OPTUMRx®

RxOutlook®

2nd Quarter 2017

Pending drug approvals

Drug name	Manufacturer	Indication/use	Expected FDA decision date
glecaprevir/pibrentasvir	AbbVie/Enanta	Hepatitis C virus infection	8/2017
sofosbuvir/velpatasvir/ voxilaprevir	Gilead	Hepatitis C virus infection	8/8/2017
enasidenib	Celgene/Agios	Acute myeloid leukemia	8/30/2017
inotuzumab ozogamicin	Pfizer/UCB	Acute lymphoblastic leukemia	8/2017
neratinib	Puma Biotechnology/ Pfizer	Breast cancer	2Q2017–3Q2017
rituximab/hyaluronidase	Genentech/Halozyme	Follicular lymphoma, diffuse large B-cell lymphoma, chronic lymphocytic leukemia	6/26/2017
romosozumab (Evenity)	Amgen/Astellas/UCB	Osteoporosis	7/19/2017
secnidazole (Solosec)	Symbiomix Therapeutics	Bacterial vaginosis	9/17/2017
sirukumab	GlaxoSmithKline	Rheumatoid arthritis	9/2017
voretigene neparvovec	Spark Therapeutics	Inherited retinal disease/dystrophy	Late 2017–early 2018

glecaprevir/pibrentasvir

Manufacturers: AbbVie/Enanta

Therapeutic use

Glecaprevir/pibrentasvir (GLE/PIB) is in development for the treatment of patients with genotype 1–6 chronic hepatitis C virus (HCV) infection.

- Treatment of patients with genotype 1–6 HCV infection

Clinical profile

GLE/PIB is a pan-genotypic, fixed-dose combination product containing an NS3/4A protease inhibitor and an NS5A inhibitor, respectively. GLE/PIB works by targeting different stages of the HCV replication process.

GLE/PIB's four major trial programs include ENDURANCE, SURVEYOR, EXPEDITION, and MAGELLAN. Collectively, these programs evaluated all six genotypes with and without compensated cirrhosis, including prior failures to direct acting antiviral (DAA) therapy. Across most of the trials, 96–99% of patients achieved a cure with 8–12 weeks of therapy. In one trial, which evaluated treatment-experienced genotype 3 patients without cirrhosis, 91% of patients achieved a cure with 12 weeks of therapy. However, the cure rate increased to 96% with 16 weeks of therapy.

Overall, GLE/PIB was well tolerated. The most common adverse events reported in trials were headache and fatigue.

GLE/PIB is administered as 3 pills orally once daily. Most patients will require 8–12 weeks of therapy.

- NS3/4A protease inhibitor/ NS5A inhibitor
- Oral formulation
- Cure rates: 96–99%
- Common adverse events: headache, fatigue
- Dose: 3 pills once daily for 8–12 weeks

Continued…

glecaprevir/pibrentasvir (Continued…)

Manufacturers: AbbVie/Enanta

Competitive environment

If approved, GLE/PIB may benefit patients who have previously tried and failed DAA therapy, in particular those who were given a course of sofosbuvir plus ribavirin with or without peg-interferon. In addition, because it is minimally metabolized and minimally excreted through the kidneys, GLE/PIB is expected to pose a low risk for drug interactions and may offer a treatment option for renally impaired patients, including those on hemodialysis.

Approximately 80% of patients may only need 8 weeks of therapy with GLE/PIB, which may positively impact drug adherence and shorten the treatment burden for patients.

Nonetheless, GLE/PIB requires multiple pills per day. GLE/PIB is also entering an increasingly competitive HCV market, and some clinicians do not believe GLE/PIB targets a significant unmet need given the numerous HCV products on the market.

Currently, the price for the various oral HCV regimens range from $54,600 for a 12-week regimen of Zepatier to as high as $294,000 for a 24-week regimen of sofosbuvir plus daclatasvir.

- Advantages: addresses DAA treatment failures, low risk for drug interactions, useful in renally impaired patients, requires only 8 weeks of therapy for most patients
- Disadvantages: multiple pills per day, competitive market
- Price range for oral HCV regimens: $54,600–$294,000

Expected FDA decision date

The FDA granted breakthrough status to GLE/PIB for chronic HCV patients who failed previous therapy with DAAs in genotype 1 patients, including therapy with an NS5A inhibitor and/or protease inhibitor. It was also granted a priority review.

GLE/PIB also has an orphan drug designation for the treatment of pediatric patients with chronic HCV infection.

An FDA decision regarding the approval of GLE/PIB is expected in August 2017.

- Orphan drug
- Breakthrough status
- Priority review
- PDUFA: 8/2017

sofosbuvir/velpatasvir/voxilaprevir

Manufacturers: Gilead

Therapeutic use

Sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) is in development for the treatment of patients with genotype 1–6 chronic HCV infection.

- Treatment of patients with genotype 1–6 HCV infection

Clinical profile

SOF/VEL/VOX is a triple fixed-dose combination product containing an NS5B polymerase inhibitor, NS5A inhibitor, and NS3/4A protease inhibitor, respectively.

Sofosbuvir is commercially available as a single agent (Sovaldi®) and as dual combination products with either ledipasvir (Harvoni®) or velpatasvir (Epclusa®).

In trials, SOF/VEL/VOX was evaluated in genotype 1–6 chronic HCV patients with and without compensated cirrhosis, including previous DAA treatment failures. Across all trials, a cure was achieved in 95–98% of patients. However, in a recent trial comparing SOF/VEL/VOX for 8 weeks to Epclusa for 12 weeks, SOF/VEL/VOX failed to demonstrate non-inferiority to Epclusa.

Common adverse events reported in trials include fatigue, headache, diarrhea, and nausea.

SOF/VEL/VOX is administered as 1 pill orally once daily for 8–12 weeks.

- NS5B polymerase inhibitor/ NS5A inhibitor/ NS3/4A protease inhibitor
- Oral formulation
- Cure rates: 95–98%
- SOF/VEL/VOX for 8 weeks failed to show non-inferiority to Epclusa for 12 weeks
- Common adverse events: fatigue, headache, diarrhea, nausea
- Dose: 1 pill orally once daily for 8–12 weeks

Competitive environment

If approved, SOF/VEL/VOX may benefit patients who have tried and failed prior DAA therapy. Moreover, unlike GLE/PIB, SOF/VEL/VOX only requires 1 pill once daily.

Nonetheless, SOF/VEL/VOX is entering an increasingly competitive market. Some clinicians do not think the reduction in treatment duration from 12 weeks to 8 weeks outweighs the increased potential for adverse events by adding voxilaprevir to sofosbuvir and velpatasvir, the components of Epclusa. Moreover, 8 weeks of therapy with SOF/VEL/VOX failed to demonstrate non-inferiority to 12 weeks of Epclusa.

Currently, the price for the various oral HCV regimens range from $54,600 for a 12-week regimen of Zepatier to as high as $294,000 for a 24-week regimen of sofosbuvir plus daclatasvir.

- Advantages: addresses DAA treatment failures, requires only 1 pill for 8–12 weeks
- Disadvantages: competitive market, benefits of reduced treatment duration may not outweigh risks, SOF/VEL/VOX for 8 weeks failed to show non-inferiority to Epclusa for 12 weeks
- Price range for oral HCV regimens: $54,600–$294,000

Continued…

sofosbuvir/velpatasvir/voxilaprevir (Continued…)

Manufacturers: Gilead

Expected FDA decision date
SOF/VEL/VOX was granted breakthrough status for the treatment of genotype 1 chronic HCV patients who have previously failed an NS5A inhibitor-containing regimen.

The FDA also granted a priority review, and a decision regarding the approval of SOF/VEL/VOX is expected by August 8, 2017.

- Breakthrough status
- Priority review
- PDUFA: 8/8/2017

enasidenib

Manufacturer: Celgene/Agios Pharmaceuticals

Therapeutic use

Enasidenib is in development for the treatment of patients with relapsed or refractory acute myeloid leukemia (AML) with isocitrate dehydrogenase 2 (IDH2) mutation.

- Treatment of patients with relapsed or refractory AML with IDH2 mutation

Clinical profile

Enasidenib is an IDH2 inhibitor. IDH2 is an enzyme located in the mitochondria of cells and plays a critical role in cellular metabolism. Mutations in IDH2 are associated with various cancers, including AML.

In an early stage trial involving adult patients with AML, the overall response rate (ORR) with enasidenib was 38% overall and 37% in patients with relapsed or refractory AML. In addition, the ORR in myelodysplastic patients was 50%. However, the overall complete remission (CR) rate was only 17.7%.

The most common adverse events reported in the trial were nausea, diarrhea, fatigue, and febrile neutropenia. Serious adverse events included atrial flutter, cardiac tamponade, pericardial effusion, and respiratory failure. Deaths were also reported in the trial, including deaths associated with atrial flutter and sepsis.

Currently, enasidenib is being studied as a once daily and twice daily oral regimen.

- IDH2 inhibitor
- Oral formulation
- ORR = 37% in relapsed and refractory AML
- Serious adverse events: atrial flutter, cardiac tamponade, pericardial effusion, and respiratory failure
- Dose: once or twice daily

Competitive environment

Enasidenib is an oral product with a novel mechanism that targets IDH2.

However, data from mid-stage and late-stage trials are not available. Thus, limited information is available to properly evaluate the efficacy or safety of the drug. In addition, the CR rate from an early stage trial was disappointing and there were serious cardiac-related adverse events associated with enasidenib.

The projected peak annual U.S. sales for enasidenib are $132–$162 million by 2020.

- Advantages: oral, novel mechanism
- Disadvantages: limited data available, low CR rate, serious cardiac-related adverse events
- Projected annual peak sales are $132–$162 million by 2020

Expected FDA decision date

Enasidenib was granted an orphan drug designation, fast track status, and priority review by the FDA.

An FDA decision regarding the approval of enasidenib is expected by August 30, 2017.

- Orphan drug
- Fast track status
- Priority review
- PDUFA: 8/30/2017

inotuzumab ozogamicin

Manufacturer: Pfizer/UCB

Therapeutic use
Inotuzumab ozogamicin is in development for the treatment of adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).

- Treatment of adult patients with relapsed or refractory B-cell precursor ALL

Clinical profile
Inotuzumab ozogamicin is an antibody-antigen complex consisting of a humanized IgG antibody conjugated to a cytotoxic agent (N-acetyl gamma-1-calicheamicin). It blocks CD22, a beta-lymphocyte lineage-specific surface protein expressed by most B-cell malignancies. Upon binding to the tumor cell, the complex is internalized; the cytotoxic agent damages the tumor cell DNA resulting in cell death.

In one open label study involving 325 subjects with CD22-positive relapsed or refractory ALL, inotuzumab ozogamicin was compared to standard chemotherapy consisting of a cytarabine-based regimen. Overall, CR or CR with incomplete hematologic recovery was achieved in 80.7% of inotuzumab ozogamicin subjects vs. 29.4% of subjects in the comparator arm. However, the median overall survival (OS) was only 7.7 months (95% CI: 6.0, 9.2) in the inotuzumab ozogamicin arm vs. 6.7 months (95% CI: 4.9, 8.3) in the standard chemotherapy arm.

- Conjugated CD22 antagonist
- IV formulation
- Greater CR rate with inotuzumab ozogamicin vs. chemotherapy
- Small improvement in OS

Common adverse events reported in the trial included hematologic cytopenias, nausea, headache, and pyrexia.

- Common adverse events: hematologic cytopenias, nausea, headache, and pyrexia

Adverse events occurring more frequently with inotuzumab ozogamicin vs. standard chemotherapy included veno-occlusive disease (11% vs. 1%), liver-related adverse events such as increased aspartate aminotransferase (20% vs. 10%), hyperbilirubinemia (15% vs. 10%) and increased alanine aminotransferase levels (14% vs. 11%). In addition, 4 treatment-related deaths occurred in the inotuzumab ozogamicin arm vs. 2 treatment-related deaths in the standard chemotherapy arm.

Inotuzumab ozogamicin is dosed by body surface area (BSA) intravenously (IV) on days 1, 8, and 15 of each treatment cycle.

- Dose: by BSA IV on days 1, 8, and 15 of each cycle

Continued…

inotuzumab ozogamicin (Continued…)

Manufacturer: Pfizer/UCB

Competitive environment

Inotuzumab ozogamicin is a first in-class conjugated agent that may benefit patients with relapsed or refractory ALL. Currently, there are limited treatment options in this population. Furthermore, CR rates with inotuzumab ozogamicin were significantly higher compared to standard chemotherapy.

However, inotuzumab ozogamicin is not intended as first-line therapy and still requires IV administration. In addition, the improvement in median OS was small vs. chemotherapy.

The projected annual U.S. sales for inotuzumab ozogamicin are $179 million by 2020.

- Advantages: novel mechanism, limited treatment options in relapsed/refractory ALL, high CR rate vs. chemotherapy
- Disadvantages: not first-line therapy, IV administration, small improvement in OS
- Projected annual U.S. sales are $179 million by 2020

Expected FDA decision date

The FDA granted inotuzumab ozogamicin an orphan drug designation and priority review.

An FDA decision regarding the approval of inotuzumab ozogamicin is expected in August 2017.

- Orphan drug designation
- Priority review
- PDUFA: 82017

neratinib

Manufacturers: Puma Biotechnology/Pfizer

Therapeutic use

Neratinib is in development for extended adjuvant treatment in patients with early stage human epidermal growth factor receptor 2 (HER2)-overexpressed/amplified breast cancer who have received prior trastuzumab-based therapy.

- Extended adjuvant treatment in HER2-overexpressed breast cancer patients who have received prior trastuzumab-based therapy

Clinical profile

Neratinib is an irreversible tyrosine kinase inhibitor.

In one pivotal trial, neratinib was compared against placebo in over 2,800 patients with HER2-overexpressed breast cancer who received neoadjuvant or adjuvant therapy with trastuzumab. The 2-year disease-free survival (DFS) rate was greater with neratinib vs. placebo (93.9% [95% CI: 92.4, 95.2] vs. 91.6% [95% CI: 90.0, 93.0]). Furthermore, there was a 33% risk reduction in invasive disease progression or death with neratinib for all patients ($p = 0.009$) and a 49% risk reduction in hormone-receptor positive patients ($p = 0.001$). By year 5, the interim DFS rate was 90.4% with neratinib vs. 87.9% with placebo.

Common adverse events reported in the trial included vomiting, nausea, and high rates of diarrhea. There were 7 deaths total in the trial, including 4 patients in the neratinib arm vs. 3 patients in the placebo arm. However, none of the deaths were attributed to the study treatment in either group.

In a mid-stage trial, neratinib was compared to Tykerb® (lapatinib) plus Xeloda® (capecitabine) in HER2-positive breast cancer patients. However, neratinib failed to beat Tykerb plus Xeloda in terms of ORR and progression-free survival (PFS) (ORR = 29% vs. 40%; PFS = 4.5 months vs. 6.8 months, respectively).

A second trial comparing neratinib to Tykerb plus Xeloda is currently in progress. Results are expected in the 2nd or 3rd quarter of 2017.

Based on trial protocols, neratinib is expected to be dosed as 240mg orally once daily during each 21-day cycle.

- Tyrosine kinase inhibitor
- Oral formulation
- DFS rate was greater with neratinib vs. placebo
- Neratinib failed to show greater ORR or PFS vs. Tykerb plus Xeloda
- Common adverse events: vomiting, nausea, and diarrhea
- Dose: 240 mg once daily

Continued…

neratinib (Continued…)

Manufacturers: Puma Biotechnology/Pfizer

Competitive environment

Neratinib offers another oral, once daily treatment option for select patients with breast cancer. It may also have use as monotherapy or combination therapy.

However, the overall improvement in DFS over placebo was disappointing, and OS data have not been reported at this time. Moreover, in a mid-stage trial, neratinib failed to show improvement in ORR or PFS over Tykerb plus Xeloda. Finally, there were high incidences of diarrhea in the trials with reports as high as 85% to 97%.

The projected annual U.S. sales for neratinib are $433 million by 2020.

- Advantages: offers another treatment option, oral, once daily, possible use as monotherapy or combination therapy
- Disadvantages: small improvement in DFS, not superior to Tykerb plus Xeloda, high incidence of diarrhea
- Projected annual U.S. sales are $433 million by 2020

Expected FDA decision date

An FDA advisory committee (AdCom) is scheduled to convene and discuss the efficacy and safety of neratinib on May 24, 2017.

An FDA decision regarding the approval of neratinib is expected in July 2017.

- PDUFA: 7/2017

rituximab/hyaluronidase

Manufacturer: Genentech/Halozyme Therapeutics

Therapeutic use

Rituximab/hyaluronidase is a combination product in development for three indications:

1) For use in combination with CHOP or CVP chemotherapy in previously untreated follicular non-Hodgkin lymphoma (NHL) followed by maintenance treatment with either rituximab SC or IV

2) Treatment of CD20-positive diffuse large B-cell lymphoma (DLBCL)

3) For use in combination with fludarabine and cyclophosphamide in previously untreated chronic lymphocytic leukemia (CLL)

CHOP consists of cyclophosphamide, doxorubicin, vincristine, and prednisolone. CVP consists of cyclophosphamide, vincristine, and prednisolone.

Currently, rituximab is available as Rituxan®, which is administered by IV infusion, and is approved for use in follicular NHL, DLBCL, and CLL.

- In combination with CHOP or CVP in untreated follicular NHL followed by maintenance rituximab
- Treatment of CD20-positive DLBCL
- In combination with fludarabine and cyclophosphamide in untreated CLL

Clinical profile

Rituximab/hyaluronidase contains a CD20 antagonist (rituximab) plus a dispersing agent (hyaluronidase). Hyaluronidase breaks down hyaluronic acid in connective tissue, improving permeability and enhancing the diffusion of rituximab.

The presence of hyaluronidase permits delivery of rituximab via the SC route and reduces the administration time to 5–7 minutes. The current formulation of rituximab requires at least 90 minutes of IV infusion.

In trials, rituximab SC was compared to rituximab IV. Trough serum concentrations and ORR at the end of induction and maintenance periods were comparable with both routes of administration.

Overall, the number and type of adverse events were comparable between SC and IV rituximab. However, there were slightly higher reports of neutropenia with the SC route (32% vs. 27%). Furthermore, while the incidence of grade ≥ 3 adverse events were similar between the two groups, there were more grade 1 and 2 adverse events and more administration-related reactions with the SC route.

The dose and frequency of rituximab SC are expected to be similar to rituximab IV for each respective indication.

- CD20 antagonist/ dispersing agent
- SC formulation
- Reduces administration time to 5–7 minutes
- Comparable efficacy and safety profile to rituximab IV
- Dose: similar to rituximab

Continued…

rituximab/hyaluronidase (Continued…)

Manufacturer: Genentech/Halozyme Therapeutics

Competitive environment

The primary advantage of rituximab/hyaluronidase is its fast administration time. In addition, unlike the existing formulation of rituximab, which requires IV administration, rituximab/hyaluronidase may be given SC.

However, rituximab/hyaluronidase will be competing against rituximab IV, which is already available. Furthermore, biosimilar rituximab products are also in development.

Also, based on trial protocols, patients may still require administration with rituximab IV during the first cycle of therapy.

The estimated annual drug cost of rituximab IV is $158,485.

- Advantages: fast administration time, may be given SC
- Disadvantages: rituximab IV is available, biosimilar rituximab products are in development, rituximab IV may still be required for the initial treatment cycle

Expected FDA decision date

The FDA's AdCom panel voted unanimously (11-0) to approve rituximab/hyaluronidase, stating that the benefits outweighed the overall risks.

An FDA decision regarding the approval of rituximab/hyaluronidase is expected by June 26, 2017.

- AdCom: voted 11–0 in favor of approval
- PDUFA: 6/26/2017

romosozumab (Evenity)

Manufacturers: Amgen/Astellas/UCB

Therapeutic use
Romosozumab is in development for the treatment of osteoporosis in postmenopausal women at increased risk for fracture.

- Treatment of osteoporosis in postmenopausal women at increased risk for fracture

Clinical profile
Romosozumab is a sclerostin inhibitor. Sclerostin is a naturally occurring protein that plays a critical role in regulating bone mass by decreasing bone resorption and increasing bone formation.

In a pivotal trial, romosozumab was compared against placebo in postmenopausal women with low bone mineral density. Severe osteoporotic patients were excluded from the study. Patients were given romosozumab or placebo in year 1 followed by Prolia® (denosumab) in year 2. Romosozumab achieved a greater reduction in the incidence of new vertebral fractures vs. placebo at both year 1 (0.5% vs. 1.8%, $p < 0.001$) and year 2 (0.6% vs. 2.5%, $p < 0.001$); however, the differences in non-vertebral fracture rates were not statistically significant.

Common adverse events reported in the pivotal trial included nasopharyngitis, arthralgia, back pain, headache, and falls.

Romosozumab is administered SC once monthly.

- Sclerostin inhibitor
- SC formulation
- Greater reduction in new vertebral fractures vs. placebo
- No significant difference in non-vertebral fractures vs. placebo
- Dose: once monthly

Competitive environment
Romosozumab offers a novel mechanism of action for treating postmenopausal osteoporosis. It also offers another anabolic treatment option to patients with osteoporosis. Currently, only two related anabolic treatments are available for osteoporosis — Forteo® (teriparatide) and Tymlos™ (abaloparatide). Furthermore, unlike these anabolic agents, which require daily administration, romosozumab is dosed once monthly.

Nonetheless, romosozumab failed to improve non-vertebral fracture rates, which accounted for the majority of clinical fracture occurrences in the pivotal trial. Moreover, the safety of romosozumab use beyond one year and the benefit in patients with severe osteoporosis are uncertain. In addition, romosozumab still requires administration by SC injection.

The projected annual U.S. sales for romosozumab are $382 million by 2020.

- Advantages: novel mechanism, limited anabolic treatment options, once monthly dosing
- Disadvantages: failed to reduce non-vertebral fractures, long term safety is unknown, severe osteoporotic patients were excluded in the pivotal trial, and SC injection
- Projected annual U.S. sales are $382 million by 2020

Expected FDA decision date
An FDA decision regarding the approval of romosozumab is expected by July 19, 2017.

- PDUFA: 7/19/2017

secnidazole (Solosec)

Manufacturers: Symbiomix Therapeutics

Therapeutic use
Secnidazole is in development for the treatment of bacterial vaginosis (BV).

- Treatment of BV

Clinical profile
Secnidazole is a nitroimidazole anti-infective agent and is related to metronidazole and tinidazole. Both metronidazole and tinidazole are generically available.

In a pivotal trial, secnidazole was evaluated against placebo in 189 female patients (≥ 12 years old) with BV. More patients in the secnidazole group responded to therapy vs. placebo ($p < 0.001$). A positive response was determined by normalization of vaginal discharge, negative potassium hydroxide "Whiff" test, and Clue cells < 20%.

Secnidazole was well-tolerated; however, safety details were not disclosed.

Secnidazole is administered as a single oral dose.

- Nitroimidazole anti-infective
- Greater response vs. placebo
- Dose: one-time dose

Competitive environment
Secnidazole offers another oral treatment option for BV. It only requires a one-time dose, compared to metronidazole or tinidazole, which require multiple days of therapy.

However, both efficacy and safety data are limited. Detailed trial results have not been disclosed at this time. In addition, metronidazole and tinidazole are similar products that are generically available and widely used for treating BV, and metronidazole is available as both oral pills and vaginal gel.

It is unclear whether secnidazole will carry a boxed warning. Both oral metronidazole and tinidazole carry a boxed warning regarding the potential risk of carcinogenicity based on animal studies involving metronidazole.

BV affects an estimated 30% of women of child-bearing age each year.

- Advantages: oral, one-time dose
- Disadvantages: limited efficacy and safety data, related products are available (ie, metronidazole, tinidazole), possible boxed warning

Expected FDA decision date
The FDA designated secnidazole as a Qualified Infectious Disease Product (QIDP). The QIDP designation qualifies secnidazole for an expedited FDA review and 5 years of market exclusivity in addition to certain exclusivities already offered under the Food, Drug, and Cosmetic Act.

The FDA has also granted fast track status to secnidazole.

An FDA decision regarding the approval of secnidazole is expected by September 17, 2017.

- QIDP
- Fast track status
- PDUFA: 9/17/2017

sirukumab

Manufacturer: GlaxoSmithKline

Therapeutic use
Sirukumab is in development for the treatment of active moderate-to-severe rheumatoid arthritis (RA) in patients who have failed or are intolerant to ≥ 1 disease-modifying anti-rheumatic drug (DMARD).

- Treatment of moderate-to-severe RA in patients who have failed or are intolerant to ≥ 1 DMARD

Clinical profile
Sirukumab is a human monoclonal IgG1 kappa antibody that targets and inhibits interleukin-6 (IL-6), a pro-inflammatory cytokine.

In multiple placebo-controlled trials, more patients in the sirukumab group achieved at least a 20% improvement from baseline in the signs and symptoms of RA vs. placebo ($p < 0.001$). In addition, secondary endpoints were also met, including achievement of ≥ 50% improvement from baseline, and improvements in the Health Assessment Questionnaire Disability Index and Disease Activity Scores.

In one active-controlled trial comparing sirukumab to Humira® (adalimumab), sirukumab did not demonstrate a significant difference vs. Humira in a secondary endpoint, which measured the proportion of patients achieving ≥ 50% improvement in RA signs and symptoms. However, the clinically relevant primary endpoint of disease activity showed greater improvement with sirukumab vs. Humira.

Serious adverse events reported in trials included infection, osteomyelitis, ovarian tumor, and acute sinusitis.

Sirukumab is being studied as a SC injection dosed once every 2 weeks and once every 4 weeks.

- IL-6 antagonist
- SC formulation
- Greater improvement in RA signs/symptoms vs. placebo
- Greater improvement in RA disease activity vs. Humira
- Serious adverse events: infection, osteomyelitis, ovarian tumor, and acute sinusitis
- Dose: every 2–4 weeks

Continued…

sirukumab (Continued…)

Manufacturer: GlaxoSmithKline

Competitive environment

While sirukumab offers another treatment alternative for patients with moderate-to-severe RA, its primary advantage may be its proposed once monthly dosing regimen.

Nonetheless, sirukumab is not intended for first-line therapy. Sirukumab is for patients who have failed on or are intolerant to ≥ 1 DMARD. Furthermore, sirukumab is entering an increasingly crowded market and does not offer a significantly novel mechanism. Currently, Actemra® (tocilizumab), also an IL-6 antagonist, is available for the treatment of moderately to severely active RA in patients who have had an inadequate response to ≥ 1 DMARD. Actemra is also indicated for polyarticular juvenile idiopathic arthritis (JIA) and systemic JIA.

The projected annual U.S. sales for sirukumab are $150 million by 2020.

- Advantages: offers another treatment option, possible once monthly dosing
- Disadvantages: not first-line therapy, alternatives are available (eg, Actemra)
- Projected annual U.S. sales are $150 million by 2020

Expected FDA decision date

An FDA decision regarding the approval of sirukumab is expected in September 2017.

- PDUFA: 9/2017

voretigene neparvovec

Manufacturers: Spark Therapeutics

Therapeutic use

Voretigene neparvovec is in development for the treatment of inherited retinal disease/dystrophy (IRD) due to bi-allelic RPE65 gene mutations.

RPE65 is a necessary gene for normal vision. The product of the RPE65 gene is a protein that is responsible for converting light into electrical signals, which are transmitted to the brain. Mutations in the RPE65 gene affect peripheral and central vision and the ability to see under low light conditions.

One of the most severe forms of IRD is Leber congenital amaurosis (LCA), an inherited disease characterized by significantly reduced vision. Symptoms may appear as early as 2–3 months of age and patients eventually progress to complete loss of vision. LCA is thought to affect approximately 1,800 to 2,280 Americans.

- Treatment of IRD due to bi-allelic RPE65 gene mutations
- RPE65 is necessary for normal vision
- LCA affects 1,800–2,280 Americans

Clinical profile

Voretigene neparvovec is a gene therapy vector platform. A viral vector containing a healthy RPE65 gene is injected into the eye, thereby delivering a functioning copy of the RPE65 gene. Because the viral vector requires a host cell, sufficiently viable retinal cells are necessary for patients to experience improved vision.

In a phase 3 clinical trial, young patients (≥ 3 years old) given voretigene neparvovec were compared to a non-interventional control group. Diagnosis of LCA due to RPE65 mutation was required for inclusion into the trial.

Patients were assessed by mobility test and evaluated for their ability to navigate a course under a variety of light conditions. At year 1, the mean change in mobility test score was greater with voretigene neparvovec vs. control (difference = 1.6, 95%CI: 0.76, 2.50). Moreover, at year 1, 65% of subjects receiving voretigene neparvovec were able to pass the mobility test at 1 lux vs. 0% in the control group.

However, there was no improvement in visual acuity from baseline to year 3 ($p > 0.49$).

Adverse events reported in the trial included transient elevation in intraocular pressure (IOP), cataracts, retinal tear, and mild eye inflammation. While there were subjects who tested positive against voretigene neparvovec, no deleterious immune responses occurred in the trial.

Voretigene neparvovec is administered by subretinal injection as a one-time treatment per eye.

- Gene therapy viral vector platform
- Subretinal formulation
- Greater improvement in mobility test score vs. control
- Adverse events: increased IOP, cataracts, retinal tear, eye inflammation
- Dose: one-time injection per eye

Continued…

voretigene neparvovec (Continued…)

Manufacturers: Spark Therapeutics

Competitive environment

If approved, voretigene neparvovec will be the first FDA-approved gene therapy agent for IRD. Moreover, voretigene neparvovec will only require one treatment per eye and appears to have a sustained clinical benefit in patients.

However, voretigene neparvovec requires subretinal administration, subjecting patients to possible procedure-related adverse events. In addition, given the small target population and medical risks associated with this treatment, the drug cost for voretigene neparvovec is expected to be high.

- Advantages: may be the first FDA-approved drug for IRD, requires one treatment per eye, sustained benefit
- Disadvantages: subretinal injection, procedure-related adverse events, potential high cost

Expected FDA decision date

An orphan drug designation was granted for voretigene neparvovec by the FDA.

A rolling submission is in progress with the FDA. While Spark Therapeutics' application has not been finalized, the company expects to complete its application soon and is projecting an FDA decision sometime in late 2017 or early 2018.

- Orphan drug
- Projected FDA decision in late 2017–early 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.

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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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