OPTUMRx®

RxOutlook®

2nd Quarter 2018

Pending drug approvals

Drug Name	Manufacturer	Indication/Use	Expected FDA Decision Date
dasotraline	Sumitomo Dainippon	Attention deficit hyperactivity disorder	3Q2018
galcanezumab	Eli Lilly/Arteaus	Migraine prophylaxis	3Q2018
inotersen	Ionis Pharmaceuticals	Transthyretin amyloidosis	7/6/2018
ivosidenib	Agios Pharmaceuticals	Acute myeloid leukemia	8/21/2018
lanadelumab	Shire	Hereditary angioedema	8/26/2018
lofexidine	US WorldMeds	Opioid withdrawal	5/26/2018
lorlatinib	Pfizer	Non-small cell lung cancer	8/29/2018
lusutrombopag	Shionogi	Thrombocytopenia	8/26/2018
migalastat	Amicus/ GlaxoSmithKline	Fabry disease	8/13/2018
moxetumomab pasudotox	AstraZeneca	Hairy cell leukemia	3Q2018
patisiran	Alnylam/Arbutus/ Ionis/Sanofi	Transthyretin amyloidosis	8/11/2018
plazomicin	Achaogen/Ionis	Urinary tract infections, bloodstream infections	6/25/2018
volanesorsen	Akcea	Familial chylomicronemia syndrome	8/30/2018

dasotraline

Manufacturer: Sumitomo Dainippon

Therapeutic use

Dasotraline is in development for the treatment of attention deficit hyperactivity disorder (ADHD) in children, adolescents and adults.

- Treatment of ADHD

Clinical profile

Dasotraline is an oral dual dopamine and norepinephrine reuptake inhibitor (DNRI).

- DNRI
- Oral formulation

Dasotraline was evaluated in three trials: one in adults and two in children 6 – 12 years of age. At week 8, the adult trial did not show a statistically significant improvement in ADHD symptoms vs. placebo at either a 4 mg or 6 mg daily dose. The first pediatric study evaluated dasotraline 2 mg and 4 mg daily doses against placebo and found that only the 4 mg strength produced an improvement in ADHD symptoms at week 6 as compared to baseline ($p < 0.0001$). Similarly, a 2 week study in children using only a 4 mg dose vs. placebo also found a statistically significant improvement in ADHD symptoms, using a different measurement instrument than the first pediatric trial ($p < 0.0001$).

- Failed to achieve statistical significance vs. placebo in adult patients
- Greater improvement in ADHD symptoms vs. placebo in two pediatric trials

Common adverse events in the trials included insomnia, headache, dry mouth, decrease appetite, anxiety, decrease in weight, affect lability (rapid change in emotion), and irritability.

- Common adverse events: insomnia, headache, dry mouth, decrease appetite, anxiety, decrease in weight, affect lability, and irritability

In the trials, dasotraline was given orally once daily.

- Dose: once daily

Continued…

dasotraline (continued...)

Competitive environment

Dasotraline presents an additional once-daily, oral option for ADHD patients who may not wish to use central nervous system (CNS) stimulants, cannot tolerate the adverse effects of CNS stimulants, or who may have concerns about diversion. Dasotraline's extended half-life also potentially makes it a good option for patients who require a longer duration of coverage than current long-acting CNS stimulants.

However, in pivotal trials, dasotraline did not meet its efficacy endpoint for the adult population. Practice guidelines for ADHD currently recommend use of CNS stimulants over non-CNS stimulants as first-line therapy due to their superior efficacy and acceptable safety profile. Finally, generic treatment options for ADHD (CNS stimulants and non-CNS stimulants alike) are readily and affordably available.

The projected annual U.S. sales for dasotraline are between $76 – $261 million by 2020.

- Advantages: additional non-CNS stimulant treatment option, extended duration of action
- Disadvantages: efficacy concerns in adults, guidelines currently prefer CNS stimulants, availability of generic alternatives
- Projected annual U.S. sales = $76 – $261 million by 2020

Expected FDA decision date

An FDA decision regarding the approval of dasotraline is expected by the third quarter of 2018.

- PDUFA: 3Q2018

galcanezumab

Manufacturers: Eli Lilly/Arteaus

Therapeutic use

Galcanezumab is in development for the prevention of migraines in adult patients.

- Prevention of migraines in adults

Clinical profile

Galcanezumab is a humanized monoclonal antibody and represents a new class of medication known as calcitonin gene-related peptide (CGRP) antagonists. Galcanezumab disrupts the CGRP signaling pathway, which has been implicated in migraine vasodilation and pain.

Galcanezumab was evaluated in studies for prevention of both episodic and chronic migraines. In two trials for episodic migraine, greater reductions in the mean number of monthly migraine headache days (MHD) were achieved with galcanezumab vs. placebo (-4.6 to -4.7 days vs. -2.8 days, $p < 0.001$; -4.2 to -4.3 days vs. 2.3 days, $p < 0.001$). In addition, between 56.5% – 62.3% of galcanezumab patients achieved at least a 50% reduction in monthly MHD vs. 36.0% – 38.6% of placebo patients ($p < 0.001$).

A similar improvement was seen in the chronic migraine trial (-4.62 to -4.83 days vs. -2.74 days, $p < 0.001$), with 27.6% of galcanezumab patients experiencing at least a 50% reduction in monthly MHD vs. 15.4% of placebo patients ($p < 0.001$). Furthermore, a greater reduction in monthly headache days with acute medication use was observed in the chronic migraine population (-4.3 days vs. -2.2 days, $p< 0.001$).

Common adverse events reported in the trials included injection site reactions such as pruritus and erythema, and sinusitis.

Galcanezumab was evaluated as a once-monthly subcutaneous (SC) injection at two doses: 120mg and 240mg.

- CGRP antagonist
- SC formulation
- Greater reduction in mean monthly migraine days vs. placebo in episodic and chronic migraine patients
- Common adverse events: injection site reactions and sinusitis
- Dose: once monthly

Competitive environment

Galcanezumab represents a new class of medication for the prevention of migraines, and may fulfill an important niche in the treatment of patients insufficiently managed on or resistant to current prophylactic therapy. Galcanezumab is dosed just once monthly, may be self-administered by the patient, and has demonstrated efficacy in migraine prevention.

However, galcanezumab is administered via SC injection, which can present a barrier to some patients. Additionally, other CGRPs with similar efficacy data will likely be on the market by the time galcanezumab launches – ie, erenumab (Amgen) and fremanezumab (Teva). Long-term safety data for galcanezumab is currently unknown, despite the expected chronic nature of use. Like other monoclonal antibodies, galcanezumab could carry a high drug cost.

Analysts expect the annual cost for galcanezumab to fall between $8,500 – $20,000.

- Advantages: first in-class, useful option for treatment-resistant patients, infrequent dosing, self-administered
- Disadvantages: SC injection, long-term safety unknown, potential high cost
- Projected annual cost = $8,500 – $20,000

Continued…

galcanezumab (continued...)

Expected FDA decision date

An FDA decision regarding the approval of galcanezumab is expected by the third quarter of 2018.

- PDUFA: 3Q2018

inotersen

Manufacturer: Ionis Pharmaceuticals

Therapeutic use

Inotersen is in development for the treatment of patients with hereditary transthyretin amyloidosis (hATTR) with polyneuropathy.

Caused by a mutation in the transthyretin (TTR) gene, hATTR is a rare genetic condition that results in misfolding of the resultant TTR protein and buildup of abnormal protein deposits. The disease affects 10,000-50,000 people worldwide, and typically manifests in the central nervous system, heart, or peripheral nervous system, where it causes polyneuropathy.

No disease-modifying therapies are available in the U.S. for this condition. However, because TTR is produced in the liver, liver transplantation may be an option for some patients.

- Treatment of patients with hATTR with polyneuropathy

Clinical profile

Inotersen is an antisense RNA modulator designed to reduce the production of mutated TTR by inhibiting gene expression.

Inotersen was evaluated in one trial against placebo. The primary endpoint was improvement in neuropathy as measured by two patient-reported outcome measures: the Norfolk Quality of Life Questionnaire-Diabetic Neuropathy (Norfolk QoL-DN), and the Modified Neuropathy Impairment Score +7 (mNIS+7). At the end of 65 weeks, a significantly larger improvement was seen in the inotersen group vs. placebo for both endpoints (Norfolk QoL-DN: mean difference = 11.68, $p = 0.036$; and mNIS+7: mean difference = 19.73, $p < 0.0001$). A 12-month open-label extension (OLE) of this study appears to confirm extended benefit with continued use, and no additional safety concerns were identified outside of those already observed.

Common adverse events reported in the trial included thrombocytopenia, nausea, pyrexia, chills, vomiting, and anemia. A safety signal for thrombocytopenia and renal dysfunction was noted in the trials, with one drug-related fatality due to intracranial hemorrhage.

In the trials, inotersen was given as 300 mg SC three times on alternate days for the first week, followed by once weekly dosing thereafter.

- Antisense RNA modulator
- SC formulation
- Greater improvement in neuropathy vs. placebo
- Common adverse events: thrombocytopenia, nausea, pyrexia, chills, vomiting, and anemia
- Dose: once weekly

Continued…

inotersen(continued...)

Competitive environment

No FDA-approved therapies for this rare condition are currently available. Therefore, inotersen would represent the first potential disease-modifying treatment available to patients in the U.S. SC administration is typically a drawback, but may be a benefit here since patisiran (see below), the other hATTR treatment option currently under FDA consideration, is administered via the intravenous (IV) route. Moreover, inotersen is expected to be formulated for self-administration.

The OLE results seem to confirm long-term benefit of the therapy without any new safety signals. Nonetheless, safety signals identified during the trial relating to thrombocytopenia and renal dysfunction are concerning, especially as there was one drug-related death.

The projected annual U.S. sales for inotersen are $96 million by 2020.

- Advantages: first in-class treatment for a rare disease with no true alternatives, self-administered SC injection, OLE appears to confirm long-term benefit
- Disadvantages: safety signals for thrombocytopenia and renal dysfunction
- The projected annual U.S. sales are $96 million by 2020

Expected FDA decision date

The FDA granted inotersen fast track and orphan drug status.

The FDA also granted inotersen a priority review, and a decision regarding its approval is expected by 7/6/2018.

- Fast track status
- Orphan drug status
- Priority review
- PDUFA: 7/6/2018

ivosidenib

Manufacturer: Agios Pharmaceuticals

Therapeutic use

Ivosidenib is in development for the treatment of patients with relapsed or refractory (R/R) acute myeloid leukemia (AML) with an isocitrate dehydrogenase 1 (IDH1) mutation.

AML has an incidence of 21,000 in the U.S., of which an estimated 6% – 10% will have an IDH1 mutation.

- Treatment of R/R AML with IDH1 mutation

Clinical profile

Ivosidenib is an oral IDH1 inhibitor that prevents mutated IDH1 enzymes from producing an oncogenic metabolite, 2-hydroxyglutarate.

Ivosidenib was evaluated in one open-label, uncontrolled Phase 1 dose-escalation and expansion study. The primary efficacy endpoint was the composite of complete response (CR) and CR with partial hematologic recovery (CRh). For the 125 R/R AML patients who received 500 mg of ivosidenib daily, the rate of CR plus CRh was 30.4% [95% CI: 22.5, 39.3]. Evaluating each component of the composite endpoint separately, the CR rate was 21.6% [95% CI: 14.7, 29.8], and the CRh rate was 8.8% (no 95% CI was provided).

For comparison, Idhifa® (enasidenib), which is indicated in AML patients with the IDH2 mutation, reported a combined CR/CRh rate of 23% and a median duration of response of 8.2 months. In contrast, the CR/CRh rate for ivosidenib was 30.4% and achieved a comparable median duration of response of 8.2 months.

Common adverse events reported in the trial included diarrhea, leukocytosis, nausea, fatigue, and febrile neutropenia. Safety concerns with grade 3 or higher leukocytosis, QT prolongation, and IDH-differentiation syndrome (IDH-DS) were identified.

As this was a dose-escalation study, increasing doses of ivosidenib were administered in the trial. However, for the population evaluated for efficacy, patients received 500 mg orally once daily.

- IDH1 inhibitor
- Oral formulation
- CR plus CRh rate = 30.4%
- Common adverse events: diarrhea, leukocytosis, nausea, fatigue, and febrile neutropenia
- Dose: once daily

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ivosidenib (continued...)

Competitive environment

There is currently no IDH1 mutation-specific treatment option for AML. Ivosidenib presents a good option for those patients who may have failed traditional chemotherapy (commonly cytarabine and an anthracycline, such as daunorubicin). As compared to traditional chemotherapy, which is administered IV, ivosidenib is a once daily oral medication.

However, trials did reveal safety concerns including IDH-DS, for which the IDH2 inhibitor Idhifa carries a boxed warning. Also, efficacy data for ivosidenib is limited as data is based upon a phase 1, uncontrolled, unblinded trial.

The projected annual U.S. sales for ivosidenib are $47 million by 2020.

- Advantages: first IDH-1 targeted medication, oral daily formulation
- Disadvantages: limited clinical data, safety concerns (ie, leukocytosis, QT prolongation, IDH-DS)
- Projected U.S. annual sales are $47 million by 2020

Expected FDA decision date

The FDA granted ivosidenib fast track status, orphan drug designation, and priority review.

An FDA decision regarding the approval of ivosidenib is expected by 8/11/2018.

- Fast track status
- Orphan drug status
- Priority review
- PDUFA: 8/11/2018

lanadelumab

Manufacturer: Shire

Therapeutic use

Lanadelumab is in development for the prevention of angioedema attacks in patients 12 years and older with hereditary angioedema (HAE).

HAE is caused by a genetic defect in the C1 esterase inhibitor protein, which can lead to attacks of sudden swelling of the extremities, intestines, face, and airways. It is estimated to affect 1 in every 10,000 to 50,000 people worldwide.

- Prevention of angioedema attacks in patients 12 years and older with HAE

Clinical profile

Lanadelumab is a monoclonal antibody that specifically binds and inhibits plasma kallikrein. There is currently a non-antibody protein inhibitor of kallikrein, Kalbitor® (ecallantide), that is approved for treatment of acute HAE attacks. Two human C1esterase inhibitors are currently indicated for the prevention of angioedema attacks: Cinryze® (human C1 esterase inhibitor), and Haegarda® (human C1 esterase inhibitor).

In a pivotal trial, several doses of lanadelumab given either every 2 or 4 weeks were evaluated against placebo in patients 12 years and older with HAE. The primary endpoint was the number of HAE attacks per week observed in each treatment arm vs. placebo between days 14 and 182 of the 26 week trial. Overall, the change in HAE attack frequency vs. placebo was -76% for lanadelumab 150 mg every 4 weeks ($p < 0.001$), -87% for 300 mg every 2 weeks ($p < 0.001$), and -73% for 300 mg every 4 weeks ($p < 0.001$).

Common adverse events reported in the trial were injection site pain, viral upper respiratory tract infections, headache, injection site erythema, injection site bruising, and dizziness.

As noted above, lanadelumab was dosed every 2 or 4 weeks in the various arms of the pivotal trial.

- Kallikrein inhibitor
- SC formulation
- 73% to 87% greater reduction in HAE attacks vs. placebo, depending on dose and frequency of lanadelumab
- Common adverse events: injection site pain, viral upper respiratory tract infections, headache, injection site erythema, injection site bruising, and dizziness
- Dose: every 2 or 4 weeks

Competitive environment

If approved, lanadelumab will be the first kallikrein inhibitor available for prevention of HAE attacks. Additionally, the dosing of lanadelumab is less frequent than other preventative agents available such as Cinryze or Haegarda, which require administration every 3 or 4 days.

Despite these advantages, lanadelumab has no long-term safety data in chronic treatment. Like most monoclonal antibodies, lanadelumab is expected to be a high cost specialty medication. It is also expected to be marketed as a solution for injection in a vial, with no prefilled syringe or auto-injector formulation.

The projected annual U.S. sales for lanadelumab are $263 million by 2020.

- Advantages: first SC kallikrein inhibitor for prevention of HAE attacks, infrequent dosing
- Disadvantages: long-term safety unknown, potential high cost, no prefilled syringe or auto-injector
- Projected annual U.S. sales are $263 million by 2020

Continued…

lanadelumab (continued...)

Expected FDA decision date

The FDA granted lanadelumab fast track status, breakthrough therapy status, orphan drug designation, and priority review.

An FDA decision regarding the approval of lanadelumab is expected by 8/26/2018.

- Fast track status
- Breakthrough therapy
- Orphan drug status
- Priority review
- PDUFA: 8/26/2018

lofexidine

Manufacturer: US WorldMeds

Therapeutic use

Lofexidine is in development to mitigate symptoms associated with opioid withdrawal and facilitate completion of opioid discontinuation treatment.

- Mitigate symptoms associated with opioid withdrawal and facilitate completion of opioid discontinuation treatment

Clinical profile

Lofexidine is an oral alpha-2-receptor agonist believed to have a high affinity for alpha-2A receptor subtypes.

Lofexidine was evaluated in two phase 3 placebo-controlled trials. The manufacturer has stated that in one of the two trials, lofexidine met the primary efficacy endpoint of reduction in withdrawal symptoms associated with opiate detoxification vs. placebo. However, results of the second study have not been released.

Some adverse events including syncope, bradycardia, and hypotension were associated with lofexidine use, particularly at the higher dose of 3.2 mg daily. However, detailed safety and efficacy results from either study have not been published in journals or press releases and do not appear available at this time.

The trials dosed lofexidine at 2.4 mg or 3.2 mg daily, divided into four daily doses administered as 0.2 mg tablets.

- Alpha-2-receptor antagonist
- Oral formulation
- Reduced withdrawal symptoms vs. placebo
- Dose: four times daily

Competitive environment

If approved, lofexidine would be the first non-narcotic with an FDA-approved indication for opioid withdrawal. In theory, the selectivity of lofexidine for the alpha-2A receptor subtype could decrease the hypotension risk compared to other alpha-2 agonists such as clonidine, which is used off-label for this indication and carries the American Society of Addiction Medicine guideline support.

However, lofexidine has a high pill burden and frequent dosing. Additionally, lofexidine does not have evidence of superiority over clonidine, which is available generically. Finally, some safety concerns for syncope and bradycardia were noted, especially with the higher dose of lofexidine.

- Advantages: potential first FDA-approved non-narcotic for opioid withdrawal indication, theoretically lower risk of hypotension vs. clonidine
- Disadvantages: high pill burden, frequent dosing, no evidence of superiority over clonidine, higher cost than alternatives, potential safety concerns

Expected FDA decision date

The FDA granted lofexidine fast track status and priority review.

An FDA decision regarding the approval of lofexidine is expected by 5/20/2018.

- Fast track status
- Priority review
- PDUFA: 5/20/2018

lorlatinib

Manufacturer: Pfizer

Therapeutic use

Lorlatinib is in development for the treatment of patients with anaplastic lymphoma kinase (ALK) positive metastatic non-small cell lung cancer (NSCLC) previously treated with one or more ALK tyrosine kinase inhibitors (TKIs).

- Treatment of ALK-positive metastatic NSCLC previously treated with one or more ALK TKIs

Clinical profile

Lorlatinib is an ALK TKI developed with the goal of overcoming resistance to first- and second-generation ALK-targeted therapies, as well as to penetrate the blood-brain barrier in order to treat brain metastases. Approximately 3% – 7% of NSCLC patients have the ALK translocation that makes them a candidate for therapy with an ALK TKI. Currently, treatment consists of either the first-generation TKI, Xalkori® (crizotinib), or a second-generation TKI, such as Alecensa® (alectinib) or Alunbrig® (brigatinib).

While a phase 3 trial is underway, the study used to support FDA submission of lorlatinib was an open-label phase 1/2 clinical trial. Lorlatinib was evaluated in five different treatment arms with the primary endpoints of objective response rate (ORR) and intracranial ORR (IC-ORR). Response rates varied between treatment arms. For the more difficult-to-treat population of ALK positive patients previously treated with a non-crizotinib ALK inhibitor, an ORR of 33% [95% CI: 16, 54] and IC-ORR of 42% [95% CI: 15, 72] was observed. For treatment naïve ALK positive patients, an ORR of 90% [95% CI: 74, 98] and IC-ORR of 75% [95% CI: 35, 97] was observed.

Common adverse events reported in the trial included hypercholesterolemia (81%), hypertriglyceridemia (60%), edema (43%), peripheral neuropathy (30%), increased weight (18%), cognitive effects (18%), mood effects (15%), fatigue (13%), diarrhea (!1%), arthralgia (10%), and increased aspartate transaminase (AST) (10%).

For the efficacy evaluation presented above, lorlatinib was given as 100 mg orally once daily.

- ALK TKI
- Oral formulation
- ORR = 33% to 90%
- IC-ORR = 42% to 75%
- Common adverse events: hypercholesterolemia, hypertriglyceridemia, edema, peripheral neuropathy, weight increase, cognitive effects, mood effects, fatigue, diarrhea, arthralgia, and increased AST
- Dose: once daily

Continued…

lorlatinib (continued...)

Competitive environment

Resistance to ALK inhibitors can develop in NSCLC patients, and lorlatinib represents a new option for resistant NSCLC. The manufacturer states that lorlatinib was designed to inhibit mutations that drive resistance to currently available therapies, making it useful as a second- or third-line agent. Intracranial penetration allows lorlatinib to potentially treat brain metastases, unlike Xalkori.

However, lorlatinib was evaluated in an open-label phase 1/2 clinical trial without results from a control group, providing limited clinical data. Also, significant rates of adverse events raise safety concerns.

For reference, the average monthly wholesale acquisition cost (WAC) for Alecensa is $14,511. The average monthly WAC for Alunbrig is $15,533.

- Advantages: option for resistant NSCLC, potentially more effective than first- or second-generation TKIs, intracranial penetration
- Disadvantages: limited clinical data, safety concerns
- Average monthly WAC (Alecensa) ~$14,511
- Average monthly WAC (Alunbrig) ~$15,533

Expected FDA decision date

The FDA granted lorlatinib breakthrough therapy status and priority review.

An FDA decision regarding the approval of lorlatinib is expected by 8/29/2018.

- Breakthrough therapy
- Priority review
- PDUFA: 8/29/2018

lusutrombopag

Manufacturer: Shionogi

Therapeutic use

Lusutrombopag is in development for the treatment of thrombocytopenia in patients with chronic liver disease (CLD) who are at increased risk for bleeding associated with invasive procedures.

Thrombocytopenia, or low platelet count, is a common complication of CLD, occurring in up to 78% of patients with cirrhosis, and 6% of those without cirrhosis. The risk for excess bleeding during procedures may be elevated in patients with thrombocytopenia.

- Treatment of thrombocytopenia in patients with CLD who are at increased risk for bleeding associated with invasive procedures

Clinical profile

Lusutrombopag is a thrombopoietin receptor agonist (TRA) that promotes production of platelets, similar to Promacta® (eltrombopag). Promacta is indicated for several non-procedural indications including chronic immune thrombocytopenia, thrombocytopenia in chronic hepatitis C patients, and aplastic anemia in patients who have had insufficient response to immunosuppressive therapy.

Two pivotal trials support the new drug application (NDA) submission for lusutrombopag, but only one was conducted in the U.S. and has available data. The primary endpoint of the trial was the proportion of patients who required no platelet transfusion prior to procedure and no rescue therapy from bleeding. The lusutrombopag group had 64.8% of patients meet the primary endpoint vs. 29.0% in the placebo group ($p < 0.0001$).

Treatment-emergent adverse events (TEAEs) were noted in 47.7% of lusutrombopag patients vs. 48.6% of placebo patients. Adverse events deemed treatment-related occurred in 5.6% of lusutrombopag patients vs. 12.1% of placebo. In addition, there were 3 total portal vein thrombosis events (1 in treatment group and 2 in placebo), and 9 total bleeding-related TEAEs (3 in treatment group and 6 in placebo).

In the trials, lusutrombopag was dosed at 3 mg orally daily for 4 – 7 days, starting 9 – 14 days before an invasive procedure.

- TRA
- Oral formulation
- Greater number of patients did not require platelet transfusions or any rescue therapy from bleeding vs. placebo
- Notable adverse events included portal vein thrombosis and bleeding
- Dose: once daily for 4-7 days

Continued…

lusutrombopag (continued...)

Competitive environment

There is no current treatment available specifically for pre-procedural thrombocytopenia in CLD patients. If approved, lusutrombopag could be the first such therapy. Lusutrombopag also offers a relatively short oral course of therapy for prevention of bleeding prior to an invasive procedure.

However, while Promacta does not share an indication with lusutrombopag, it is already on the market and could be used off-label for pre-procedural thrombocytopenia. Additionally, avatrombopag is also under FDA review and seeking a similar indication to lusutrombopag, and could reach the market prior to the approval of lusutrombopag. Specific safety data are also not currently available for lusutrombopag.

For reference, the average monthly WAC for Promacta is approximately $7,400.

- Advantages: potential first treatment for procedural thrombocytopenia, short course oral therapy
- Disadvantage: competitors in Promacta and potentially avatrombopag, limited adverse event data
- Average monthly WAC (Promacta) is ~$7,400

Expected FDA decision date

The FDA granted lusutrombopag fast track status and priority review.

An FDA decision regarding the approval of lusutrombopag is expected by 8/26/2018.

- Fast track status
- Priority review
- PDUFA: 8/26/2018

migalastat

Manufacturers: Amicus/GlaxoSmithKline

Therapeutic use

Migalastat is in development for the treatment of patients at least 16 years of age with Fabry disease who have amenable genetic mutations.

Fabry disease is an X-linked lysosomal storage disorder due to α-galactosidase deficiency that causes a buildup of globotriaosylceramide (GL3). It affects about 1,500 people in the U.S, and symptoms are varied and can include kidney damage, heart attack, and skin conditions. Current standard of care includes IV infusions of recombinant α-galactosidase enzyme in order to replace the patient's deficiency. This is known as enzyme replacement therapy (ERT).

- Treatment of patients at least 16 years of age with Fabry disease who have amenable genetic mutations

Clinical profile

Migalastat is an oral pharmacologic chaperone that stabilizes specific mutant forms of α-galactosidase, increasing enzyme trafficking to lysosomes.

There were two trials performed. In a 6-month placebo-controlled trial, migalastat failed the primary endpoint of ≥ 50% mean change in GL-3 ($p = 0.30$). The second trial evaluated renal function changes over 18 months in patients converted from ERT to migalastat. Primary endpoints were estimated glomerular filtration rate (eGFR) and measured glomerular filtration rate (GFR) by iohexol clearance. Migalastat and ERT showed comparable effects on renal function. In addition, left ventricular mass index decreased significantly with migalastat but showed no change with ERT. Predefined renal, cardiac, and cerebrovascular events occurred in 29% of migalastat patients vs. 44% of ERT patients.

Adverse events occurred at comparable frequency between treatment and placebo groups, and included nasopharyngitis, headache, and bronchitis.

In the trials migalastat was dosed as 150 mg every other day.

- Pharmacologic chaperone
- Oral formulation
- Did not meet endpoint of GL-3 reduction vs. placebo
- Comparable effects on renal function to ERT
- Common adverse events: nasopharyngitis, headache, and bronchitis
- Dose: every other day

Competitive environment

If approved, migalastat would be the first molecular chaperone for the treatment of Fabry disease. It would not only have a novel mechanism of action, but also be the first oral therapy option for Fabry disease; Fabrazyme® is currently the only FDA-approved medication for Fabry disease, but is administered intravenously. Also, based on clinical trials, the safety profile appears to be favorable.

However, the efficacy of migalastat is in question due to failure of the first pivotal trial. Although it did meet the endpoint of renal function in the ERT switch trial, renal function is a surrogate endpoint and may not reflect migalastat's ability to improve disease outcome. Finally, use of migalastat is for ~ 35% – 50% of Fabry disease patients that have a mutation that is amenable to treatment, thus not all Fabry patients may benefit from therapy with migalastat.

For reference, the monthly WAC for Fabrazyme® is approximately $65,251.

- Advantages: first chaperone for disease, oral formulation, good safety profile
- Disadvantages: questionable efficacy, only treats subset of population
- Monthly WAC (Fabrazyme) ~$65,251

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migalastat (continued...)

Expected FDA decision date

The FDA granted migalastat fast track status, orphan drug designation, and priority review.

An FDA decision regarding the approval of migalastat is expected by 8/13/2018.

- Fast track status
- Orphan drug status
- Priority review
- PDUFA: 8/13/2018

moxetumomab pasudotox

Manufacturer: AstraZeneca

Therapeutic use

Moxetumomab pasudotox is in development for the treatment of adult patients with hairy cell leukemia (HCL) who have received at least two prior lines of therapy.

HCL is a rare, incurable, slow-growing leukemia for whom many patients are not immediately treated, but carefully observed until symptoms necessitate initiation of therapy. Approximately 1,000 people are diagnosed with HCL in the U.S. each year.

- Treatment of adult patients with HCL who have received at least two prior lines of therapy.

Clinical profile

Moxetumomab pasudotox is an IV recombinant immunotoxin formed by fusing anti-CD22 antibody to Pseudomonas exotoxin-A (PE38). CD22 is present on B-lymphocytes in higher concentration on HCL cells than on healthy B-cells. Thus, CD22 helps with targeting and PE38 inhibits protein translation on the tumor cell, leading to apoptotic cell death.

The FDA submission for moxetumomab pasudotox is supported by an open-label uncontrolled phase 3 trial that met its primary endpoint of durable CR in patients treated with moxetumomab pasudotox. No further data are readily available for this trial. A phase 1 trial evaluating 33 patients treated with 50 µg/kg every other day for 3 doses in 4-week cycles found 64% of patients achieved a CR and 88% of patients had an overall response to therapy.

Common adverse events reported with moxetumomab pasudotox use in the phase 1 trial included hypoalbuminemia, aminotransferase elevations, edema, headache, hypotension, nausea and fatigue. In trials for other disease states, grade 4 and 5 adverse events for hypercalcemia and capillary leak syndrome were seen at higher doses.

In the trials, moxetumomab pasudotox was dosed at either 40 or 50 mcg/kg IV on days 1, 3, and 5 of each 28 day cycle.

- Anti-CD22 immunotoxin
- IV formulation
- Met endpoint of durable response rate
- Common adverse events: hypoalbuminemia, aminotransferase elevations, edema, headache, hypotension, nausea and fatigue
- Dose: weight-based on days 1, 3, and 5 of each 28 day cycle

Competitive environment

There are currently limited treatments for HCL, with each subsequent cycle of therapy resulting in shorter durations of remission. If approved, moxetumomab pasudotox would represent a novel method of treatment for HCL and add to the available therapeutic options.

However, no safety or efficacy data have been released from the phase 3 trial used to support moxetumomab pasudotox. Furthermore, severe grade 4 and 5 adverse events were seen in trials investigating use in higher doses for other disease states.

The projected annual U.S. sales for moxetumomab pasudotox are $125 million by 2020.

- Advantage: novel treatment option
- Disadvantages: limited clinical data available, potential safety concerns
- Projected annual U.S. sales are $125 million by 2020

Continued…

moxetumomab pasudotox (continued...)

Expected FDA decision date

The FDA granted moxetumomab pasudotox an orphan drug designation.

An FDA decision regarding the approval of moxetumomab pasudotox is expected by the third quarter of 2018.

- Orphan drug
- PDUFA: 3Q2018

patisiran

Manufacturers: Alnylam/Arbutus/Ionis/Sanofi

Therapeutic use

Patisiran is in development for the treatment of patients with hATTR with polyneuropathy.

- Treatment of patients with hATTR with polyneuropathy

Clinical profile

Patisiran is an RNA interference (RNAi) therapeutic that is designed to reduce production of TTR to improve disease symptoms similar to inotersen. However, whereas inotersen's antisense mechanism physically blocks translation of RNA into protein, patisiran's RNAi mechanism targets specific RNA sequences and activates ribonucleases to cleave and degrade it, inhibiting protein synthesis.

Patisiran was evaluated in one trial against placebo. The primary endpoint was change from baseline in mNIS+7, a measure of neuropathic function and impairment. After 18 months, a significantly larger improvement was seen in the patisiran group vs. placebo (-6.0 mean change [improvement] in treatment group vs. +28.0 mean change [worsening] in placebo, $p < 0.00001$). An open-label extension evaluating 24 patients who had been taking patisiran for a total of 36 months found an improvement in mNIS+7 (mean change = -4.1).

Common adverse events reported in the trial included peripheral edema and infusion-related reactions. Serious adverse event rates were similar between treatment and placebo groups (36.5% vs. 40.3%), and included diarrhea, cardiac failure, orthostatic hypertension, pneumonia, and AV block.

In the trial, patisiran was given as 0.3 mg/kg administered IV once every 3 weeks.

- RNAi therapeutic
- IV formulation
- Greater improvement in neuropathy vs. placebo
- Common adverse events: peripheral edema and infusion-related reactions
- Dose: once every 3 weeks

Competitive environment

No FDA-approved therapies for this rare condition are currently available. Therefore, patisiran could represent one of the first potential disease-modifying treatments available to patients in the U.S. Although not evaluated in a head-to-head trial, the magnitude of improvement in mNIS+7 appeared to be slightly greater with patisiran than inotersen. Safety data also seems to suggest fewer serious adverse events than with inotersen.

However, open label extension data shows a more modest treatment effect than seen in the pivotal trial. Also, patisiran is administered by IV infusion, which could present a barrier to some patients.

The projected annual U.S. sales are $219 – $548 million by 2020.

- Advantages: first in-class treatment for rare disease with no true alternatives, potentially fewer safety concerns than inotersen
- Disadvantages: IV administration, long-term data suggests more modest treatment effect
- Projected annual U.S. sales are $219 – $548 million by 2020

Continued…

patisiran (continued...)

Expected FDA decision date

The FDA granted patisiran fast track status, breakthrough therapy status, orphan drug designation, and priority review.

An FDA decision regarding the approval of patisiran is expected by 8/11/2018.

- Fast track status
- Breakthrough therapy
- Orphan drug status
- Priority review
- PDUFA: 8/11/2018

plazomicin

Manufacturers: Achaogen/Ionis

Therapeutic use

Plazomicin is in development for the treatment of complicated urinary tract infections (cUTI), including pyelonephritis, and bloodstream infections due to certain Enterobacteriaceae in patients who have limited or no alternative treatment options.

- Treatment of cUTI, including pyelonephritis, and bloodstream infections due to certain Enterobacteriaceae

Clinical profile

Plazomicin is a novel small molecule aminoglycoside antibiotic with broad-spectrum bactericidal activity against multi-drug resistant Gram-negative bacteria, including carbapenem-resistant Enterobacteriaceae, and methicillin-resistant Staphylococcus aureus (MRSA).

Plazomicin was evaluated in two pivotal studies. The first evaluated a primary composite endpoint of microbiological eradication and clinical cure. Plazomicin was found to be non-inferior to meropenem five days following the end of plazomicin administration (88.0% plazomicin vs. 91.4% meropenem), and superior at 17 ± 2 days after study drug initiation (81.7% vs. 70.1%, respectively). In the second study, in patients with or suspected of having a carbapenem-resistant Enterobacteriaceae (CRE) infection, plazomicin achieved lower all-cause mortality or significant disease-related complications than colistin at day 28 (24% vs 50%, respectively).

Common adverse events reported in trials for plazomicin and comparator drugs included increase in serum creatinine, headache, diarrhea, dizziness, nausea, vomiting, and gastritis.

In trials, plazomicin was given once daily based on weight as an IV infusion. Dosing was adjusted based on pharmacokinetic monitoring of serum drug levels.

- Aminoglycoside antibiotic
- IV formulation
- Non-inferior to meropenem at five days; superior at 17 ± 2 days
- Lower all-cause mortality or disease-related complications than colistin
- Common adverse events: increase in serum creatinine, headache, diarrhea, dizziness, nausea, vomiting, and gastritis
- Dose: weight-based every 24 hours

Competitive environment

Plazomicin is a novel second-generation aminoglycoside that has activity against antibiotic-resistant bacteria that are typically difficult to treat. As such, it represents a useful addition in managing CRE. Efficacy was also demonstrated against two currently available treatment options: meropenem and colistin.

However, alternative treatments are available generically, including gentamicin. Plazomicin also requires pharmacokinetic drug monitoring and dose adjustment to minimize the risk of renal impairment.

- Advantages: effective against certain treatment-resistant bacteria, demonstrated efficacy against two currently available options
- Disadvantages: alternatives are generically available, requires drug monitoring

Continued…

plazomicin (continued...)

Expected FDA decision date

The FDA granted plazomicin breakthrough therapy status and a qualified infectious disease product designation.

An FDA advisory committee (AdCom) meeting regarding plazomicin is being convened on 5/2/2018.

An FDA decision regarding the approval of plazomicin is expected by 6/25/2018.

- Breakthrough therapy
- Qualified infectious disease product
- AdCom: 5/2/2018
- PDUFA: 6/25/2018

volanesorsen

Manufacturer: Akcea

Therapeutic use

Volanesorsen is in development for the treatment of patients with familial chylomicronemia syndrome (FCS).

FCS is a severe, rare disorder caused by a deficiency in lipoprotein lipase, an enzyme that helps to break down triglycerides. It is characterized by extremely high levels of triglycerides, daily symptoms such as abdominal pain, and the risk of recurrent, potentially fatal, acute pancreatitis. The prevalence is estimated to be 1 per one million worldwide.

- Treatment of patients with FCS

Clinical profile

Volanesorsen is an antisense drug that inhibits production of apolipoprotein C-III (apoC-III), which plays a central role in the regulation of triglycerides.

Volanesorsen was evaluated in one pivotal trial for treatment of adults with confirmed FCS. The primary endpoint was the mean reduction in fasting triglycerides from baseline. After two months, the volanesorsen group had a 77% decrease in triglycerides from baseline vs. an 18% increase in the placebo group ($p < 0.0001$).

Common adverse events in the volanesorsen trial included mild injection site reactions. A safety signal was seen for thrombocytopenia, with 5 of 33 patients receiving the study drug discontinuing due to low platelet counts, including three cases of grade 4 thrombocytopenia.

In the trial, volanesorsen was given as a SC injection once per week.

- Antisense apoC-III inhibitor
- SC formulation
- Greater decrease in triglycerides vs. placebo
- Common adverse events: injection site reactions, thrombocytopenia
- Dose: once weekly

Competitive environment

There is currently no treatment for FCS. Volanesorsen is a first in-class medication and if approved, would represent the first FDA-approved treatment for the condition. Currently, there are few effective treatment options for FCS. Clinical trial data also appears to show a large treatment effect.

However, there is a safety concern regarding the incidence of thrombocytopenia in the pivotal study, and frequent platelet monitoring would likely be required. The primary outcome was also for a surrogate endpoint rather than pancreatitis or other relevant clinical outcomes. Moreover, no long-term data are available.

The projected annual U.S. sales for volanesorsen are $69 million by 2020.

- Advantages: first in-class, few other effective options, large treatment effect
- Disadvantages: safety concerns, requires monitoring, surrogate endpoint, no long term data
- Projected annual U.S. sales are $69 million by 2020

Continued…

volanesorsen (continued...)

Expected FDA decision date

The FDA granted volanesorsen an orphan drug designation.

An FDA Advisory Committee meeting regarding volanesorsen is being convened on 5/10/2018.

An FDA decision regarding the approval of volanesorsen is expected by 8/30/2018.

- Orphan drug status
- AdCom: 5/10/2018
- PDUFA: 8/30/2018

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

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

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