OPTUMRx®

RxOutlook®

3rd Quarter 2017

Pending drug approvals

Drug Name	Manufacturer	Indication/Use	Expected FDA Decision Date
aprepitant (Cinvanti)	Heron Therapeutics	Chemotherapy-induced nausea and vomiting	11/2017
ataluren (Translarna)	PTC Therapeutics	Duchenne muscular dystrophy	10/24/2017
benralizumab	AstraZeneca/Kyowa Hakko Kirin	Asthma	4Q2017
beta-glucuronidase	Ultragenyx	Mucopolysaccharidosis VII	11/16/2017
copanlisib	Bayer	Follicular lymphoma	11/2017
ertugliflozin	Merck/Pfizer	Type 2 diabetes mellitus	12/2017
ertugliflozin/sitagliptin	Merck/Pfizer	Type 2 diabetes mellitus	12/2017
ertugliflozin/metformin	Merck/Pfizer	Type 2 diabetes mellitus	12/2017
exenatide (ITCA650)	Intarcia/Johnson & Johnson	Type 2 diabetes mellitus	9/2017
fluticasone/umeclidinium/ vilanterol	GlaxoSmithKline	Chronic obstructive pulmonary disease	11/2017
semaglutide	Novo Nordisk	Type 2 diabetes mellitus	12/2017

aprepitant (Cinvanti)

Manufacturer: Heron Therapeutics

Therapeutic use

Aprepitant is a new injectable formulation of Emend® (aprepitant) in development for the prevention of both acute and delayed chemotherapy-induced nausea and vomiting (CINV) associated with moderately emetogenic chemotherapy and highly emetogenic chemotherapy.

In contrast, the current intravenous (IV) formulation of Emend (fosaprepitant) is a prodrug and contains polysorbate 80, a common surfactant used in certain pharmaceutical preparations. Polysorbate 80 has been associated with hypersensitivity reactions, including anaphylaxis, and infusion-site reactions in some patients.

- Prevention of acute and delayed CINV associated with moderately and highly emetogenic chemotherapy

Clinical profile

Aprepitant is a neurokinin-1 (NK-1) receptor antagonist.

In a bioequivalency study, Heron Therapeutics' aprepitant, Cinvanti, was compared to Emend IV in healthy volunteers and found to be bioequivalent.

In addition, Cinvanti demonstrated lower rates of adverse events vs. Emend IV (28% vs. 56%) and lower rates of hypersensitivity reactions (0% vs. 3%).

Cinvanti is expected to be dosed similarly to Emend IV, given as a single dose prior to chemotherapy on day 1 by IV administration.

- NK-1 receptor antagonist
- IV formulation
- Bioequivalent to IV Emend
- Lower rates of adverse events and hypersensitivity reactions than Emend IV
- Dose: prior to chemotherapy on day 1

Competitive environment

Currently, Emend IV is the only FDA-approved NK-1 receptor antagonist on the market. However, Emend IV contains polysorbate 80. Heron Therapeutics is touting that the removal of polysorbate 80 in the Cinvanti formulation will reduce the risk for hypersensitivity and infusion-related reactions in patients.

However, alternative antiemetic agents are widely available, including generic 5HT-1 antagonists and various oral NK-1 receptor antagonists, such as Varubi™ (rolapitant), Akynzeo™ (netupitant/palonosetron), and Emend (aprepitant). Moreover, an IV formulation of Varubi is also in development, and if approved, will add to the overall competition in the marketplace.

For reference, the wholesale acquisition cost (WAC) for Emend IV is $306.43 per 50 mg vial.

- Advantages: limited IV NK-1 receptor antagonists on the market, offers a polysorbate 80-free formulation
- Disadvantages: alternative antiemetics are available (eg, 5HT-1 antagonists, other NK-1 receptor antagonists)
- WAC for Emend IV = $306.43 per 150 mg vial

Expected FDA decision date

An FDA decision regarding the approval of Cinvanti is expected in November 2017.

- PDUFA: 11/2017

ataluren (Translarna)

Manufacturer: PTC Therapeutics

Therapeutic use

Ataluren is in development for protein restoration therapy for the treatment of nonsense mutation Duchenne muscular dystrophy (DMD).

DMD is a rare genetic disorder caused by non-functional dystrophin proteins. It is characterized by progressive muscle degeneration and weakness. The onset of DMD symptoms typically occurs before the age of 5, and patients are often wheelchair-bound before or in their early teenage years due to declining muscle strength. Patients rarely survive to their fourth decade of life due to cardiac or respiratory failure.

- Protein restoration for the treatment of nonsense DMD

Clinical profile

Ataluren is believed to work by interacting with the ribosome, a cellular component that decodes the messenger RNA (mRNA) to produce proteins. It restores the normal translation process by enabling the ribosome to read-through the premature nonsense stop signals on the mRNA, thereby, producing a full-length, functional dystrophin molecule.

In trials, ataluren failed to improve or slow the progression of disease vs. placebo in the overall DMD trial populations. However, in a subgroup of patients at risk for 10% worsening by 48 weeks, 26% of ataluren-treated patients showed disease progression vs. 44% for placebo patients in a phase 2 trial.

Similar results were seen in a subgroup of patients at high risk for declining ambulation in a phase 3 trial. In this study, a notable 42.9 meter benefit was witnessed with no loss of ambulation in the ataluren group vs. 4 patients losing ambulation in the placebo group.

However, in one of the trials, patients given low dose ataluren showed reductions in ambulation decline compared to placebo while no benefit was observed in the high dose ataluren group. Furthermore, both dosing groups failed to achieve statistically significant results. Thus, some clinicians have expressed disappointment and caution when interpreting the various trial results.

Overall, ataluren was well-tolerated. Serious side effects were infrequent and none were related to ataluren. Nonetheless, reports from Europe, where the drug is approved, indicate risks for worsening hypertension, especially when used concomitantly with corticosteroids. Ataluren may also increase blood lipid levels and increase the risk for renal and hepatic toxicity.

Common adverse events reported in the trials include vomiting, headache, diarrhea, nasopharyngitis, fever, cough, and upper abdominal pain.

In the trials, ataluren was dosed by weight and given orally three times daily.

- Restores normal dystrophin production
- Oral formulation
- Failed to improve or slow disease progression vs. placebo in the overall DMD study populations
- Patients at risk for 10% worsening disease showed slower rates of progression vs. placebo
- Risk of hypertension, renal toxicity, and hepatotoxicity
- Common AEs: vomiting, headache, diarrhea, nasopharyngitis, fever, cough, and upper abdominal pain
- Dose: weight-based three times daily

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ataluren (Translarna) (continued...)

Competitive environment

If approved, ataluren will be the first gene therapy treatment for DMD patients with nonsense mutations. Ataluren also offers the convenience of oral administration.

However, ataluren requires frequent dosing. In addition, the efficacy results from its pivotal trials are controversial, and long-term safety data are unavailable at this time.

The cost for ataluren is projected to be comparable to Exondys 51™ (eteplirsen), another DMD agent administered by weight-based dosing. Exondys 51 is indicated for DMD patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.

- Advantages: first gene therapy treatment for nonsense mutations, oral
- Disadvantages: frequent dosing, controversial trial results, long-term safety data are unavailable
- Projected cost comparable to Exondys 51

Expected FDA decision date

Ataluren was granted orphan drug and fast track designations by the FDA.

An FDA advisory committee (AdCom) will meet to discuss ataluren on September 28, 2017, and a decision regarding the approval of ataluren is expected by October 24, 2017.

- Orphan drug
- Fast track status
- AdCom: 9/28/2017
- PDUFA: 10/24/2017

benralizumab

Manufacturers: AstraZeneca/Kyowa Hakko Kirin

Therapeutic use

Benralizumab is in development for the treatment of severe, uncontrolled asthma.

- Treatment of severe, uncontrolled asthma

Clinical profile

Benralizumab is an interleukin-5 (IL-5) receptor antagonist. The IL-5 receptor alpha chain is largely restricted to eosinophils. Its blockade is believed to inhibit cellular activation and asthma severity.

In placebo-controlled trials, greater improvement in annual asthma exacerbation (AAE) rates was observed with benralizumab vs. placebo.

In addition, in one trial, greater reduction in oral corticosteroid use was achieved with benralizumab, with the median dose reduced by 75% vs. 25% for placebo ($p < 0.05$).

The most common adverse events reported in the trials were nasopharyngitis, worsening asthma, upper respiratory tract infection, headache, bronchitis, and sinusitis.

Benralizumab is being studied as a subcutaneously (SC) administered injection for once every 4 week and once every 8 week dosing.

- IL-5 receptor antagonist
- SC formulation
- Greater improvement in AAE rates vs. placebo
- Greater reductions in oral corticosteroid use vs. placebo
- Common AEs: nasopharyngitis, worsening asthma, upper respiratory tract infection, headache, bronchitis, and sinusitis
- Dose: once every 4 or 8 weeks

Competitive environment

Similar to Nucala® (mepolizumab) and Cinqair® (reslizumab), benralizumab targets the IL-5 pathway. However, while Nucala and Cinqair antagonize the IL-5 cytokine, benralizumab targets the IL-5 receptor.

Furthermore, benralizumab may offer patients a once every 8 week dosing option based on trials. It is also being studied in adolescent patients ≥ 12 years old.

However, benralizumab still requires injection. There are also other related products available (ie, Nucala, Cinqair).

For reference, the WAC for Nucala and Cinqair are $33,421 and $30,960 per year, respectively.

- Advantages: novel mechanism, possible 8 week dosing regimen, being studied in adolescent patients
- Disadvantages: requires injection, related products are available (ie, Nucala, Cinqair)
- WAC for Nucala = $33,421 per year
- WAC for Cinqair = $30,960 per year

Expected FDA decision date

An FDA decision regarding the approval of benralizumab is expected in the 4th quarter of 2017.

- PDUFA: 4Q2017

beta-glucuronidase

Manufacturer: Ultragenyx

Therapeutic use

Beta-glucuronidase is in development for the treatment of patients with mucopolysaccharidosis type VII (MPS VII).

Also referred to as Sly Syndrome, MPS VII is a type of lysosomal storage disorder, which is a group of rare inherited metabolic conditions involving a defect in lysosome function. Lysosomes are intracellular enzymes that breakdown molecules such as lipids and certain sugars. When this process is defective, these molecules accumulate and disrupt normal cell function.

An estimated 100 patients in the U.S. are known to have MPS VII. Currently, there are no FDA-approved treatments for this condition.

- Treatment of MPS VII

Clinical profile

Beta-glucuronidase is an enzyme replacement therapy. By replacing the missing enzyme in MPS VII, it is thought that patients will show improvement or slower disease progression.

In a small crossover trial involving 12 patients, the change in urinary glycosaminoglycan (GAG) excretion was decreased by 65% after 24 weeks of therapy, suggesting disease improvement. However, other clinical indices failed to show significant differences. Moreover, the trial investigators did not declare a primary endpoint, instead choosing to evaluate the "totality of the clinical data on a per subject basis".

Notable adverse events reported in the trial included infusion-related reactions, hypersensitivity reactions, and fever.

Based on the trial, beta-glucuronidase is expected to be dosed 4 mg/kg by IV administration every other week.

- Enzyme replacement therapy
- IV formulation
- 65% reduction in urinary GAG after 24 weeks
- Notable AEs: infusion-related reactions, hypersensitivity reactions, fever
- Dose: 4 mg/kg IV every other week

Competitive environment

If approved, beta-glucuronidase will be the first FDA approved drug for MPS VII.

However, beta-glucuronidase requires IV administration and frequent every other week dosing. Moreover, given that beta-glucuronidase is used to treat an orphan disease, it is expected to carry a high cost.

For reference, the WAC for other MPS drugs is approximately $40,000 per month.

- Advantage: first FDA-approved drug for MPS VII
- Disadvantages: IV administration, frequent dosing, high cost
- WAC for other MPS drugs ~$40,000 per month

Expected FDA decision date

Beta-glucuronidase was granted orphan drug and fast track designations by the FDA.

An FDA decision regarding the approval of beta-glucuronidase is expected by November 16, 2017.

- Orphan drug
- Fast track status
- PDUFA: 11/16/2017

copanlisib

Manufacturer: Bayer

Therapeutic use

Copanlisib is in development for the treatment of relapsed or refractory follicular lymphoma (FL) in patients who have received at least 2 prior therapies.

- Treatment of relapsed or refractory FL in patients who have received ≥ 2 prior therapies

Clinical profile

Copanlisib is a phosphatidylinositol-3 kinase (PI3K) inhibitor.

In a non-controlled trial, copanlisib was evaluated in patients with non-Hodgkin lymphoma (NHL), including FL. In the overall NHL population, 59.2% ($p < 0.05$) of patients achieved an objective response with a median duration of response of 687 days. In patients with FL, 58.7% achieved an objective response with a median duration of response of 370 days.

Common adverse events reported in the trial included hypertension, hyperglycemia, fatigue, diarrhea, neutropenia, and anemia. In addition, 4 deaths occurred – 1 case of progressive disease, 1 case of acute respiratory insufficiency, 1 case of Cryptococcal meningitis, and 1 case of sepsis after start of a salvage chemotherapy regimen.

For each cycle, copanlisib is given by IV infusion every week for 3 weeks followed by one week of rest.

- PI3K inhibitor
- IV formulation
- ORR in NHL = 59.2%
- ORR in FL = 58.7%
- Common adverse events: hypertension, hyperglycemia, fatigue, diarrhea, neutropenia, and anemia
- Dose: weekly for 3 weeks per 4-week cycle

Competitive environment

The primary benefit of copanlisib is its high objective response rate (ORR) with nearly 60% achieving a partial or complete response.

Nonetheless, copanlisib still requires IV administration, which must be given weekly. There were also high incidences of hypertension and hyperglycemia.

Zydelig® (idelalisib) is a related drug that is currently available as an oral option for a similar indication.

If copanlisib is priced comparably to Zydelig, the WAC is expected to be approximately $9,000 to $10,000 per month.

- Advantage: high ORR
- Disadvantages: IV administration, frequent dosing, high incidences of hypertension and hyperglycemia, alternative is available (ie, Zydelig)
- Projected WAC based on Zydelig ~$9,000 - $10,000 per month

Expected FDA decision date

Copanlisib was granted orphan drug and fast track designations by the FDA.

The FDA also granted copanlisib a priority review with a decision regarding the approval of copanlisib by November 2017.

- Orphan drug
- Fast track status
- Priority review
- PDUFA: 11/2017

ertugliflozin

Manufacturers: Merck/Pfizer

Therapeutic use

Ertugliflozin is in development as an adjunct to diet and exercise for the treatment of type 2 diabetes mellitus (T2DM).

- Treatment of T2DM

Clinical profile

Ertugliflozin is a selective sodium-dependent glucose transporter 2 (SGLT2) inhibitor.

In placebo-controlled trials, greater improvements in hemoglobin A1c (HbA1c) were achieved with ertugliflozin vs. placebo. Reductions in HbA1c ranged from -0.76 to -1.16 percentage points over placebo.

In addition, greater improvements in body weight (-1.76 kg to -2.16 kg difference from placebo, $p < 0.001$) and blood pressure (BP) were also achieved with ertugliflozin.

The overall rate of adverse events was comparable between ertugliflozin and placebo, with a similar rate of serious adverse events across groups. However, higher incidences of genital mycotic infections were observed with ertugliflozin. There was no increase in urinary tract infections, symptomatic hypoglycemia, or hypovolemia vs. placebo.

Ertugliflozin has been studied as 5 mg – 15 mg given orally once daily.

Currently, a cardiovascular (CV) outcomes trial for ertugliflozin is in progress. The study is enrolling an estimated 8,000 patients with T2DM and established vascular disease. The objective of the study is to demonstrate the non-inferiority of ertugliflozin vs. placebo based on a composite endpoint of CV death, nonfatal myocardial infarction, and nonfatal stroke. A superiority test will also examine the composite endpoint of CV death and hospitalization due to heart failure, as well as CV death alone. The estimated primary study completion date is in October 2019.

- SGLT2 inhibitor
- Oral formulation
- Greater reductions in HbA1c, body weight, and BP vs. placebo
- Notable adverse event: genital mycotic infections
- Dose: once daily
- A CV outcomes trial is in progress

Continued…

ertugliflozin (continued...)

Competitive environment

Similar to other SGLT2 inhibitors, ertugliflozin is given once daily and has shown improvements in HbA1c, body weight, and BP relative to placebo. A CV outcomes trial is also in progress.

Other SGLT2 inhibitors are available, including Jardiance® (empagliflozin), Invokana® (canagliflozin), and Farxiga® (dapagliflozin). Currently, there is insufficient data in renally-impaired patients.

Based on the WAC for other SGLT2 inhibitors, the projected cost for ertugliflozin is approximately $430 per month.

- Advantages: once daily dosing; greater improvements in HbA1c, body weight, and BP; CV outcomes trial in progress
- Disadvantages: other SGLT2 inhibitors are available, insufficient data in renally-impaired patients
- Projected WAC ~$430 per month

Expected FDA decision date

An FDA decision regarding the approval of ertugliflozin is expected in December 2017.

- PDUFA: 12/2017

ertugliflozin/sitagliptin and ertugliflozin/metformin

Manufacturers: Merck/Pfizer

Therapeutic use

Ertugliflozin/sitagliptin (ERTU/SITA) and ertugliflozin/metformin (ERTU/MET) are combination products in development as an adjunct to diet and exercise for the treatment of type 2 diabetes mellitus (T2DM).

- Treatment of T2DM

Clinical profile

ERTU/SITA and ERTU/MET are fixed-dose combinations containing the SGLT2 inhibitor, ertugliflozin, plus a dipeptidyl peptidase-4 (DPP-4) inhibitor or biguanide, respectively.

In trials, ERTU/SITA was compared against the individual components alone and greater reductions in HbA1c were achieved with the combination vs. the individual components. Compared to sitagliptin, the combination improved HbA1c by -0.82 to -1.39 percentage points ($p < 0.001$).

Greater reductions in HbA1c were also observed with ERTU/MET vs. placebo (-0.7 to -0.9 percentage points vs. no change, $p < 0.001$).

Similar to the trials with single-agent ertugliflozin, the combination products were associated with higher incidences of genital mycotic infections.

Both ERTU/SITA and ERTU/MET are administered orally once daily.

- SGLT2 inhibitor combinations
- Oral formulation
- ERTU/SITA: greater reductions in HbA1c vs. components
- ERTU/MET: greater reductions in HbA1c vs. placebo
- Notable adverse event: genital mycotic infections
- Dose: once daily

Competitive environment

While the combination products are administered once daily and offer patients greater dosing convenience, alternative SGLT2 inhibitor combinations are available.

Related products include Glyxambi® (empagliflozin/linagliptin), Invokamet® (canagliflozin/metformin), Invokamet® XR (canagliflozin/metformin extended-release), Synjardy® (empagliflozin/metformin), Synjardy® XR (empagliflozin/metformin extended-release), and Xigduo® XR (dapagliflozin/metformin extended-release).

Based on the WAC for existing SGLT2 inhibitor combinations, the projected cost for ERTU/SITA and ERTU/MET ranges from approximately $430 to $525 per month.

- Advantages: once daily administration, offers dosing convenience
- Disadvantages: other SGLT2 inhibitors combinations are available
- Projected WAC ~$430 - $525 per month

Expected FDA decision date

FDA decisions regarding the approval of ERTU/SITA and ERTU/MET are expected in December 2017.

- PDUFA: 12/2017

exenatide (ITCA 650)

Manufacturers: Intarcia/Johnson & Johnson

Therapeutic use

This new formulation of exenatide is in development as a SC implant for the continuous treatment of patients with T2DM.

- Treatment of T2DM

Clinical profile

Exenatide is a glucagon-like peptide-1 (GLP-1) receptor agonist.

In a trial comparing continuous exenatide to sitagliptin, greater reductions in HbA1c were achieved with exenatide over sitagliptin by -0.8 to -1.5 percentage points ($p < 0.001$).

In addition, a CV outcomes trial comparing continuous exenatide to placebo in over 4,000 patients met its primary endpoint for non-inferiority for CV safety. Thus, Intarcia is now planning a superiority trial against other leading oral and injectable diabetes products; however, the specific comparator drugs that will be studied have not been disclosed yet.

While no major hypoglycemic events were reported, in one trial, approximately 25% of patients developed anti-exenatide antibodies. However, this effect decreased over time and was not different from other formulations of exenatide. No adverse impact was observed.

Common adverse events reported in trials included nausea, vomiting, diarrhea, application site reactions, headache, urinary tract infections, and hypoglycemia.

The SC implant is inserted in the office setting as a 15 minute procedure. The mini-pump is the length of a match stick and is expected to deliver continuous exenatide doses for 6 to 12 months.

- GLP-1 receptor agonist
- SC implant
- Greater reductions in HbA1c vs. sitagliptin
- Non-inferior for CV safety vs. placebo
- Common adverse events: nausea, vomiting, diarrhea, application site reactions, headache, urinary tract infections, and hypoglycemia
- Dose: continuous dosing for 6 to 12 months

Competitive environment

The primary advantage of this product is the continuous delivery of exenatide, which reduces the need for chronic injections. In addition, no CV risks were reported vs. placebo.

However, this product is entering a highly competitive market. Currently, other GLP-1 agonists are available. Similar to Bydureon® (exenatide), a boxed warning may be added to continuous exenatide for the risk of C-cell thyroid tumors.

For reference, the WAC for Bydureon is $623 per month.

- Advantages: offers patient convenience, no CV risks vs. placebo
- Disadvantages: highly competitive market, other GLP-1 agonists are available, uncertain if boxed warning will apply
- WAC for Bydureon = $623 per month

Expected FDA decision date

An FDA decision regarding the approval of continuous exenatide is expected by November 2017.

- PDUFA: 9/2017

fluticasone furoate/umeclidinium bromide/vilanterol

Manufacturer: GlaxoSmithKline

Therapeutic use

Fluticasone furoate/umeclidinium bromide/vilanterol (FF/UME/VIL) is in development for the treatment of chronic obstructive pulmonary disease (COPD).

- Treatment of COPD

Clinical profile

FF/UME/VIL is a triple combination product containing a corticosteroid, long-acting muscarinic antagonist (LAMA), and long-acting beta-agonist (LABA), respectively.

Interim results from a phase 3 trial comparing FF/UME/VIL against budesonide/formoterol demonstrated a 171 mL greater improvement in lung function with FF/UME/VIL, as measured by trough forced expiratory volume in 1 second (FEV1).

In addition, annual moderate to severe exacerbation rates were reduced by 35% at 24 weeks and 44% at 52 weeks.

The most common adverse events were nasopharyngitis, headache, and worsening COPD symptoms.

In trials, FF/UME/VIL was administered by oral inhalation once daily.

- Corticosteroid/LAMA/LABA combination
- Inhalation formulation
- Greater improvement in FEV1 vs. budesonide/formoterol
- Common adverse events: nasopharyngitis, headache, and worsening COPD symptoms
- Dose: once daily

Competitive environment

Unlike Symbicort® (budesonide/formoterol) or Advair Diskus® 250 mcg/50 mcg (fluticasone/salmeterol), which are dosed twice daily, FF/UME/VIL only requires once daily dosing. In addition, it combines three distinct mechanisms of action (MOA) in a single inhaler to improve patients' COPD symptoms, and was shown to be superior to a common budesonide/formoterol formulation.

However, similar to other LABA-containing products, FF/UME/VIL is expected to carry a boxed warning regarding the risk for asthma-related death. Moreover, FF/UME/VIL is not appropriate for use in acute bronchospasms, and if approved, will be entering a highly competitive market.

The WAC for related inhalers is $300 – $373 per month.

- Advantages: once daily dosing, combines three distinct MOA, superior to budesonide/formoterol
- Disadvantages: expected to carry a boxed warning, not appropriate for acute bronchospasms, highly competitive market
- WAC for related inhalers = $300 – $373 per month

Expected FDA decision date

An FDA decision regarding the approval of FF/UME/VIL is expected by November 2017.

- PDUFA: 11/2017

semaglutide

Manufacturer: Novo Nordisk

Therapeutic use

Semaglutide is in development as an adjunct to diet and exercise for the treatment of T2DM.

- Treatment of T2DM

Clinical profile

Semaglutide is a GLP-1 receptor agonist.

In a trial against sitagliptin, semaglutide demonstrated a greater reduction in HbA1c by -0.77 to -1.06 percentage points ($p < 0.0001$), and a greater reduction in body weight by -2.35 kg to -4.20 kg ($p < 0.0001$).

In another trial, greater HbA1c improvements were also observed with semaglutide vs. once weekly exenatide (-1.5 percentage points vs. -0.9 percentage points, $p < 0.0001$). Greater body weight reductions were also achieved (-5.6 kg vs. -1.9 kg, $p < 0.0001$) and more patients achieved HbA1c levels below 7% (67% vs. 40%).

Semaglutide also achieved greater HbA1c reductions vs. insulin glargine by week 30 (-1.21 to -1.64 percentage points vs. -0.83 percentage points, $p < 0.0001$). Moreover, patients taking insulin gained 1.15 kg while patients on semaglutide reduced weight by -3.47 kg to -5.17 kg.

In a CV outcomes trial (SUSTAIN 6), semaglutide also demonstrated a 26% ($p = 0.02$) reduction in CV risk vs. placebo, defined as the composite endpoint of time to first major adverse CV event (ie, CV death, nonfatal myocardial infarction, or nonfatal stroke). However, there was no improvement in CV death or overall mortality.

Common adverse events reported in trials included nausea, vomiting, diarrhea, hypoglycemia, and injection site reactions. In addition, malignant neoplasms were observed in some trials, including cases of C-cell thyroid hyperplasia in connection with thyroid follicular carcinoma.

In other trials, more fatalities were reported in the semaglutide arms vs. the comparator arms; however, it was not clear if the fatalities were directly related to semaglutide.

Based on the trials, semaglutide is given by SC injection once weekly.

- GLP-1 receptor agonist
- SC formulation
- Greater HbA1c reduction vs. sitagliptin, exenatide, and insulin glargine
- 26% reduction in CV risk vs. placebo
- No improvement in CV death or overall mortality
- Common adverse events: nausea, vomiting, diarrhea, hypoglycemia, and injection site reactions
- Dose: once weekly

Continued…

semaglutide (continued...)

Competitive environment

Semaglutide is dosed once weekly, which offers an advantage over many of the existing GLP-1 agonists such as Adlyxin® (lixisenatide), Byetta® (exenatide), and Victoza® (liraglutide). Moreover, semaglutide demonstrated a 26% reduction in CV risk compared to placebo.

However, semaglutide still requires SC administration and is entering a highly competitive market. In addition, there was no improvement in CV death or overall mortality in its CV outcomes trial.

Similar to many of the other GLP-1 agonists, semaglutide is expected to carry a boxed warning regarding the risk for thyroid C-cell tumors.

The WAC for existing GLP-1 agonists is approximately $522 to $675 per month.

- Advantages: once weekly dosing, 26% reduction in CV risk vs. placebo
- Disadvantages: SC administration, highly competitive market, no improvement in CV death or overall mortality, expected to carry a boxed warning
- WAC for existing GLP-1 agonists ~$522 – $675 per month

Expected FDA decision date

An FDA decision regarding the approval of semaglutide is expected by December 2017.

- PDUFA: 12/2017

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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