

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

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BLA submitted in September 2016

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Cabozantinib
For the treatment of advanced renal cell carcinoma
Tofacitinib
For the treatment of moderate-to-severely active ulcerative colitis

FDA Updates

Andexanet alfa
Manufacturer received complete response letter
Deutetrabenazine
FDA decision expected April 3, 2017
Etelcalcetide
Manufacturer received complete response letter

Promising New Agents

Drug Name: Abaloparatide
Manufacturer: Radius Health
Indication: Osteoporosis
Formulation: Subcutaneous injection

Abaloparatide is an anabolic agent that selectively activates the parathyroid hormone type 1 receptor. Abaloparatide is currently being developed for the treatment of osteoporosis in postmenopausal women.

The randomized, controlled, double-blind, international Phase III ACTIVE trial (N=2,463) compared abaloparatide 80 mcg daily to placebo or open-label teriparatide 20 mcg daily. There was a 0.6 percent incidence of new vertebral fractures at 18 months among patients treated with abaloparatide compared to 4.2 percent incidence among patients in the placebo group (RR 0.14, 95 percent CI 0.05 to 0.39, P<0.001). There was a 2.7 percent incidence of nonvertebral fractures at 18 months among patients treated with abaloparatide compared to 4.7 percent incidence among patients in the placebo group (hazard ratio [HR] 0.57, 95 percent CI 0.32 to 1.00, P=0.049). In addition, treatment with abaloparatide resulted in significant increases in bone mineral density compared to placebo and teriparatide at 6, 12, and 18 months (P<0.001). The incidence of hypercalcemia was lower in patients treated with abaloparatide compared to teriparatide (3.4 versus 6.4 percent, respectively, P=0.006).

If approved, abaloparatide may provide an efficacious treatment option for osteoporosis in postmenopausal women. A New Drug Application (NDA) for abaloparatide has been accepted for review by the FDA and a decision is expected by March 30, 2017.

Drug Name: Cannabidiol
Manufacturer: GW Pharmaceuticals
Indication: Dravet syndrome, LGS
Formulation: Oral liquid

Epidiolex® (cannabidiol) is a liquid formulation of pure plant-derived cannabidiol. Cannabidiol is currently being investigated for the treatment of multiple pediatric epilepsy disorders, including Dravet syndrome and Lennox-Gastaut syndrome (LGS).

In a randomized, placebo-controlled Phase III trial of patients with Dravet syndrome (N=120), cannabidiol was added to the current anti-epileptic drug (AED) regimen of patients who had previously tried an average of ≥4 AEDs. Treatment with cannabidiol resulted in a median reduction in monthly convulsive seizures of 39 percent compared to 13 percent with placebo after 14 weeks (P=0.01). In a randomized, placebo-controlled Phase III trial of patients with LGS who were uncontrolled on their current AED regimens (N=171), treatment with cannabidiol resulted in a median reduction in monthly drop seizures of 44 percent compared to 22 percent with placebo after 14 weeks (P=0.0135). Additional Phase III trials of cannabidiol for both Dravet syndrome and LGS are currently underway.

Currently, there are no FDA-approved treatments for Dravet syndrome. The FDA has granted the Orphan Drug designation to cannabidiol for the treatment of Dravet syndrome, LGS, Tuberous Sclerosis Complex, and infantile spasms. In addition, the FDA granted the Fast Track designation to cannabidiol for the treatment of Dravet syndrome in June 2014. An NDA submission for cannabidiol is anticipated in the first half of 2017.

Promising New Agents

BLA

Drug Name: Dupilumab

Manufacturer: Regeneron, Sanofi
 Indication: Atopic dermatitis
 Formulation: Subcutaneous injection

Dupixent® (dupilumab) is a fully human monoclonal antibody that blocks the signaling of interleukin (IL)-4 and IL-13, two cytokines that are integral to the type 2 immune response. Dupilumab is currently being studied for the treatment of moderate-to-severe atopic dermatitis (AD).

Two identical Phase III studies, SOLO 1 (N=671) and SOLO 2 (N=708), compared

treatment with dupilumab 300 mg weekly or every other week to placebo in patients with moderate-to-severe AD who were inadequate responders to or ineligible for topical treatment. Compared to placebo, treatment with either dupilumab regimen resulted in significant improvements in the primary endpoint, defined as a score of 0 or 1 (clear or almost clear) on the Investigator’s Global Assessment (IGA) and a reduction from baseline of ≥2 points in the IGA score from baseline to week 16 in both trials (P<0.001 for both comparisons). The most common adverse events were

exacerbations of AD, injection-site reactions, and nasopharyngitis.

If approved, dupilumab may offer an alternative for patients with AD who are uncontrolled on topical treatment, and would be the first targeted therapy available for the treatment of AD. Dupilumab is also being studied for the treatment of asthma, nasal polyposis, and eosinophilic esophagitis. Dupilumab was granted the Breakthrough Therapy designation and Priority Review status by the FDA, with a decision expected by March 29, 2017.

Phase III

Drug Name: Elagolix

Manufacturer: AbbVie, Neurocrine
 Indication: Endometriosis
 Formulation: Oral tablet

Elagolix is an orally-administered gonadotropin-releasing hormone (GnRH) antagonist that blocks GnRH signaling by binding to GnRH receptors in the pituitary gland. It is currently being investigated for the treatment of endometriosis and uterine fibroids.

The safety and efficacy of elagolix were evaluated in two randomized, double-blind

Phase III trials which compared elagolix 150 mg once daily or 200 mg twice daily to placebo in premenopausal women with moderate-to-severe endometriosis-associated pain. The co-primary endpoints of dysmenorrhea and non-menstrual pelvic pain (NMPP), as measured by the Daily Assessment of Endometriosis Pain scale, were evaluated in both trials at months three and six. In the Violet PETAL study (N=872), 46 and 76 percent of patients treated with elagolix 150 mg and 200 mg, respectively, were classified as dysmenorrhea responders at three

months compared to 20 percent of patients receiving placebo. In addition, 50 and 55 percent of patients treated with elagolix 150 mg and 200 mg, respectively, were classified as NMPP responders at three months, compared to 36 percent of patients receiving placebo. The results of the Solstice study (N=815) were similar, with both elagolix groups achieving the co-primary endpoints at six months.

If approved, elagolix would be the first GnRH antagonist approved for the treatment of endometriosis. An NDA submission is planned for 2017.

BLA

Drug Name: Guselkumab

Manufacturer: Janssen
 Indication: Plaque psoriasis
 Formulation: Subcutaneous injection

Guselkumab is a fully humanized anti-IL-23 monoclonal antibody with anti-inflammatory properties. This agent is currently in development for the treatment of moderate-to-severe plaque psoriasis.

The Phase II X-PLORE trial (N=293) compared guselkumab to placebo and adalimumab in adults with moderate-to-severe plaque psoriasis. A greater proportion of patients treated with

guselkumab achieved a Physician’s Global Assessment score of 0 or 1 at 16 weeks compared to adalimumab (79, 86, and 83 percent for guselkumab 50 mg, 100 mg, and 200 mg, respectively, compared to 58 percent for adalimumab, P<0.05 for all comparisons).

The Phase III VOYAGE 1 trial (N=837) compared guselkumab to placebo and adalimumab in adults with moderate-to-severe plaque psoriasis. Treatment with guselkumab resulted in significant improvements in the proportion of patients achieving IGA scores of 0 or 1 compared to adalimumab (85.1 versus 65.9 percent,

respectively) and in the proportion of patients with at least a 90 percent improvement in the Psoriasis Area and Severity Index (PASI 90) at 16 weeks (73.3 versus 49.7 percent, respectively, P<0.001 for both). The difference between groups in the proportion of patients achieving PASI 90 was similar at 24 weeks (80.2 versus 53.0 percent, respectively, P<0.001).

If approved, guselkumab would be the first anti-IL-23 monoclonal antibody indicated for the treatment of moderate-to-severe plaque psoriasis. A Biologics License Application (BLA) was submitted to the FDA in November 2016.

Promising New Agents

NDA

Drug Name: Midostaurin

Manufacturer: Novartis
 Indication: AML, SM
 Formulation: Oral capsule

Midostaurin is a multi-targeted kinase inhibitor that targets both wild-type KIT and D816V-mutated KIT. Midostaurin is currently being studied for the treatment of patients with acute myeloid leukemia (AML) with an FMS-like tyrosine kinase-3 (FLT3) mutation, as well as patients with advanced systemic mastocytosis (SM).

In the randomized, placebo-controlled

Phase III RATIFY trial (N=717), treatment with midostaurin, in combination with standard induction and consolidation chemotherapy, was compared to chemotherapy alone for the treatment of newly-diagnosed FLT3-mutated AML in patients ages 18 to 59. Treatment with midostaurin resulted in a 23 percent improvement in overall survival (OS) compared to chemotherapy alone (HR 0.77, P=0.0074). The median OS with midostaurin was 74.7 months compared to 25.6 months with chemotherapy alone (95 percent CI 31.7 to not attained and 95 percent CI 18.6 to 42.9, respectively). In an open-label Phase II

study of patients with SM (N=89), patients treated with midostaurin had an overall response rate of 60 percent (95 percent CI 49 to 70, P<0.001), a median OS of 28.7 months, and a median progression-free survival (PFS) of 14.1 months.

If approved, midostaurin would be the first targeted therapy for AML, with significant improvements in OS compared to chemotherapy alone. The FDA granted the Breakthrough Therapy designation to midostaurin on Feb. 19, 2016. Following a priority review, an FDA decision is expected in the first half of 2017.

BLA

Drug Name: Sirukumab

Manufacturer: GSK, Janssen
 Indication: Rheumatoid arthritis
 Formulation: Subcutaneous injection

Sirukumab is a human anti-IL-6 monoclonal antibody being studied for the treatment of moderate-to-severely active rheumatoid arthritis (RA) in adults. By binding to IL-6, sirukumab inhibits inflammation in RA.

The Phase III SIRROUND-H study (N=559) compared treatment with sirukumab 50 mg every four weeks or 100 mg every

two weeks to adalimumab 40 mg every two weeks for 52 weeks, all given as monotherapy in patients who were ineligible for methotrexate due to a history of an adverse reaction, inadequate response, or contraindication. Co-primary endpoints included change from baseline in Disease Activity Index Score 28 using erythrocyte sedimentation rate [DAS28 (ESR)] and American College of Rheumatology 50 (ACR50) response, both assessed at 24 weeks. Improvements in DAS28 (ESR) were greater in the sirukumab 100 mg and 50 mg groups compared to the adalimumab

group (-2.96, -2.58 versus -2.19, respectively, P<0.001 and P=0.013, respectively). The ACR50 response was similar between the sirukumab and adalimumab groups.

The SIRROUND clinical program includes five studies evaluating sirukumab in more than 3,000 patients as monotherapy or combined with conventional disease-modifying antirheumatic drugs (DMARDs). If approved, sirukumab may offer an efficacious alternative for patients with RA who are ineligible for or who have failed DMARDs. A BLA was submitted for FDA review in September 2016.

NDA

Drug Name: Solithromycin

Manufacturer: Cempra
 Indication: CABP
 Formulation: IV/oral

Solithera™ (solithromycin) is a novel fourth-generation macrolide and the first fluoroketolide. This agent is currently being studied for the treatment of community-acquired bacterial pneumonia (CABP).

In the SOLITAIRE-ORAL trial (N=860), adults with confirmed pneumonia were randomized to receive oral solithromycin 800 mg on day one, followed by 400 mg on days two through five and placebo on days

six through seven, or oral moxifloxacin 400 mg on days one through seven. The primary endpoint of early clinical response (ECR) was defined as an improvement in ≥2 of 4 symptoms (cough, chest pain, sputum production, dyspnea) and no worsening in any symptom at 72 hours after the first dose. Treatment with solithromycin was non-inferior to moxifloxacin, with 78.2 and 77.9 percent of patients, respectively, achieving an ECR (treatment difference 0.29, 95 percent CI -5.5 to 6.1).

In the SOLITAIRE-IV trial (N=863), adults with CABP were randomized to receive intravenous (IV)-to-oral solithromycin or

moxifloxacin for seven once-daily doses. The primary endpoint of ECR was achieved by 79.3 and 79.7 percent of patients treated with solithromycin and moxifloxacin, respectively (treatment difference -0.46, 95 percent CI -6.1 to 5.2).

Solithromycin has activity against most macrolide-resistant strains of bacteria and may provide a potent macrolide monotherapy option for CABP. On Nov. 4, 2016, an FDA advisory committee voted 7 to 6 that the efficacy of solithromycin outweighs the risks. FDA decisions for the oral and IV formulations are expected by Dec. 27 and 28, 2016, respectively.

Projected Generic Entry*

- **Azilect® (rasagiline mesylate)**
2/2017
- **Tamiflu® (oseltamivir capsules)**
2/2017
- **Minastrin™ 24 Fe (ethinyl estradiol/norethindrone acetate/ferrous fumarate)**
3/2017
- **Pristiq® (desvenlafaxine succinate extended-release tablet)**
3/2017
- **Vytorin® (ezetimibe/simvastatin)**
4/2017
- **Zetia® (ezetimibe)**
4/2017
- **Strattera® (atomoxetine)**
5/2017
- **Adcirca® (tadalafil)**
11/2017
- **Prezista® (darunavir tablet)**
11/2017
- **Reyataz® (atazanavir)**
12/2017
- **Sustiva® (efavirenz)**
12/2017
- **Truvada® (emtricitabine/tenofovir disoproxil fumarate)**
12/2017
- **Viagra® (sildenafil)**
12/2017
- **Viread® (tenofovir disoproxil fumarate tablet)**
12/2017
- **Treximet® (sumatriptan/naproxen)**
2/2018
- **Solodyn® (minocycline extended-release tablet)**
2/2018

*Dates are estimates, current as of 12/2/16, and are subject to change due to any patent litigation or additional patents.

Investigational Indications

Cabometyx™ (cabozantinib)

The Phase II randomized, active-controlled CABOSUN trial (N=157) compared treatment with cabozantinib 60 mg once daily to sunitinib 50 mg once daily, given in cycles of four weeks on and two weeks off, in patients with previously untreated advanced renal cell carcinoma. Treatment with cabozantinib resulted in a 31 percent reduction in the rate of disease progression or death at a median follow-up of 20.8 months (HR 0.69, 95 percent CI 0.48 to 0.99, P=0.012), as well as a greater median PFS (8.2 versus 5.6 months) and median OS (30.3 versus 21.8 months) compared to sunitinib. An NDA submission is planned based on these findings.

Xeljanz® (tofacitinib)

The Phase III randomized, double-blind, parallel group, placebo-controlled OCTAVE Sustain trial (N=593) compared maintenance treatment with tofacitinib 5 mg and 10 mg twice daily to placebo in patients with moderate-to-severely active ulcerative colitis who had previously achieved a response in the OCTAVE Induction 1 or 2 trials, which evaluated the efficacy of tofacitinib in inducing remission after eight weeks. At week 52, the proportion of patients who achieved remission was significantly greater in both tofacitinib treatment groups compared to placebo. The long-term OCTAVE Open extension trial is currently ongoing.



FDA Updates

AndexXa™ (andexanet alfa)

On Aug. 17, 2016, Portola Pharmaceuticals Inc. announced that the FDA issued a Complete Response Letter (CRL) regarding the BLA for andexanet alfa, to which the Breakthrough Therapy designation had previously been granted for the reversal of direct or indirect Factor Xa inhibition in the setting of life-threatening or uncontrolled bleeding. The FDA requested additional information related to product manufacturing, as well as data to support the inclusion of edoxaban and enoxaparin in the product label. Currently, there is no FDA-approved antidote for Factor Xa inhibitor therapy.

Deutetrabenazine (SD-809)

On Oct. 20, 2016, Teva announced that the FDA had accepted for review the NDA resubmission for deutetrabenazine, an oral small molecule inhibitor of vesicular monoamine 2 transporter (VMAT2) that is being studied for the treatment of chorea associated with Huntington disease. This resubmission follows the CRL issued by the FDA in May 2016. In the CRL, the FDA did not request additional clinical trials, but requested that the manufacturer examine blood levels of certain metabolites that have been observed in individuals taking tetrabenazine or deutetrabenazine. An FDA decision is expected by April 3, 2017.

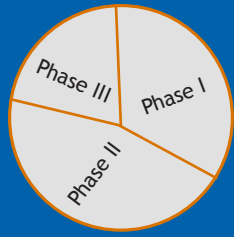
Parsabiv™ (etelcalcetide)

On Aug. 24, 2016, Amgen announced that the FDA issued a CRL declining approval of the NDA for etelcalcetide in its current form. Etelcalcetide is a novel, IV calcimimetic agent in development for the treatment of secondary hyperparathyroidism in adult patients with chronic kidney disease who are receiving hemodialysis. Amgen is currently reviewing the CRL decision and anticipates a post-action meeting with the FDA later this year to discuss further. Although the details of the CRL were not disclosed, Amgen has indicated that it does not impact their regulatory submissions in other regions.



Industry Trends

Agents in Clinical Development



Phase I: 36.6%
Phase II: 44.6%
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. Rheumatoid arthritis
7. Ovarian cancer
8. Alzheimer's disease
9. Prostate cancer
10. Melanoma

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Additional Promising New Agents

Drug Name	Manufacturer	Indication	Product Timeline
Ocrevus® (ocrelizumab)* (IV)	Genentech	Relapsing-remitting, primary progressive MS	PDUFA date 12/28/2016
Crisaborole (topical)	Anacor Pharmaceuticals	Atopic dermatitis	PDUFA date 01/07/2017
Rolapitant (IV)	Tesaro	CINV prophylaxis	PDUFA date 01/11/2017
Plecanatide	Synergy Pharmaceuticals	IBS-C, CIC	PDUFA date 01/29/2017
Siliq (brodalumab)* (SC)	Valeant Pharmaceuticals	Plaque psoriasis	PDUFA date 02/16/2017
Rucaparib*	Clovis Oncology	Advanced BRCA-mutated ovarian cancer	PDUFA date 02/23/2017
Telotristat etiprate*	Lexicon Pharmaceuticals	Carcinoid syndrome	PDUFA date 02/28/2017
Deflazacort	Marathon Pharmaceuticals	Duchenne muscular dystrophy	PDUFA date 02/2017
Naldemedine	Shionogi	Opioid-induced constipation in CNCP	PDUFA date 03/23/2017
INGREZZA™ (valbenazine)	Neurocrine Biosciences	Tardive dyskinesia	PDUFA date 04/11/2017
Brineura™ (cerliponase alfa)* (ICV)	BioMarin Pharmaceutical	CLN2 disease	PDUFA date 04/27/2017
Brigatinib*	Ariad Pharmaceuticals	Metastatic ALK+ NSCLC	PDUFA date 04/29/2017
CHS-1701 (pegfilgrastim biosimilar)* (SC)	Coherus Biosciences	Prevention of chemotherapy-induced febrile neutropenia	PDUFA date 06/09/2017
Radicava™ (edaravone)* (IV)	Mitsubishi Tanabe Pharma Corporation	ALS	PDUFA date 06/16/2017
Ozenoxacin (topical)	Medimetriks Pharmaceuticals	Impetigo	PDUFA date 06/22/2017
Ribociclib*	Novartis	HR+/HER2- advanced breast cancer	NDA accepted 11/2016

Table Abbreviations: ALK=anaplastic lymphoma kinase, ALS=amyotrophic lateral sclerosis, CIC=chronic idiopathic constipation, CINV=chemotherapy-induced nausea and vomiting, CNCP=chronic non-cancer pain, HR=hormone receptor, HER2=human epidermal growth factor receptor 2, IBS-C=irritable bowel syndrome with constipation, ICV=intracerebroventricular, MS=multiple sclerosis, NSCLC=non-small cell lung cancer, PDUFA=Prescription Drug User Fee Act, 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.



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