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Pipeline Trends - December 2017

Nicole M. Trask
University of Massachusetts Medical School

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For the prophylaxis of major adverse cardiovascular events

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Promising New Agents

NDA

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.

BLA

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

Phase III

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.

Phase III

Drug Name: Lasmiditan

Manufacturer: Eli Lilly
 Indication: Migraine
 Formulation: Oral tablet

Lasmiditan is a first-in-class serotonin (5HT)_{1F} agonist 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 5HT_{1B/1D} receptor agonists, such as triptans. An NDA submission for lasmiditan is anticipated in the second half of 2018.

Phase III

Drug Name: Omadacycline

Manufacturer: Paratek
 Indication: ABSSSI, CABP
 Formulation: Oral, intravenous

Omadacycline is a first-in-class aminomethylcycline 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

Phase III

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)

orally once daily to Avonex® (interferon [IFN] beta-1a) intramuscularly once weekly for the treatment of RMS. In SUNBEAM™, patients receiving ozanimod 1 mg and 0.5 mg achieved a greater reduction in annualized relapse rate (ARR) compared to patients receiving IFN beta-1a (ARR=0.18, P<0.0001; ARR=0.24, P=0.0013; and ARR=0.35, 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). In a pre-specified pooled analysis of both trials,

treatment with ozanimod did not achieve statistical significance in the time to three-month confirmed disability progression. Both trials reported no episodes of second or third degree atrioventricular block, similar infection rates between groups, and that most alanine aminotransferase increases that occurred were self-limiting.

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.

NDA

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 10⁻²⁴). Patients receiving patisiran achieved a mean 6.7-point reduction (improvement) in Norfolk-Quality of Life-Diabetic Neuropathy score from baseline at 18 months compared to a mean 14.4-point

increase (worsening) with placebo (mean difference 21.1 points, P=1.10 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.

NDA

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 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
- **Acanya® (benzoyl peroxide/
clindamycin phosphate 2.5%/1.2%)** 7/2018
- **Ampyra® (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
- **Finacea® (azelaic acid gel)** 11/2018
- **Fortesta® (testosterone gel)** 11/2018
- **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.

Investigational Indications

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.



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.

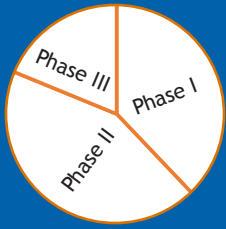
Evenity™ (romosozumab)

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.



Industry Trends

Agents in Clinical Development



Phase I: 37.9%
Phase II: 43.3%
Phase III: 18.8%

Leading Indications with Agents in Late-Stage Development

1. Breast cancer
2. Non-small cell lung cancer
3. Colorectal cancer
4. Pancreatic cancer
5. Type 2 diabetes mellitus
6. Ovarian cancer
7. Alzheimer's disease
8. Rheumatoid arthritis
9. Prostate cancer
10. Brain cancer

Production Staff

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Clinical Consultant Pharmacist
Clinical Pharmacy Services

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Stephanie Tran, PharmD
Clinical Consultant Pharmacists
Clinical Pharmacy Services

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Additional Promising New Agents

Drug Name	Manufacturer	Indication	Product Timeline
Luxturna™ (voretigene neparvovec) (subretinal)*	Spark Therapeutics	RPE65-mediated inherited retinal dystrophy	PDUFA date 1/12/2018
Lutathera® (lutetium Lu 177 dotatate) (IV)*	Advanced Accelerator Applications	Neuroendocrine tumors	PDUFA date 1/27/2018
AndexXa® (andexanet alfa) (IV)	Portola Pharmaceuticals	Factor Xa inhibitor antidote	PDUFA date 2/2/2018
Bictegravir/emtricitabine/tenofovir alafenamide	Gilead Sciences	HIV-1	PDUFA date 2/12/2018
Makena® auto-injector (hydroxyprogesterone caproate) (SC)	AMAG Pharmaceuticals	Prevention of preterm birth	PDUFA date 2/14/2018
Netarsudil (ophthalmic)	Aerie Pharmaceuticals	Glaucoma, ocular hypertension	PDUFA date 2/28/2018
Ibalizumab (IV)*	Theratechnologies	Multidrug-resistant HIV-1	PDUFA date 4/3/2018
Burosumab (SC)*	Ultragenyx, Kyowa Hakko Kirin	X-linked hypophosphatemia	PDUFA date 4/17/2018
Pegvaliase (SC)*	BioMarin Pharmaceuticals	PKU	PDUFA date 6/29/2018
Volanesorsen (SC)*	Akcea Therapeutics	Familial chylomicronemia syndrome	PDUFA date 8/30/2018
BAY94-9027 (IV)*	Bayer	Hemophilia A	BLA accepted 10/2017
Fremanezumab (SC)*	Teva Pharmaceuticals	Migraine prevention	BLA submitted 10/2017
Elagolix	AbbVie	Endometriosis	NDA accepted 10/2017
Dasotraline	Sunovion Pharmaceuticals	ADHD	NDA accepted 11/2017
Epidiolex® (cannabidiol)*	GW Pharmaceuticals	LGS, Dravet syndrome	NDA submitted 10/2017
Olinvo™ (oliceridine) (IV)	Trevena	Moderate-to-severe acute pain	NDA submitted 11/2017

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.



Who We Are and What We Do



The University of Massachusetts Medical School's Clinical Pharmacy Services is a national leader in clinical pharmacy support. Established in 1999 to provide drug utilization review services for the Massachusetts Medicaid program, Clinical Pharmacy Services now provides clinical and operational support, consulting and service delivery in a broad range of areas such as evidence-based pharmaceutical care management, medication therapy management, patient-centered medical homes, pharmacy analytics, pharmaco-economic analysis, and patient/prescriber outreach. We have assembled a team with exceptional depth and experience in multiple fields. Our clients include state Medicaid agencies, pharmacy benefit managers and managed care plans. PIPELINE TRxENDS is produced annually to provide our clients with critical information about drugs in development.



University of Massachusetts Medical School
Clinical Pharmacy Services

UMass Medical School
333 South Street
Shrewsbury, MA 01545

Contact:

Timothy Cummins, MBA, RPh
Executive Director

Clinical Pharmacy Services

Tel: 774-455-3440

Fax: 877-208-7428

Website: commed.umassmed.edu/cps

Email: Timothy.Cummins@umassmed.edu