4-15-2016

Pipeline Trends April 2016

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April 2016

University of Massachusetts Medical School

PIPELINE TRENDS

PIPELINE TRENDS is produced by the University of Massachusetts Medical School's Clinical Pharmacy Services division and distributed to our clients annually.

In This Issue

Promising New Agents

Pimavanserin
FDA decision expected May 1, 2016

Sarilumab
FDA decision expected Oct. 30, 2016

Projected Generic Entry

Crestor®
ProAir®
Seroquel XR®
Strattera®

Investigational Indications

Afatinib
For the treatment of squamous cell carcinoma of the lung

Ustekinumab
For the treatment of Crohn's disease

FDA Updates

Drisapersen
Manufacturer received complete response letter

Nivolumab
Manufacturer received complete response letter

Rociletinib
FDA decision expected June 28, 2016

Promising New Agents

Drug Name: Atezolizumab

BLA

Manufacturer: Genentech
Indication: mUC
Formulation: Intravenous infusion

Atezolizumab is a monoclonal antibody that inhibits the programmed death ligand-1 (PD-L1), resulting in the activation of thymus (T)-cells against tumor cells. Atezolizumab is currently being investigated for the treatment of patients with locally advanced or metastatic urothelial carcinoma (mUC) whose disease progressed during or after standard treatments.

In the open-label, single-arm Phase II IMvigor 210 trial (N=310), patients with locally advanced or mUC, with or without PD-L1 expression, and whose disease progressed during or after previous treatment with a platinum-based regimen, received atezolizumab 1,200 mg intravenous (IV) once every three weeks until loss of clinical benefit. After a median follow-up of 11.7 months, the median overall survival (OS) was 11.4 months in patients with higher PD-L1 expression (95 percent CI 9.0 to not estimable) and 7.9 months in the overall study population (95 percent CI 6.6 to 9.3). Additionally, 15 percent of patients in the overall study group and 26 percent of patients with medium or high PD-L1 expression achieved a reduction in tumor burden (95 percent CI 11 to 19 and 95 percent CI 18 to 36, respectively). The median duration of response was not reached, with 84 percent of patients experiencing an ongoing response at follow-up.

If approved, atezolizumab may offer a novel approach to the treatment of locally advanced or mUC. This agent is also being evaluated for use in kidney, breast, and lung cancer. Atezolizumab was granted Priority Review status with a Prescription Drug User Fee Act (PDUFA) date of Sep. 12, 2016.

Drug Name: Ocrelizumab

Phase III

Manufacturer: Genentech
Indication: RRMS and PPMS
Formulation: Intravenous infusion

Ocrelizumab is an investigational, humanized monoclonal antibody designed to selectively target CD20-positive B cells, which are key contributors to myelin and axonal damage in patients with multiple sclerosis. Ocrelizumab is being studied for the treatment of relapsing-remitting multiple sclerosis (RRMS) and primary progressive multiple sclerosis (PPMS).

Ocrelizumab was evaluated in three Phase III randomized, double-blind studies, including OPERA I and OPERA II in RRMS, and ORATORIO in PPMS. In OPERA I and OPERA II (N=1,656), treatment with ocrelizumab resulted in 46 and 47 percent reductions in annualized relapse rate, respectively, compared to treatment with Rebif® (interferon B-1a) over two years (P<0.0001 for both). In ORATORIO (N=732), treatment with ocrelizumab reduced the risk of clinical disability progression by 24 percent, sustained for at least 12 weeks, as measured by the Expanded Disability Status Scale, compared to placebo over two years (P=0.0321). Treatment with ocrelizumab also resulted in a statistically significant reduction in the risk of clinical disability progression by 25 percent for at least 24 weeks, time to walk 25 feet by 29 percent, volume of hyperintense T2 lesions by 3.4 percent, and rate of whole brain volume loss by 17.5 percent compared to placebo over 120 weeks.

If approved, ocrelizumab may offer the first treatment option for PPMS and an additional treatment option for RRMS. A Biologics License Application (BLA) submission is planned for 2016.

Non-Specialty Specialty

Promising New Agents

NDA

Drug Name: Pimavanserin
Manufacturer: Acadia
Indication: PDP
Formulation: Oral tablet

Nuplazid™ (pimavanserin), a selective 5-HT_{2A} inverse agonist, is being investigated for the treatment of Parkinson's disease psychosis (PDP).

The Phase III -020 Study (N=185) investigated treatment with pimavanserin 40 mg daily compared to placebo. Pimavanserin recipients experienced a greater decrease in Parkinson's disease-adapted Scale for Assessment of Positive Symptoms Scores compared to placebo (-5.79 and -2.73, respectively, 95 percent CI -4.91 to -1.20, P=0.001). A greater improvement in psychosis from baseline was reported with pimavanserin compared to placebo (37 versus 14 percent, respectively, P=0.0006). Treatment with pimavanserin resulted in greater improvements in the Clinical Global Impression-Severity and Improvement scores compared to placebo (-0.58 and -0.67, P=0.0007 and P=0.0011, respectively). In addition, caregivers of subjects in the pimavanserin group reported a significant improvement in sleep and daytime wakefulness compared to placebo.

If approved, pimavanserin may provide the first Food and Drug Administration (FDA)-approved treatment option for PDP. On March 29, 2016, an FDA Advisory Committee voted 12 to 2 that the benefits of treatment with pimavanserin outweighed the risks; however, they did not formally make a recommendation for or against approval. Pimavanserin was granted the Breakthrough Therapy designation and Priority Review status with a PDUFA date of May 1, 2016.

NDA

Drug Name: Plecanatide
Manufacturer: Synergy
Indication: CIC
Formulation: Oral tablet

Plecanatide is a uroguanylin analog that stimulates guanylate cyclase-c, thereby increasing fluid movement. This agent is being studied for the treatment of chronic idiopathic constipation (CIC) and irritable bowel syndrome with constipation.

The safety and efficacy of plecanatide were evaluated in two Phase III clinical trials (N=2,683) which compared plecanatide 3 mg or 6 mg to placebo for the treatment of CIC. The primary and secondary endpoints for both studies were durable overall response and stool consistency.

In the first study, the primary endpoint of durable overall response was achieved by 21.0 and 19.5 percent of plecanatide 3 mg and 6 mg recipients, respectively, compared to 10.2 percent with placebo (P<0.001 for both). The average increases in Bristol Stool Form Scale (BSFS) scores were 1.53 and 1.52 for the plecanatide 3 mg and 6 mg recipients, respectively, compared to 0.77 with placebo (P<0.001 for both).

In the second study, durable overall response was achieved by 20.1 and 20.0 percent of plecanatide 3 mg and 6 mg recipients, respectively, compared to 12.8 percent with placebo (P=0.004 for both). The average increases in BSFS were 1.49 and 1.50 for the plecanatide 3 mg and 6 mg recipients, respectively, compared to 0.87 with placebo (P<0.001 for both).

If approved, this agent may provide an additional treatment option for CIC with an improved tolerability profile compared to other available agents. An NDA was submitted in January 2016.

Phase III

Drug Name: Romosozumab
Manufacturer: Amgen and UCB
Indication: Osteoporosis
Formulation: Subcutaneous injection

Romosozumab is a monoclonal antibody that is being studied for the treatment of osteoporosis. Romosozumab inhibits sclerostin, thereby increasing bone formation and decreasing bone breakdown.

The randomized, open-label Phase III STRUCTURE trial (N=436) compared the safety and efficacy of romosozumab to Forteo® (teriparatide) in postmenopausal women who were previously treated with bisphosphonates. Monthly treatment with romosozumab 210 mg resulted in a greater average change in hip bone mineral density over 12 months compared to daily Forteo® (teriparatide) 20 mcg injections. The incidence of adverse events was similar between groups, with the most common adverse events in the romosozumab group being nasopharyngitis, arthralgia, back pain, headache, and falls.

The randomized, double-blind, parallel-group Phase III FRAME study (N=7,180) evaluated treatment with romosozumab for reducing the risk of new vertebral fractures in postmenopausal women with osteoporosis over 12 and 24 months compared to placebo, followed by open-label treatment with Prolia® (denosumab) in both groups. Monthly treatment with romosozumab resulted in a statistically significant 73 percent reduction in relative risk for vertebral fracture through 12 months compared to placebo, and the effect was sustained through 24 months during the open-label Prolia® (denosumab) phase (75 percent reduction).

If approved, romosozumab could provide a novel monthly treatment option for women at high risk of fractures. A BLA submission is planned for 2016.

Promising New Agents

BLA

Drug Name: Sarilumab
Manufacturer: Regeneron and Sanofi
Indication: Moderate-to-severe RA
Formulation: Subcutaneous injection

Sarilumab is a fully human monoclonal antibody that works by inhibiting the interleukin-6 receptor. It is currently being studied for the treatment of moderate-to-severe rheumatoid arthritis (RA).

The Phase III SARIL-RA-TARGET trial (N=546) compared treatment with sarilumab 200 mg or 150 mg every two weeks to placebo, in combination with conventional disease-modifying anti-rheumatic drug therapy, in patients who had an inadequate response or intolerance to tumor necrosis factor (TNF)-α inhibitors. Both sarilumab groups experienced improvement in physical function, as measured by mean change from baseline in Health Assessment Questionnaire-Disability Index at week 12 (P=0.0004 and P=0.0007, respectively) and signs and symptoms of RA, as measured by the proportion of patients achieving a 20 percent improvement in the American College of Rheumatology score at week 24 compared to placebo (P<0.0001 for both).

The Phase III SARIL-RA-MONARCH trial (N=369), which compared sarilumab 200 mg every two weeks to adalimumab 40 mg every two weeks, found that treatment with sarilumab was associated with a significant improvement in Disease Activity Score 28-Erythrocyte Sedimentation Rate at 24 weeks compared to adalimumab (-3.25 versus -2.22, respectively, P<0.0001).

Sarilumab may offer another treatment option for patients who had an inadequate response to TNF-α inhibitors, a current standard-of-care therapy. An FDA decision is expected by Oct. 30, 2016.

NDA

Drug Name: Sofosbuvir/velpatasvir
Manufacturer: Gilead Sciences
Indication: HCV infection
Formulation: Oral tablet

Sofosbuvir/velpatasvir is a fixed-dose combination of Sovaldi® (sofosbuvir), a nucleotide analog nonstructural protein 5B (NS5B) polymerase inhibitor, and velpatasvir, an investigational pan-genotypic nonstructural protein 5A (NS5A) inhibitor. This agent is currently being studied for the treatment of genotype 1 through 6 chronic hepatitis C virus (HCV) infection.

The randomized, double-blind Phase III ASTRAL-1 study (N=624) compared sofosbuvir 400 mg/velpatasvir 100 mg once daily for 12 weeks to placebo in patients with HCV genotypes 1a, 1b, 2, 4, 5, or 6. The prevalence of these genotypes among patients receiving active treatment was 34, 19, 17, 19, 6, and 7 percent, respectively.

Of the active treatment recipients (N=624), 68 percent were treatment-naïve and 19 percent had compensated cirrhosis. Sustained virologic response at 12 weeks post-treatment (SVR12) was achieved in 99 percent of patients overall and ranged from 97 to 100 percent, depending on genotype (95 percent CI 98 to >99). In two additional Phase III studies, ASTRAL-2 and ASTRAL-3, treatment with this regimen in HCV genotype 2 and 3 infection resulted in SVR12 rates of 99 and 95 percent, respectively.

The once-daily interferon- and ribavirin-free regimen of sofosbuvir/velpatasvir offers high cure rates in all six HCV genotypes which is an advantage over currently available regimens. The FDA granted the Breakthrough Therapy designation to this agent for the treatment of HCV and an FDA decision is expected by June 28, 2016.

NDA

Drug Name: Venetoclax
Manufacturer: Genentech and AbbVie
Indication: Relapsed/refractory CLL
Formulation: Oral tablet

Venetoclax, an oral B-cell lymphoma-2 inhibitor, is currently being investigated for the treatment of various cancer types, including chronic lymphocytic leukemia (CLL) and acute myeloid leukemia.

The pivotal Phase II, open-label, single arm M13-982 study (N=107) met its primary endpoint of overall response rate (ORR) by demonstrating a clinically meaningful reduction in the number of cancer cells in 79.4 percent of patients with relapsed or refractory CLL with the 17p (petit arm of chromosome 17) deletion who received treatment with venetoclax.

The one-year progression-free survival (PFS), OS, and complete response rates were 72.0, 86.7, and 7.5 percent, respectively. The most common serious adverse events were fever, low red blood cell count, pneumonia, and low white blood cell count with fever. The study also included a safety expansion cohort (N=50), the results of which demonstrated that the safety of venetoclax was similar to what was observed in previous studies.

The FDA granted venetoclax the Breakthrough Therapy designation for the treatment of relapsed or refractory CLL in patients with the 17p deletion and Priority Review status for the treatment of CLL in patients who have received at least one prior therapy, including those with the 17p deletion.

If approved, venetoclax may provide a novel treatment option for relapsed or refractory cases of CLL with the 17p deletion. This agent is also being studied in combination with anti-CD20 monoclonal antibodies. An FDA decision is expected in the first half of 2016.

Projected Generic Entry*

- **Crestor® (rosuvastatin calcium)** 5/2016
- **Cubicin® (daptomycin)** 6/2016
- **Nuvigil® (armodafinil)** 6/2016
- **Ziana® (clindamycin phosphate/ tretinoin)** 7/2016
- **Azor® (olmesartan/amlodipine)** 10/2016
- **Benicar® (olmesartan)** 10/2016
- **Benicar HCT® (olmesartan/ hydrochlorothiazide)** 10/2016
- **Seroquel XR® (quetiapine extended-release)** 11/2016
- **Kaletra® (lopinavir/ritonavir)** 12/2016
- **ProAir® HFA (albuterol sulfate)** 12/2016
- **Relpax® (eletriptan)** 12/2016
- **Zetia® (ezetimibe)** 12/2016
- **Azilect® (rasagiline mesylate)** 2/2017
- **Tamiflu® (oseltamivir capsules)** 2/2017
- **Vytorin® (ezetimibe/ simvastatin)** 4/2017
- **Strattera® (atomoxetine)** 5/2017
- **Reyataz® (atazanavir)** 7/2017

*Dates are estimates, current as of 4/6/16, and are subject to change due to any patent litigation or additional patents.

Investigational Indications

Gilotrif® (afatinib)

The Phase III, open-label LUX-Lung 8 trial (N=795) compared treatment with afatinib 40 mg daily to erlotinib 150 mg daily in adults with stage IIIB or IV squamous cell carcinoma of the lung who progressed following at least four cycles of platinum-based chemotherapy. Patients treated with afatinib achieved an OS of 7.9 months compared to 6.8 months with erlotinib (HR 0.81, 95 percent CI 0.69 to 0.95, P=0.0077) and a PFS of 2.6 months compared to 1.9 months, respectively (HR 0.81, 95 percent CI 0.69 to 0.96, P=0.0103). An FDA decision is expected in the first half of 2016.

Stelara® (ustekinumab)

The Phase III UNITI-2 trial (N=628) compared treatment with ustekinumab 130 mg or 6 mg/kg IV to placebo in adults with moderately-to-severely active Crohn's disease who had previously failed or were intolerant to corticosteroids or immunomodulators. At week six, clinical response was achieved by 51.7, 55.5, and 28.7 percent of patients in the ustekinumab 130 mg, 6 mg/kg, and placebo groups, respectively (P<0.001). At week eight, clinical remission was achieved by 30.6, 40.2, and 19.6 percent of patients in the ustekinumab 130 mg, 6 mg/kg, and placebo groups, respectively (P<0.009). An FDA decision is expected in the second half of 2016.

FDA Updates

Kyndrisa™ (drisapersen)

On Jan. 14, 2016, BioMarin Pharmaceutical Inc. announced that the FDA issued a complete response letter declining approval of the NDA for drisapersen. Drisapersen is currently being studied for the treatment of Duchenne muscular dystrophy that is amenable to exon 51 skipping. The complete response letter indicated that the NDA was not accepted because the standard of substantial evidence of effectiveness was not met and the FDA requested the completion of another trial before the drug would be reconsidered for approval. The manufacturer announced its intention to work with the FDA to determine the appropriate next steps.

Opdivo® (nivolumab)

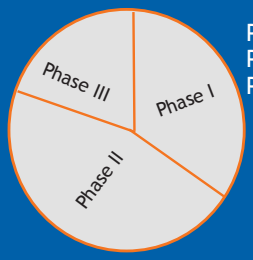
On Nov. 27, 2015, Bristol-Myers Squibb announced that the FDA issued a complete response letter requesting additional data for the supplemental BLA for the use of nivolumab as monotherapy in previously untreated patients with BRAF V600 mutation-positive unresectable or metastatic melanoma. Specifically, the FDA requested additional data in the BRAF-mutated population. The manufacturer announced that it is currently analyzing additional clinical trial data and intends to continue to work with the FDA to determine if that data addresses the FDA's request.

Rociletinib (CO-1686)

On Dec. 15, 2015, Clovis Oncology, Inc. announced that the FDA extended the PDUFA date from March 30, 2016 to June 28, 2016 for the review of the NDA for rociletinib for the treatment of patients with mutant epidermal growth factor receptor (EGFR) non-small cell lung cancer who have the EGFR T790M mutation and have been previously treated with an EGFR-targeted therapy. A major amendment was submitted to the FDA on Nov. 16, 2015 to address the FDA's request for additional clinical data for both the 500 mg and 625 mg dosing groups. The FDA's Oncologic Drugs Advisory Committee is scheduled to review the NDA on April 12, 2016.

Industry Trends

Agents in Clinical Development



Phase I: 36.0%
Phase II: 46.5%
Phase III: 17.5%

Leading Indications with Agents in Late-Stage Development

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

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Additional Promising New Agents

Drug Name	Manufacturer	Indication	Product Timeline
Deutetrabenazine	Teva Pharmaceutical Industries	Chorea associated with Huntington disease	PDUFA date 5/2016
Obeticholic acid	Intercept Pharmaceuticals	Primary biliary cholangitis	PDUFA date 5/29/2016
TBRIA™ (calcitonin-salmon [rDNA origin])	Tarsa Therapeutics, Inc.	Postmenopausal osteoporosis	PDUFA date 5/30/2016
Benzhydrocodone/ acetaminophen	KemPharm, Inc.	Pain	PDUFA date 6/9/2016
Lixisenatide (SC)	Sanofi	Type 2 diabetes mellitus	PDUFA date 7/2016
Bezlotoxumab (IV)*	Merck	Prevention of *C. diff* recurrence	PDUFA date 7/23/2016
Andexanet alfa (IV)	Portola Pharmaceuticals	Factor Xa inhibitor antidote	PDUFA date 8/17/2016
ABP 501 (adalimumab biosimilar) (SC)*	Amgen	Plaque psoriasis, rheumatoid arthritis	BsUFA date 9/25/2016
Brodalumab (SC)*	AstraZeneca	Plaque psoriasis	PDUFA date 11/16/2016
Baricitinib*	Eli Lilly, Incyte Corporation	Rheumatoid arthritis	NDA submitted 1/2016
Telotristat etiprate*	Lexicon Pharmaceuticals	Carcinoid syndrome	NDA submitted 3/2016
Valbenazine	Neurocrine	Tardive dyskinesia	NDA submission expected in 2016
Binimetinib*	Array BioPharma	NRAS-mutant melanoma	NDA submission expected in 2016
ADS-5102	Adamas Pharmaceuticals, Inc.	Levodopa-induced dyskinesia in Parkinson's disease	NDA submission expected in 2016
Elagolix	Neurocrine, AbbVie	Endometriosis	NDA submission expected in 2017
ITI-007	Intra-Cellular Therapies, Inc.	Schizophrenia	NDA submission expected in 2017

Table Abbreviations: BLA = Biologics License Application, BsUFA = Biosimilar User Fee Act, *C. diff* = *Clostridium difficile*, IV = intravenous, NDA = New Drug Application, PDUFA = Prescription Drug User Fee Act, rDNA = ribosomal deoxyribonucleic acid, SC = subcutaneous

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

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