OPTUMRx®

RxOutlook®

4th Quarter 2018

Pending drug approvals

Drug Name	Manufacturer	Indication/Use	Expected FDA Decision Date
apomorphine	Sunovion/Sumitomo Dainippon Pharma	Parkinson's disease	1/29/2019
bremelanotide (Rekynda)	Palatin/AMAG	Hypoactive sexual desire disorder	3/23/2019
buprenorphine/samidorphan	Alkermes	Major depressive disorder	1/31/2019
caplacizumab (Cablivi)	Sanofi	Acquired thrombotic thrombocytopenic purpura	2/6/2019
cladribine (Mavenclad)	EMD Serono	Multiple sclerosis	1/2019
emapalumab	Sobi	Primary hemophagocytic lymphohistiocytosis	11/20/2018
levodopa (Inbrija)	Acorda Therapeutics	Parkinson's disease	1/5/2019
ravulizumab	Alexion	Paroxysmal nocturnal hemoglobinuria	2/18/2019
sacituzumab govitecan	Immunomedics	Triple-negative breast cancer	1/18/19
siponimod	Novartis	Multiple sclerosis	3/2019
sotagliflozin (Zynquista)	Sanofi/Lexicon Pharmaceuticals	Type 1 diabetes mellitus	3/22/2019
tagraxofusp (Elzonris)	Stemline Therapeutics	Blastic plasmacytoid dendritic cell neoplasm	2/21/2019

Apomorphine

Manufacturers: Sunovion/Sumitomo Dainippon Pharma

Therapeutic use

Orally administered apomorphine is in development for the treatment of motor fluctuations ("OFF" episodes) in patients with Parkinson's disease.

Currently, a subcutaneous formulation of apomorphine is available under the brand name Apokyn®, for the acute, intermittent treatment of hypomobility, "OFF" episodes in patients with advanced Parkinson's disease.

- Treatment of motor fluctuations ("OFF" episodes) in patients with advanced Parkinson's disease

Clinical profile

Apomorphine is a non-ergoline dopamine agonist. The precise mechanism of action of apomorphine is unknown; however, it is believed to be due to stimulation of post-synaptic dopamine D2-type receptors within the caudate-putamen in the brain.

In the pivotal trial for apomorphine, there was significant improvement in motor functions (Movement Disorder Society Unified Parkinson's Disease Rating Scale [MDS-UPDRS] Part III score) from pre-dose to 30 minutes after dosing at week 12 vs. placebo (treatment difference of 7.6; $p = 0.0002$). In addition, a higher percentage of patients reported full "ON" response within 30 minutes after dosing vs. placebo (35% vs. 16%; $p < 0.05$).

The most common adverse reactions in the trial were nausea, somnolence, dizziness, and headache.

In the trials, apomorphine was administered sublingually as an on-demand treatment (up to 5 times per day).

- Non-ergoline dopamine agonist
- Oral sublingual formulation
- Improvement of motor functions and "ON" response vs. placebo
- Common adverse reactions: nausea, somnolence, dizziness, headache
- Dose: on-demand (up to 5 times per day)

Continued…

Apomorphine (continued...)

Competitive environment

If approved, sublingual apomorphine would provide a rapid onset of action, oral alternative to subcutaneous apomorphine (Apokyn) for the treatment of acute "OFF" episodes in patients with Parkinson's disease. The sublingual formulation also provides an easy to administer option for patients with Parkinson's disease that have difficulty swallowing.

However, sublingual apomorphine has not been compared head-to-head to the subcutaneous formulation of apomorphine and an inhaled levodopa product is also currently in development for the treatment of acute "OFF" episodes.

For reference, the wholesale acquisition cost (WAC) for Apokyn is approximately $22,000 per prescription.

- Advantages: oral, rapid onset of action, easy administration for patients with difficulty swallowing
- Disadvantages: no head-to-head trials vs. Apokyn, potential competition with inhaled levodopa
- WAC for Apokyn is ~$22,000 per prescription

Expected FDA decision date

An FDA decision regarding the approval of apomorphine is expected by January 29, 2019.

- PDUFA: 1/29/2019

bremelanotide (Rekynda)

Manufacturers: AMAG/Palatin

Therapeutic use

Bremelanotide is in development for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women.

HSDD is a medical condition that is considered the most prevalent form of female sexual dysfunction; it's characterized by low sexual desire and marked distress, which are not attributable to existing medical, pharmacologic, or psychiatric issues. HSDD affects approximately 6 million premenopausal women in the U.S.

- Treatment of HSDD in premenopausal women

Clinical profile

Bremelanotide is a first-in-class melanocortin-4 (MC-4) receptor agonist. MC-4 receptors in the brain are associated with sexual desire and response.

In two pivotal trials in premenopausal women with HSDD, bremelanotide was evaluated vs. placebo using the co-primary endpoints of the Female Sexual Function Index: Desire Domain (FSFI-D) and Female Sexual Distress Scale-Desires/Arousal/Orgasm (FSDS-DAO) item 13. The FSFI-D is a validated patient reported outcome measurement tool of sexual desire and the FSDS-DAO item 13 is a validated patient reported outcome measurement tool of distress related to sexual dysfunction, measuring personal distress associated with low sexual desire.

Bremelanotide provided a statistically significant increase in the median FSFI-D score vs. placebo (0.60 vs. 0.00; $p = 0.0002$ and $p < 0.001$) and a significant reduction in the FSDS-DAO item 13 score (-1.0 vs. 0.0; $p < 0.0001$ and $p = 0.0057$).

The most common adverse reactions in the clinical trials were nausea, flushing, and headache.

In the trials, bremelanotide was administered as a subcutaneous (SC) injection as-needed prior to sexual activity.

- MC-4 receptor agonist
- SC formulation
- Met the co-primary endpoint of median improvement in desire and decrease in distress associated with low sexual desire vs. placebo
- Common adverse reactions: nausea, flushing, headache
- Dose: as-needed prior to sexual activity

Competitive environment

Bremelanotide works by a novel mechanism of action (MOA). Addyi® (flibanserin) is the only other drug approved for HSDD; however Addyi has a boxed warning for an interaction with alcohol and is only available via the Addyi REMS program because of the increased risk of severe hypotension and syncope.

However, bremelanotide will require SC administration. There has also been a slow uptake of Addyi which may suggest providers and patients are reluctant to treat HSDD with these types of agents, particularly when they are associated with marginal benefit.

If approved for the proposed indication, bremelanotide would only be for use in premenopausal women, which reduces the eligible patient population by about a half.

For reference, the WAC for Addyi is approximately $400 per prescription.

- Advantages: novel MOA, competitor has a boxed warning and REMS due to an alcohol interaction
- Disadvantages: SC administration, slow uptake for Addyi to treat the same condition, proposed indication is limited to premenopausal women
- WAC for Addyi is ~$400 per prescription

Continued…

bremelanotide (Rekynda) (continued...)

Expected FDA decision date

An FDA Advisory Committee meeting is scheduled in the 4th quarter of 2018.

An FDA decision regarding the approval of bremelanotide is expected by March 23, 2019.

- FDA Advisory Committee meeting: 4th Qtr 2018
- PDUFA: 3/23/2019

buprenorphine/samidorphan

Manufacturer: Alkermes

Therapeutic use

Buprenorphine/samidorphan is in development for adjunctive treatment of major depressive disorder (MDD) in patients with an inadequate response to standard antidepressant therapies.

- Adjunctive treatment of MDD in patients with an inadequate response to standard antidepressant therapies

Clinical profile

Buprenorphine is a partial mu-opioid receptor agonist and samidorphan is a mu-opioid full antagonist. Buprenorphine also acts through antagonism of the kappa-opioid receptor and through this mechanism it's thought to have antidepressant activity. The samidorphan component is intended to reduce the risks of abuse and dependence with buprenorphine.

Buprenorphine/samidorphan failed to achieve its pre-specified primary endpoint in 2 of 3 phase 3 individual trials. However, a pooled analysis of 2 pivotal trials was conducted with efficacy measured using the Montgomery–Åsberg Depression Rating Scale (MADRS-10). There was an improvement in the MADRS-10 and MADRS-6 (core symptoms) vs. placebo ($p < 0.001$ and $p = 0.004$, respectively).

The most common adverse reactions in the clinical trials were nausea, constipation, dizziness, vomiting, somnolence, fatigue, and sedation.

In the trials, buprenorphine/samidorphan was administered orally once daily.

- Buprenorphine: mu-opioid receptor partial agonist and kappa-opioid receptor antagonist; samidorphan: mu-opioid receptor antagonist
- Oral sublingual formulation (fixed-dose combination)
- Improvement in symptoms of depression in a pooled analysis of 2 pivotal trials vs. placebo
- Failed to achieve pre-specified primary endpoint in 2 of 3 individual phase 3 trials
- Common adverse events: nausea, constipation, dizziness, vomiting, somnolence, fatigue, sedation
- Dose: once daily

Competitive environment

Buprenorphine/samidorphan is an oral fixed-dose combination given once daily and it offers a novel MOA for the treatment of MDD.

However, buprenorphine/samidorphan demonstrated questionable efficacy in the clinical trials and it will likely require DEA scheduling since it is a buprenorphine-containing product.

Alternative options are also available for treatment of MDD, including selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and atypical antipsychotics. Many of the agents in these classes are available generically.

For reference, the WAC for Rexulti® (brexpiprazole), a branded atypical antipsychotic indicated for adjunctive therapy of depression, is approximately $1,100 per month.

- Advantages: novel MOA for the treatment of MDD, oral, once daily
- Disadvantages: questionable efficacy, likely DEA scheduling, generic alternatives available
- WAC for Rexulti is $1,100 per month

Continued…

buprenorphine/samidorphan (continued...)

Expected FDA decision date

The FDA granted fast track designation to buprenorphine/samidorphan.

On November 1, 2018, a FDA Advisory Committee voted that the benefit-risk profile was not adequate to support approval (vote: 2 yes/ 21 no).

An FDA decision regarding the approval of buprenorphine/samidorphan is expected by January 31, 2019.

- Fast track status
- FDA Advisory Committee: voted that the benefit-risk profile was not adequate to support approval
- PDUFA: 1/31/2019

caplacizumab (Cablivi)

Manufacturer: Sanofi

Therapeutic use

Caplacizumab is in development for the treatment of patients experiencing an episode of acquired thrombotic thrombocytopenic purpura (aTPP).

aTTP is a rare autoimmune-based disorder characterized by extensive clot formation in small blood vessels throughout the body which can lead to thrombocytopenia, microangiopathic hemolytic anemia, ischemia, and organ damage.

- Treatment of patients experiencing an episode of aTTP

Clinical profile

Caplacizumab is an anti-von Willebrand factor (vWF) nanobody (novel class of antibody-derived therapeutic proteins). Caplacizumab works by blocking the interaction of vWF multimers with platelets which reduces platelet adhesion and the accumulation of blood clots.

In a trial of patients experiencing an acute episode of aTTP, patients received either caplacizumab or placebo in addition to standard-of-care (daily plasma exchange and immunosuppression). Caplacizumab provided a significant reduction in time to platelet count response vs. placebo ($p < 0.01$) and a significant reduction in a composite secondary endpoint of patients with aTTP-related death, recurrence of aTTP, or at least one major thromboembolic event (49.3% vs. 12.7%; $p < 0.0001$). The primary contributor for the difference in the secondary endpoint was aTTP recurrence.

The most common treatment-emergent adverse event reported in the trial was bleeding-related events.

In the trials, caplacizumab was administered as an intravenous (IV) bolus followed by daily SC doses (until 30 days after the last daily plasma exchange).

- Anti-vWF nanobody
- IV and SC formulation
- Improvement in time to platelet count response and reduction of aTTP recurrence vs. placebo
- Safety: bleeding-related events
- Dose: IV bolus followed by daily SC doses (until 30 days after the last daily plasma exchange)

Competitive environment

Caplacizumab works by a novel MOA. If approved, caplacizumab would be the first FDA-approved drug for the treatment of aTTP.

However, in the clinical trial, caplacizumab was administered with current standard-of-care (ie, daily plasma exchanges and immunosuppression) and it carries a risk for bleeding events. Caplacizumab also requires IV and SC administration.

- Advantages: novel MOA, potential first FDA-approved option for aTTP
- Disadvantages: IV/SC administration, background therapy of daily plasma exchange and immunosuppression required, increased risk of bleeding events

Expected FDA decision date

The FDA granted fast track and orphan drug designations to caplacizumab.

An FDA decision regarding the approval of caplacizumab is expected by February 6, 2019.

- Fast track status
- Orphan drug status
- PDUFA: 2/6/2019

cladribine (Mavenclad)

Manufacturer: EMD Serono

Therapeutic use

Orally administered cladribine is in development for the treatment of relapsing forms of multiple sclerosis (RMS).

Currently, an IV-infused cladribine formulation is available generically for the treatment of hairy cell leukemia.

- Treatment of RMS

Clinical profile

Cladribine is a purine nucleoside analog and immunosuppressant.

In the CLARITY trial, patients with RMS receiving cladribine tablets (total dose of 3.5 mg/kg) had a significantly lower annualized relapse rate vs. placebo (0.14 vs. 0.33; $p < 0.001$) and a lower risk of 3-month sustained progression of disability ($p = 0.02$). The safety and efficacy of cladribine were also demonstrated in the CLARITY-EXT, ORACLE MS, ONWARD trials and a long-term registry-based study (PREMIERE).

The major safety concerns identified with cladribine in the clinical trials were lymphopenia, infection, and an imbalance of malignancy cases.

In the trials, cladribine was administered orally with two treatment courses administered over 2 years (each treatment course was 2 weeks).

- Purine nucleoside analog
- Oral formulation
- Significantly lower annualized relapse rate and 3-month sustained progression of disability vs. placebo
- Safety: lymphopenia, infection, malignancy
- Dose: two treatment courses over 2 years (one treatment course was 2 weeks)

Competitive environment

Cladribine offers another treatment for RMS and it can be administered orally as a short treatment course.

However, the FDA did reject the original application for cladribine due to concerns about the risk/benefit profile. There are also several alternative injectable and oral treatment options for RMS, including Aubagio® (teriflunomide), Avonex®/Rebif® (interferon beta-1a), Betaseron® (interferon beta-1b), Copaxone®/Glatopa® (glatiramer acetate), Gilenya® (fingolimod), Lemtrada® (alemtuzumab), Ocrevus™ (ocrelizumab), Tecfidera® (dimethyl fumarate), and Tysabri® (natalizumab). IV infused Lemtrada is also administered as two short treatment courses over 2 years.

For reference, the WAC for an entire treatment course (2 years) of Lemtrada is approximately $150,000.

- Advantages: another treatment for MS, oral, short treatment course
- Disadvantages: safety concerns, several oral and injectable treatment alternatives
- WAC for an entire treatment course of Lemtrada is ~$150,000

Expected FDA decision date

The FDA granted fast track designation to cladribine.

An FDA decision regarding the approval of cladribine is expected in January 2019.

- Fast track status
- PDUFA: 1/2019

emapalumab

Manufacturer: Sobi

Therapeutic use

Emapalumab is in development for the treatment of pediatric patients with primary hemophagocytic lymphohistiocytosis (HLH).

Primary HLH is a familial autosomal recessive immune disorder. HLH is mediated by a dramatic increase in interferon-gamma production. Symptoms may include fever, enlarged liver or spleen, cytopenia, and neurological abnormalities. Allogeneic hematopoietic cell transplantation is considered a cure for familial HLH. Prior to transplantation, patients are treated with chemotherapy and/or immunotherapy (eg, etoposide plus dexamethasone) to destroy excess immune cells.

If untreated, primary HLH is lethal. Even with treatment, only 21 to 26% of patients are expected to survive 5 years.

- Treatment of pediatric patients with primary HLH

Clinical profile

Emapalumab is an interferon-gamma monoclonal antibody.

In a small early stage trial, emapalumab significantly improved parameters of HLH disease activity and the majority of patients were successfully bridged to hematopoietic cell transplantation.

The most common treatment-emergent adverse event in the trial was infusion-related reactions.

In the trial, emapalumab was given as an IV infusion every 3 days for 8 weeks.

- Interferon-gamma monoclonal antibody
- IV formulation
- Significantly improved parameters of HLH disease
- Safety: limited data, infusion-related reactions
- Dose: every 3 days for 8 weeks

Competitive environment

Emapalumab works by a novel MOA. If approved, emapalumab would be the first FDA-approved drug for the treatment of primary HLH.

However, emapalumab requires IV administration. Currently, data are only available from an early to mid-stage trial.

- Advantages: novel MOA, potential first FDA-approved option for primary HLH
- Disadvantages: IV administration, data only from an early to mid-stage trial

Expected FDA decision date

The FDA granted breakthrough and orphan drug designations to emapalumab.

An FDA decision regarding the approval of emapalumab is expected by November 20, 2018.

- Breakthrough status
- Orphan drug status
- PDUFA: 11/20/2018

levodopa (Inbrija)

Manufacturer: Acorda Therapeutics

Therapeutic use

Inhaled levodopa is in development for the treatment of symptoms of "OFF" episodes in Parkinson's disease as an adjunct to a carbidopa/levodopa regimen.

Other oral formulations of levodopa are currently available for the treatment of Parkinson's disease. Inhaled levodopa is being developed as an adjunct to standard oral levodopa therapy rather than as a replacement.

- Treatment of symptoms of "OFF" episodes in Parkinson's disease as an adjunct to a carbidopa/levodopa regimen

Clinical profile

Levodopa is a dopamine precursor. This formulation of levodopa is optimized to deliver levodopa to the deep lungs for rapid and consistent absorption.

In the pivotal trial for levodopa, there was significant improvement in motor functions (UPDRS Part III score) at 30-minutes post-dose at week 12 vs. placebo (treatment difference of 3.92; p = 0.009). In addition, a higher percentage (21.6%; p = 0.003) of patients reported an "ON" response while remaining ON at 60-minutes post-dosing vs. placebo.

The most common adverse reactions in the trials were cough, nausea, and dyskinesias.

In the trials, inhaled levodopa was administered as an on-demand treatment (up to 5 times per day).

- Dopamine precursor
- Oral inhalation formulation
- Improvement of motor functions and "ON" response vs. placebo
- Common adverse events: cough, nausea, dyskinesia
- Dose: on-demand (up to 5 times per day)

Competitive environment

If approved, inhaled levodopa would provide a rapid onset of action, oral alternative to subcutaneous apomorphine (Apokyn) for the treatment of acute "OFF" episodes in patients with Parkinson's disease.

However, inhaled levodopa has not been compared head-to-head to Apokyn and it would potentially be competing with both Apokyn and the sublingual formulation of apomorphine for the treatment of "OFF" episodes in patients with Parkinson's disease.

For reference, the WAC for Apokyn is approximately $22,000 per prescription.

- Advantages: oral, rapid onset of action
- Disadvantages: no head-to-head trials vs. Apokyn, potential competition with sublingual apomorphine
- WAC for Apokyn is ~$22,000 per prescription

Expected FDA decision date

An FDA decision regarding the approval of levodopa is expected by January 5, 2019.

- PDUFA: 1/5/2019

ravulizumab

Manufacturer: Alexion

Therapeutic use

Ravulizumab is in development for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH).

PNH is a rare acquired hematopoietic stem cell disorder. PNH is characterized by chronic uncontrolled activation of the complement system, which can lead to hemolytic anemia and thrombosis.

For patients with hemolytic PNH, the only established therapies are allogeneic hematopoietic cell transplantation and complement inhibition with Soliris® (eculizumab), a C5 inhibitor that works by inhibiting the C5 protein in terminal complement cascade.

- Treatment of PNH

Clinical profile

Ravulizumab is a long-acting anti-C5 monoclonal antibody.

In the pivotal trials, the efficacy of ravulizumab was compared with Soliris in PNH patients who were naïve to compliment inhibitor treatment and in patients who had been stable on Soliris. Ravulizumab demonstrated non-inferiority in both trials for all primary and key secondary endpoints (eg, transfusion avoidance, normalization of lactate dehydrogenase levels, rate of breakthrough hemolysis, and stabilization of hemoglobin levels).

The most common adverse events in the trials were headache and upper respiratory tract infection.

In the trials, ravulizumab was administered as an IV infusion every 8 weeks.

- Anti-C5 monoclonal antibody
- IV formulation
- Non-inferior to Soliris for all primary and key secondary endpoints
- Common adverse events: headache and upper respiratory tract infection
- Dose: every 8 weeks

Competitive environment

Ravulizumab is dosed every 8 weeks vs. every 2 weeks with Soliris. The more convenient dosing frequency could also reduce overall infusion-related costs for patients and payers.

Ravulizumab did demonstrate non-inferiority to Soliris; however, ravulizumab was not found to be statistically superior. Ravulizumab will also require IV administration.

For reference, the WAC for Soliris is $39,500 per prescription

- Advantages: less frequent dosing administration vs. Soliris, reduced infusion-related costs
- Disadvantages: not found to be superior to Soliris, IV administration
- WAC for Soliris is $39,500 per prescription

Expected FDA decision date

The FDA granted orphan drug designation to ravulizumab.

An FDA approval regarding the approval of ravulizumab is expected by February 18, 2019.

- Orphan drug status
- PDUFA: 2/18/2019

sacituzumab govitecan

Manufacturer: Immunomedics

Therapeutic use

Sacituzumab govitecan is in development for the treatment of patients with metastatic triple-negative breast cancer (mTNBC) who previously received at least two prior therapies for metastatic disease.

TNBC is a term applied to breast cancers that are low in expression of the estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER2). Approximately 10 to 20% of all breast cancers are TNBC.

- Treatment of patients with mTNBC who previously received at least two prior therapies for metastatic disease

Clinical profile

Sacituzumab govitecan is a novel antibody-drug conjugate (ADC) of SN-38 (an active metabolite of irinotecan) and anti-Trop-2 humanized antibody. Trop-2 is a cell-surface receptor which is over-expressed by many human tumors, including breast cancer.

In an early phase, single-arm trial of patients with mTNBC, the overall response rate (ORR) for treatment with sacituzumab govitecan was 34% (37/110). Progression free survival (PFS) was 5.5 months (95% CI: 4.8 to 6.6) and overall survival (OS) was 12.7 months (95% CI: 10.8 to 13.6).

Key safety concerns highlighted in the trial were neutropenia, leukemia, anemia, diarrhea, and febrile neutropenia.

In the trial, sacituzumab govitecan was administered as an IV infusion on days 1 and 8 of a 21-day cycle.

- ADC of the active metabolite of irinotecan and anti-Trop-2 antibody
- IV administration
- ORR = 34%; PFS = 5.5 months; OS = 12.7 months
- Safety: neutropenia, leukemia, anemia, diarrhea, febrile neutropenia
- Dose: days 1 and 8 of a 21-day cycle

Competitive environment

Sacituzumab govitecan would potentially be the first targeted therapy for TNBC and there is a high unmet need in this subtype of breast cancer.

However, sacituzumab govitecan requires IV administration and data supporting sacituzumab govitecan is only available from an early phase trial. In addition, other products are currently being investigated for the treatment of TNBC, including Tecentriq® (atezolizumab) and Keytruda® (pembrolizumab).

- Advantages: potential first FDA-approved targeted therapy for TNBC, high unmet need
- Disadvantages: IV administration, data only from early phase trial, potential competitors in the pipeline

Expected FDA decision date

The FDA granted fast track and breakthrough designations to sacituzumab govitecan.

An FDA decision regarding the approval of sacituzumab govitecan is expected by January 18, 2019.

- Fast track status
- Breakthrough status
- PDUFA: 1/18/2019

siponimod

Manufacturer: Novartis

Therapeutic use

Siponimod is in development for the treatment of secondary progressive multiple sclerosis (SPMS).

SPMS begins as relapsing-remitting multiple sclerosis (RRMS) but gradually the disease enters a stage of steady deterioration in function, independent of acute attacks or relapses.

Prior to the development of disease modifying therapies for MS, the majority of patients developed SPMS within 20 years.

- Treatment of SPMS

Clinical profile

Siponimod is a selective modulator of the sphingosine 1-phosphate receptor (S1P-R). Siponimod is in the same therapeutic category as Gilenya® (fingolimod), which is a non-selective modulator of the same receptor. The proposed mechanism of action for siponimod is that it binds to the S1P1 sub-receptor on lymphocytes, thereby preventing them from entering the central nervous system of patients with MS.

In a pivotal trial in patients with SPMS, siponimod provided a statistically significant improvement in confirmed disability progression at 3 months vs. placebo (26% vs. 32%; $p = 0.013$). Siponimod delayed the risk of six-month confirmed disability progression by 26% vs. placebo ($p = 0.0058$). Siponimod was also associated with a 55% reduction in the annualized relapse rate ($p < 0.0001$).

Key safety concerns highlighted in the clinical trial were lymphopenia, increased liver transaminase concentration, bradycardia, and bradyarrhythmia at treatment initiation.

In the trial, siponimod was administered orally for once daily use.

- Selective S1P-R modulator
- Oral formulation
- Improvement in confirmed disability progression and the annualized relapse rate vs. placebo
- Safety: lymphopenia, increased liver transaminase concentration, bradycardia
- Dose: once daily

Competitive environment

If approved, siponimod would be the first drug approved for the treatment of SPMS since mitoxantrone, which is rarely used due to the significant safety risks. Siponimod is given orally and only requires once daily dosing.

However, the proposed indication for siponimod is expected to be limited to patients with SPMS, which is a subset of the overall RRMS population. Siponimod did not show a statistically significant improvement in the key secondary endpoints, Timed 25-Foot Walk test and the MS Walking Scale. Finally, siponimod has a similar clinical profile as Gilenya.

For reference, the WAC for Gilenya is $95,000 per year.

- Advantages: potential first approved treatment for SPMS since mitoxantrone (rarely used due to safety concerns), oral, once daily dosing
- Disadvantages: limited indication (SPMS only), no difference vs. placebo for key secondary endpoints, similar clinical profile as Gilenya
- WAC for Gilenya is $95,000 per year

Expected FDA decision date

The FDA granted fast track designation to siponimod.

An FDA decision regarding the approval of siponimod is expected in March 2019.

- Fast track status
- PDUFA: 3/2019

sotagliflozin (Zynquista)

Manufacturers: Sanofi/Lexicon Pharmaceuticals

Therapeutic use

Sotagliflozin is in development, in combination with insulin therapy, to improve glycemic control in adults with type 1 diabetes mellitus (T1DM).

- In combination with insulin therapy, to improve glycemic control in adults with T1DM

Clinical profile

Sotagliflozin inhibits both sodium-glucose co-transporter type 1 (SGLT1) and sodium-glucose co-transporter type 2 (SGLT2). SGLT2 is a transporter responsible for most of the glucose reabsorption performed by the kidney. SGLT1 is a transporter responsible for glucose absorption in the gastrointestinal tract.

Across the clinical trials, sotagliflozin significantly reduced hemoglobin A1c (HbA1c) from baseline at week 24 and 52 vs. placebo ($p < 0.001$). In addition, sotagliflozin significantly increased the proportion of patients who achieved the composite endpoint of HbA1c < 7.0% and no severe hypoglycemia and no diabetic ketoacidosis (DKA) vs. placebo ($p < 0.001$).

The key safety concerns highlighted in the trials were genital mycotic infections, diarrhea, and DKA.

In the trials, sotagliflozin was administered orally once daily.

- SGLT1/SGLT2 inhibitor
- Oral formulation
- Significantly reduced HbA1c from baseline vs. placebo
- Safety: genital mycotic infections, diarrhea, DKA
- Dose: once daily

Competitive environment

Sotagliflozin offers a novel dual MOA for the treatment of diabetes. If approved, it would be the first oral drug approved for T1DM.

However, despite the novel MOA, sotagliflozin was associated with similar adverse reactions to the other SGLT2 inhibitors and the efficacy was modest compared to the HbA1c lowering effect of the class for the treatment of type 2 diabetes mellitus (T2DM). Cardiovascular outcomes data are not yet available for sotagliflozin.

In addition, several other SGLT2 inhibitors are currently available for the treatment of T2DM and have also been studied in late stage trials for T1DM (eg, Farxiga® [dapagliflozin], Jardiance® [empagliflozin]). Based on the data available and indirect comparisons, the different SGLT2 inhibitors appear to have a similar HbA1c lowering effect in patients with T1DM.

For reference, the WAC for the currently available SGLT2 inhibitors ranges from $275 to $670 per prescription.

- Advantages: novel dual mechanism of action, potential first oral drug approved for T1DM
- Disadvantages: similar adverse events as other SGLT2s, modest HbA1c lowering effect, no cardiovascular outcomes data, potential alternatives
- WAC for the currently available SGLT2s is between $275 to $670 per prescription

Expected FDA decision date

An FDA decision regarding the approval of sotagliflozin is expected by March 22, 2019.

- PDUFA: 3/22/2019

tagraxofusp (Elzonris)

Manufacturer: Stemline Therapeutics

Therapeutic use

Tagraxofusp is in development for the treatment of patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN).

BPDCN is a very rare and highly aggressive hematologic malignancy. BPDCN accounts for about 0.7% of all primary cutaneous skin lymphomas. Median overall survival from diagnosis is 8 to 14 months. The skin is the most frequently involved site of the disease and BPDCN usually progresses with bone marrow involvement.

- Treatment of BPDCN

Clinical profile

Tagraxofusp is a targeted therapy directed to the interleukin-3 (IL-3) receptor (CD123), a cell surface receptor expressed on various malignancies. Tagraxofusp is a recombinant fusion protein that links IL-3 to a truncated diphtheria toxin carrier.

In an early phase trial, tagraxofusp demonstrated high response rates in patients with BPDCN. The ORR was 90% in the first-line setting and 69% in the relapsed/refractory setting. In addition, 45% of patients treated in first-line were bridged to stem cell transplant in remission.

The main safety concerns highlighted in the trial included transaminitis, thrombocytopenia, and capillary leak syndrome (CLS). CLS is a disorder characterized by leakage of plasma from blood vessels into neighboring body cavities and muscles which can result in a sharp drop in blood pressure that, if untreated, can lead to organ failure and death.

In the trial, tagraxofusp was administered as an IV infusion for 5 consecutive days in a 21-day cycle for a maximum of 6 cycles.

- Recombinant fusion protein (IL-3 linked to diphtheria toxin carrier)
- IV formulation
- ORR = 90% in first-line setting; 69% in relapsed/refractory cases
- 45% of patients treated in first-line were bridged to stem cell transplant in remission
- Safety: transaminitis, thrombocytopenia, CLS
- Dose: 5 consecutive days of a 21-day cycle (total of 6 cycles)

Competitive environment

There are currently no approved therapies and few drugs in the pipeline for the treatment of BPDCN. The data is from an early stage trial, although the strength of the results suggests likely approval.

CLS is a serious safety concern; however, the risk of complications may be mediated with provider monitoring since this is a known adverse event. Tagraxofusp also requires IV administration.

- Advantages: no approved therapies and few drugs in the pipeline for BPDCN, likely approval despite a lack of late-stage trial results
- Disadvantage: safety concerns, IV administration

Expected FDA decision date

The FDA granted breakthrough and orphan drug designations to tagraxofusp.

An FDA decision regarding the approval of tagraxofusp is expected by February 21, 2019.

- Breakthrough drug status
- Orphan drug status
- PDUFA: 2/21/2019

OptumRx brand pipeline forecast

OptumRx closely monitors and evaluates the pipeline landscape for upcoming brand drug approvals, including both traditional and specialty medications. This report provides a summary of developmental drugs that may be approved in the upcoming two years.

Read more

OptumRx generic pipeline forecast

OptumRx closely monitors and evaluates the pipeline landscape for upcoming first-time generics and biosimilars. This report provides a summary of upcoming first-time generic drugs and biosimilars that may be approved in the upcoming two years.

Read more

OptumRx key pending indications

OptumRx closely monitors and evaluates the pipeline landscape for pending new indications for existing medications. This report provides a summary of key pending new indications that may be approved in the upcoming year.

Read more

Getting acquainted with pipeline forecast terms

Clinical trial phases

Phase I trials	Researchers test an experimental drug or treatment in a small group of people for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.
Phase II trials	The experimental study drug or treatment is given to a larger group of people to see if it is effective and to further evaluate its safety.
Phase III trials	The experimental study drug or treatment is given to large groups of people to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the experimental drug or treatment to be used safely.
Phase IV trials	Post marketing studies delineate additional information including the drug's risks, benefits, and optimal use.

Pipeline acronyms

ANDA	Abbreviated New Drug Application
BLA	Biologic License Application
CRL	Complete Response Letter
FDA	Food and Drug Administration
NME	New Molecular Entity
NDA	New Drug Application
sBLA	Supplemental Biologic License Application
sNDA	Supplemental New Drug Application
OTC Drugs	Over-the-Counter Drugs
PDUFA	Prescription Drug User Fee Act
REMS	Risk Evaluation and Mitigation Strategy

References:

Ablynx Press Release. Ablynx Web site. Ablynx announces positive topline results from the phase III HERCULES study of caplacizumab for the treatment of acquired TTP. http://hugin.info/137912/R/2138418/818605.pdf. October 2, 2017. Accessed October 30, 2018.

Acorda Therapeutics Press Release. Acorda Therapeutics Web site. Acorda announces FDA extends Inbrija NDA review period. http://ir.acorda.com/investors/investor-news/investor-news-details/2018/Acorda-Announces-FDA-Extends-INBRIJA-NDA-Review-Period/default.aspx. September 13, 2018. Accessed October 30, 2018.

Acorda Therapeutics Press Release. Acorda Therapeutics Web site. CVT-301 phase 3 data showed significantly improved motor function during OFF periods in Parkinson's disease. http://ir.acorda.com/investors/investor-news/investor-news-details/2017/CVT-301-Phase-3-Data-Showed-Significantly-Improved-Motor-Function-During-OFF-Periods-in-Parkinsons-Disease/default.aspx. June 5, 2017. Accessed October 30, 2018.

Alexion Press Release. Alexion Web site. Alexion announces positive top-line results showing successful phase 3 clinical study of ALXN1210 in complement inhibitor treatment-naïve patients with paroxysmal nocturnal hemoglobinuria (PNH). https://news.alexion.com/press-release/product-news/alexion-announces-positive-top-line-results-showing-successful-phase-3-cl. March 15, 2018. Accessed October 30, 2018.

Alexion Press Release. Alexion Web site. Alexion reports first quarter 2018 results and positive topline data from ALXN1210 phase 3 PNH switch study. https://news.alexionpharma.com/press-release/financial-news/alexion-reports-first-quarter-2018-results-and-positive-topline-data-al. April 28, 2018. Accessed October 30, 2018.

Alexion Press Release. Alexion Web site. FDA accepts priority review of ALXN1210 as a treatment for patients with paroxysmal nocturnal hemoglobinuria (PNH) in the US. https://news.alexion.com/press-release/product-news/fda-accepts-priority-review-alxn1210-treatment-patients-paroxysmal-noctur. August 20, 2018. Accessed October 30, 2018.

Alkermes Press Release. Alkermes Web site. Alkermes announces FDA acceptance for review of New Drug Application for ALKS 5461 for the adjunctive treatment of major depressive disorder. http://phx.corporate-ir.net/phoenix.zhtml?c=92211&p=irol-newsArticle&ID=2342624. April 16, 2018. Accessed October 30, 2018.

Alkermes Press Release. Alkermes Web site. Alkermes reports on outcome of FDA Advisory Committee Meeting on ALKS 5461 for the adjunctive treatment of major depressive disorder. http://phx.corporate-ir.net/phoenix.zhtml?c=92211&p=irol-corporateNewsArticle&ID=2375026. November 1, 2018. Accessed November 5, 2018.

AMAG Pharmaceuticals Press Release. AMAG Pharmaceuticals Web site. AMAG Pharmaceuticals announces FDA acceptance of New Drug Application filing for bremelanotide. http://ir.amagpharma.com/news-releases/news-release-details/amag-pharmaceuticals-announces-fda-acceptance-new-drug-0. June 4, 2018. Accessed October 30, 2018.

BioMedTracker Drug Intelligence Platform. BioMedTracker Web site. http://www.biomedtracker.com/.

EMD Serono Press Release. EMD Serono Web site. FDA accepts file for cladribine tablets as potential treatment for relapsing forms of multiple sclerosis. http://media.emdserono.com/press_releases?item=122706. July 30, 2018. Accessed October 30, 2018.

Fava M, Thase ME, Trivedi MH, et al. Opioid system modulation with buprenorphine/samidorphan combination for major depressive disorder: two randomized controlled studies. Mol Psychiatry 2018. [Epub ahead of print]

Genetic and Rare Diseases Information Center (GARD). Diseases: hemophagocytic lymphohistiocytosis. GARD Web site. https://rarediseases.info.nih.gov/diseases/6589/hemophagocytic-lymphohistiocytosis. Last updated September 11, 2017. Accessed October 30, 2018.

Giovannoni G, Comi G, Cook S, et al; CLARITY Study Group. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. N Engl J Med. 2010;362(5):416-26.

Immunomedics Press Release. Immunomedics Web site. FDA accepts biologics license application for filing and grants priority review for sacituzumab govitecan for the treatment of metastatic triple-negative breast cancer. https://www.immunomedics.com/our-company/news-and-events/fda-accepts-biologics-license-application-for-filing-and-grants-priority-review-for-sacituzumab-govitecan-for-the-treatment-of-metastatic-triple-negative-breast-cancer/. July 18, 2018. Accessed October 30, 2018.

Immunomedics Press Release. Immunomedics Web site. Immunomedics announces updated results with sacituzumab govitecan (IMMU-132) in patients with relapsed or refractory metastatic triple-negative breast cancer (mTNBC). https://www.immunomedics.com/our-company/news-and-events/immunomedics-announces-updated-results-sacituzumab-govitecan-immu-132-patients-relapsed-refractory-metastatic-triple-negative-breast-cancer-mtnbc/. December 6, 2017. Accessed October 30, 2018.

Kappos L, Bar-Or A, Cree BAC, et al; EXPAND Clinical Investigators. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. Lancet. 2018;391(10127):1263-1273.

Lexicon Pharmaceuticals Press Release. Lexicon Pharmaceuticals Web site. FDA to review Zynquista™ (sotagliflozin) as potential treatment for type 1 diabetes. http://www.lexpharma.com/media-center/news/673-fda-to-review-zynquista-sotagliflozin-as-potential-treatment-for-type-1-diabetes. May 22, 2018. Accessed October 30, 2018.

Lexicon Pharmaceuticals Press Release. Lexicon Pharmaceuticals Web site. Lexicon Pharmaceuticals announces positive 52-week results from sotagliflozin inTandem1 study presented at ADA 2018 and published in diabetes care. http://www.lexpharma.com/media-center/news/677-lexicon-pharmaceuticals-announces-positive-52-week-results-from-sotagliflozin-intandem1-study-presented-at-ada-2018-and-published-in-diabetes-care. June 24, 2018. Accessed October 30, 2018.

Lexicon Pharmaceuticals Press Release. Lexicon Pharmaceuticals Web site. Lexicon Pharmaceuticals announces positive 52-week results from sotagliflozin inTandem2 study presented at ADA 2018 and published in diabetes care. http://www.lexpharma.com/media-center/news/676-lexicon-pharmaceuticals-announces-positive-52-week-results-from-sotagliflozin-intandem2-study-presented-at-ada-2018-and-published-in-diabetes-care. June 23, 2018. Accessed October 30, 2018.

Lexicon Pharmaceuticals Press Release. Lexicon Pharmaceuticals Web site. Sotagliflozin data from pivotal inTandem1 and inTandem2 studies in patients with type 1diabetes presented at ADA 2017. http://www.lexpharma.com/media-center/news/638-sotagliflozin-data-from-pivotal-intandem1-and-intandem2-studies-in-patients-with-type-1-diabetes-presented-at-ada-2017. June 10, 2017. October 30, 2018.

Novartis Press Release. Novartis Web site. Novartis announces FDA and EMA filing acceptance of siponimod, the first and only drug shown to meaningfully delay disability progression in typical SPMS patients. https://www.novartis.com/news/media-releases/novartis-announces-fda-and-ema-filing-acceptance-siponimod-first-and-only-drug-shown-meaningfully-delay-disability-progression-typical-spms-patients. October 8, 2018. Accessed October 30, 2018.

Novartis Press Release. Novartis Web site. Phase III data in The Lancet show Novartis siponimod significantly improves outcomes in patients with secondary progressive MS. https://www.novartis.com/news/media-releases/phase-iii-data-lancet-show-novartis-siponimod-significantly-improves-outcomes-patients-secondary-progressive-ms. March 23, 2018. Accessed October 30, 2018.

Novimmune Press Release. Novimmune Web site. FDA accepts emapalumab Biologics License Application with priority review. https://www.novimmune.com/en/swiss-biopharmaceutical-company/news/2018/fda-accepts-emapalumab-biologics-license-application-priority-review.html. May 28, 2018. Accessed October 30, 2018.

Palatin Technologies Press Release. Palatin Technologies Web site. Bremelanotide meets co-primary endpoints in Palatin's phase 3 trials for hypoactive sexual desire disorder. https://www.irdirect.net/prviewer/release/id/2174818. November 1, 2016. Accessed October 30, 2018.

Sanofi Press Release. Sanofi Web site. Cablivi™ (caplacizumab) approved in Europe for adults with acquired thrombotic thrombocytopenic purpura (aTTP). http://hugin.info/152918/R/2213684/863478.pdf. September 3, 2018. Accessed October 30, 2018.

Stemline Therapeutics Press Release. Stemline Therapeutics Web site. Stemline announces positive clinical data from three Elzonris (tagraxofusp; SL-401) trials. https://www.stemline.com/newsArticleDetails.asp?id=195. June 18, 2018. Accessed October 30, 2018.

Stemline Therapeutics Press Release. Stemline Therapeutics Web site. Stemline Therapeutics announces that FDA accepts Elzonris™ Biologics License Application (BLA) and grants priority review. https://ir.stemline.com/news-releases/news-release-details/stemline-therapeutics-announces-fda-accepts-elzonristm-biologics. August 13, 2018. Accessed October 30, 2018.

Sumitomo Dainippon Pharma Press Release. Sumitomo Dainippon Pharma Web site. Sunovion announces positive topline results from pivotal study of apomorphine sublingual film (APL-130277) in patients with Parkinson's disease. https://www.ds-pharma.com/ir/news/pdf/ene20180130.1.pdf. January 29, 2018. Accessed October 30, 2018.

Sunovion Press Release. Sunovion Web site. Sunovion announces FDA acceptance of New Drug Application for apomorphine sublingual film (APL-130277). https://news.sunovion.com/press-release/sunovion-announces-fda-acceptance-new-drug-application-apomorphine-sublingual-film. June 12, 2018. Accessed October 30, 2018.

UpToDate Database. https://www.uptodate.com/.

optum.com/optumrx

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