloxacin for 7 to 14 days. Clinically stable patients in both treatment arms transitioned to omadacycline 300 mg or moxifloxacin 400 mg orally once daily after a minimum of three days of intravenous therapy. The primary endpoint of non-inferiority to moxifloxacin at the early clinical response (ECR) was defined as an improvement in ≥2 of 4 symptoms at 72 to 120 hours. Treatment with omadacycline was non-inferior to moxifloxacin, with 81.1 and 82.7 percent of patients, respectively, achieving an ECR (treatment difference -1.6, 95 percent CI -7.1 to 3.8). In the Phase III OASIS-1 (N=645) and OASIS-2 (N=735) trials of adults with ABSSSI, treatment with omadacycline was non-inferior to linezolid at the ECR, defined as ≥20 percent reduction in lesion size at 48 to 72 hours post-first dose.

Omadacycline received the Qualified Infectious Disease Product and Fast Track designations from the FDA and may offer a treatment option for patients with ABSSSI or CABP who are not candidates for standard antibiotic therapy. Omadacycline is also being studied for the treatment of uncomplicated urinary tract infection. NDA submissions are anticipated in early 2018.
Promising New Agents

**Drug Name: Ozanimod**  
**Manufacturer:** Celgene  
**Indication:** Relapsing MS  
**Formulation:** Oral capsule  

Ozanimod is an oral, selective sphingosine 1-phosphate receptor (S1PR) 1 and 5 modulator currently being investigated for the treatment of relapsing multiple sclerosis (RMS).

The randomized, double-blind Phase III SUNBEAM™ (N=1,346) and RADIANCE™ Part B (N=1,320) trials compared ozanimod (1 mg and 0.5 mg) with placebo and ozanimod 1 mg and 0.5 mg achieved a greater reduction in annualized relapse rate (ARR) compared to patients receiving IFN beta-1a (ARR=0.17, P<0.0001; ARR=0.22, P=0.0167; and ARR=0.28, respectively). In a pre-specified pooled analysis of both trials, the Phase III APOLLO trial (N=225) compared ozanimod 1 mg and 0.5 mg achieved a greater reduction in ARR compared to patients receiving IFN beta-1a (ARR=0.17, P<0.0001; ARR=0.22, P=0.0167; and ARR=0.28, respectively). In RADIANCE™ Part B, patients receiving ozanimod 1 mg and 0.5 mg achieved a greater reduction in ARR compared to patients receiving IFN beta-1a (ARR=0.17, P<0.0001; ARR=0.22, P=0.0167; and ARR=0.28, respectively). If approved, ozanimod may provide an effective oral treatment option for RMS with a more favorable side effect profile than the currently available non-selective S1PR modulator. An NDA submission is anticipated by the end of 2017.

**Drug Name: Patisiran**  
**Manufacturer:** Alnylam  
**Indication:** hATTR amyloidosis  
**Formulation:** Intravenous infusion  

Patisiran, a small interfering ribonucleic acid (siRNA), targets a specific sequence of messenger RNA (mRNA) to reduce serum levels of transthyretin (TTR) protein. Patisiran is currently being studied for the treatment of hereditary amyloidogenic TTR (hATTR) amyloidosis.

The Phase III APOLLO trial (N=225) compared patisiran to placebo in adults with hATTR amyloidosis and polyneuropathy. The primary endpoint was the between-group difference in mean change in modified Neuropathy Impairment Score (mNIS+7) from baseline at 18 months. Patients receiving patisiran achieved a mean 6.0-point reduction (improvement) in mNIS+7 score from baseline at 18 months compared to a mean 28.0-point increase (worsening) with placebo (mean difference 34.0 points, P=9.26 x 10^-10). Peripheral edema and infusion-related reactions occurred more frequently in the patisiran group than in the placebo group.

If approved, patisiran will be the first RNA interference (RNAi) therapeutic, a new class of medications, and the first FDA-approved agent for the treatment of hATTR amyloidosis. The FDA has granted patisiran the Orphan Drug and Fast Track designations. A rolling NDA submission was initiated in November 2017.

**Drug Name: Tezacaftor/ivacaftor**  
**Manufacturer:** Vertex  
**Indication:** Cystic fibrosis  
**Formulation:** Oral tablet  

Tezacaftor/ivacaftor is a combination product that includes an FDA-approved cystic fibrosis (CF) transmembrane conductance regulator (CFTR) potentiator, ivacaftor, and an investigational CFTR corrector, tezacaftor. Tezacaftor/ivacaftor is being studied for the treatment of patients ages 12 and older with CF and two copies of the F508del mutation or one copy of the F508del mutation and one residual function mutation.

The Phase III EVOLVE trial (N=477) compared tezacaftor 100 mg once daily in combination with ivacaftor 150 mg twice daily to placebo in patients with two copies of the F508del mutation. Treatment with tezacaftor/ivacaftor resulted in a mean absolute improvement of 6.2 percentage points in absolute improvement in percent predicted forced expiratory volume in one second (ppFEV₁) of 4.0 percentage points from baseline to 24 weeks compared to placebo (P=0.0001). The Phase III EXPAND trial (N=235) evaluated tezacaftor/ivacaftor and ivacaftor monotherapy in patients with one copy of the F508del mutation and one residual function mutation. Treatment with tezacaftor/ivacaftor resulted in mean absolute improvements of 6.8 and 2.1 percentage points in ppFEV₁, compared to placebo and ivacaftor monotherapy, respectively, from baseline to the average of the week four and eight measurements (P<0.0001).

If approved, tezacaftor/ivacaftor may provide a more effective option for patients with specific combinations of F508del mutations. Tezacaftor/ivacaftor was granted the Breakthrough Therapy designation and Priority Review status by the FDA, with a decision expected by Feb. 28, 2018.
**Projected Generic Entry**

- **Treximet®** (sumatriptan/naproxen) 2/2018
- **Factive®** (gemifloxacin tablet) 3/2018
- **Sensipar®** (cinacalcet tablet) 3/2018
- **Enbrel®** (etanercept) 4/2018
- **Lexiva®** (fosamprenavir tablet) 6/2018
- **Remodulin®** (treprostinil injection) 6/2018
- **Amaryllis** (dalfampridine extended-release tablet) 7/2018
- **Aloxi®** (palonosetron injection) 9/2018
- **Cialis®** (tadalafil) 9/2018
- **Staxyn®** (vardenafil orally disintegrating tablet) 10/2018
- **Vesicare®** (solifenacin succinate) 10/2018
- **Lyrica®** (pregabalin) 12/2018
- **Rapaflo®** (silodosin) 12/2018

*Dates are estimates, current as of 12/1/17, and are subject to change due to any patent litigation or additional patents.

**FDA Updates**

**Baricitinib**

On April 14, 2017, Eli Lilly and Company and Incyte Corporation announced that the FDA issued a complete response letter (CRL) regarding the NDA for baricitinib, a Janus kinase (JAK) inhibitor being studied for the treatment of moderate-to-severe rheumatoid arthritis. The FDA requested additional data to determine the most appropriate doses and to characterize the risk-benefit profile given the thromboembolic events that occurred in clinical trials. The manufacturers announced in August 2017 that a new clinical trial would not be necessary. The NDA resubmission, which will include new safety and efficacy data, is planned for January 2018.

**Dextenza™ (dexamethasone insert)**

On July 11, 2017, Ocular Therapeutix™, Inc. announced that the FDA issued a second CRL for Dextenza™ (dexamethasone insert) for the intracanalicular treatment of ocular pain due to ophthalmic surgery. The CRL cited deficiencies in manufacturing and analytical testing. Citations from an FDA reinspection in May 2017 prompted the company to submit an amendment in July 2017; however, the FDA did not review this information prior to issuing the CRL. The CRL indicated that resolution of the deficiencies is required before approval, but applicable sections of the amendment may be included in future submissions.

**Evenity™ (romosozumab)**

On July 16, 2017, Amgen and UCB announced that the FDA issued a CRL declining approval of Evenity™ (romosozumab), a subcutaneously-administered, bone-forming monoclonal antibody targeting sclerostin that is being investigated for the treatment of postmenopausal women with osteoporosis. Although no increased CV risk was observed in the FRAME clinical trial data that was included in the BLA, the FDA has requested data from the subsequent BRIDGE and ARCH trials after increased CV risk was observed in the ARCH trial. The manufacturers are pooling the requested data and plan to resubmit the BLA as an extension of the current review.

**Ilaris® (canakinumab)**

The Phase III CANTOS trial (N=10,061) compared canakinumab 300 mg, 150 mg, and 50 mg every three months to placebo in adults with a previous myocardial infarction (MI) and elevated high-sensitivity C-reactive protein. The incidence rate of nonfatal stroke, nonfatal MI, or cardiovascular (CV) death per 100-person years was 3.90, 3.86, and 4.11 for the canakinumab 300 mg, 150 mg, and 50 mg groups, respectively, compared to 4.50 for the placebo group (P=0.031, P=0.021, and P=0.30, respectively). The incidence of CV death was not significantly lower for any of the canakinumab groups compared to placebo. A supplemental BLA submission is expected by the end of 2017.

**Ocaliva® (obeticholic acid)**

The Phase IIb FLINT trial (N=283) compared treatment with obeticholic acid (OCA) 25 mg daily to placebo for 72 weeks in patients with non-cirrhotic, non-alcoholic steatohepatitis (NASH). A greater proportion of patients treated with OCA achieved improved liver histology compared to the placebo group (45 versus 21 percent, P=0.0002). A retrospective analysis of the FLINT study found that 57 percent of patients with type 2 diabetes who were treated with OCA achieved improved liver histology (P<0.01). The Phase III pivotal REGENERATE trial is currently ongoing.
## Additional Promising New Agents

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### Table Abbreviations:
- ADHD: attention-deficit hyperactivity disorder
- BLA: Biologics License Application
- HIV: human immunodeficiency virus
- IV: intravenous
- LGS: Lennox-Gastaut syndrome
- NDA: New Drug Application
- PDUFA: Prescription Drug User Fee Act
- PKU: phenylketonuria
- SC: subcutaneous

Note: All agents are administered orally unless otherwise indicated.
*Designates specialty drug.

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**Acknowledgements**
Ashley Thrasher, PharmD Candidate
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