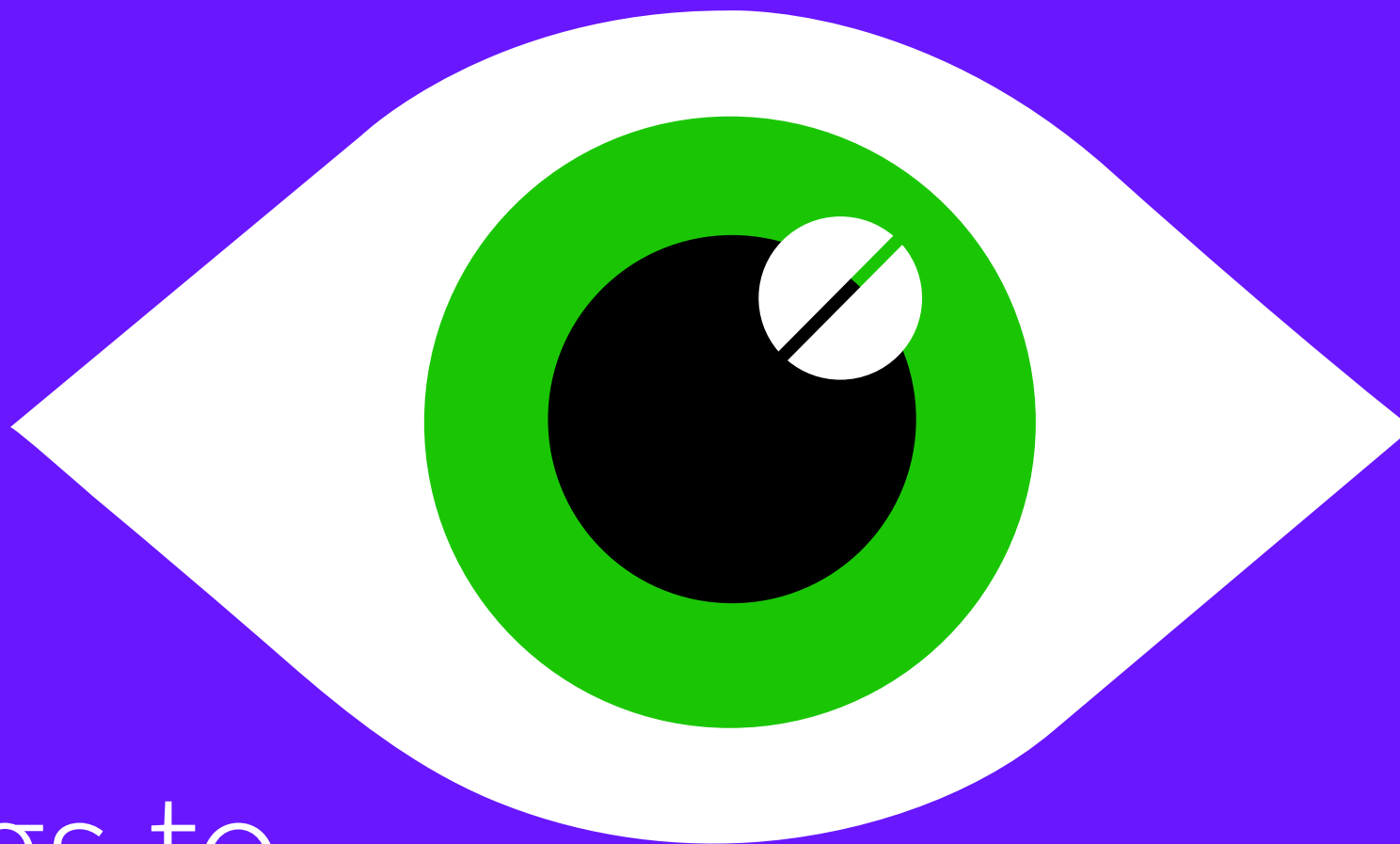


March 2018



Drugs to Watch **2018**

12 new drugs are forecast to enter the market in 2018
and achieve blockbuster sales of \$1 billion or more by 2022

#blockbusterdrugs2018

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The year of the blockbuster

As the drug-pricing debate continues in the U.S., 2017 saw a record of 46 new drug approvals by the Food and Drug Administration (FDA), the highest total in more than two decades. Of these approved drugs, 17 (37%) were approved with Breakthrough Therapy designation, a designation created in 2012 to accelerate the development of products that showed substantial improvement over existing therapies for serious and life-threatening diseases.

The approval of cancer immunotherapies—Novartis' Kymriah (tisagenlecleucel) and Gilead's Yescarta (axicabtagene ciloleucel) chimeric antigen receptor T cell (CAR-T) therapies—grabbed headlines in 2017 because of their ability to revolutionize the treatment of the disease. These therapies, a form of gene therapy, represent a major breakthrough for the development of personalized medicine and lay the groundwork for further advances in this field.



In 2017, we named eight drugs to enter the market in 2017 and reach blockbuster status (i.e., to achieve annual sales of U.S. \$1 billion or more) within five years, and all but one entered the market as expected and all are still anticipated to be future blockbusters.

2018 is forecast to see the launch of 12 new drugs that are predicted to become blockbusters within five years and could feature more potential blockbuster launches than in any year since the launching of the Drugs to Watch series in 2013. More than half of these drugs have been granted Priority Review, Breakthrough Therapy or Fast Track designations. Five drugs on the list are first-in-class and four are for orphan diseases.

In stark contrast to 2017, where more than half of the drugs on our blockbuster list were cancer treatments, only one blockbuster expected to launch in 2018 is for cancer (Erleada [apalutamide]).

Despite political and regulatory uncertainties in the U.S. and EU markets, the pace of pharmaceutical innovation continues to accelerate. 2018 is on track to see many new and potentially game-changing drugs come to market, benefiting the lives of millions of patients around the world.

Introduction

2018 is set to be an exciting year that will see valuable additions to existing treatments as well as disruptions to certain markets and first-in-class treatment options for some diseases.

By 2022, three drugs are forecast to exceed annual revenue of more than \$3 billion, while nine additional drugs are forecast to generate annual sales of between \$1 billion and \$2 billion. The below table ranks these potential blockbuster drugs by highest sales forecasts for 2022.

Glossary of terms

Breakthrough therapy: a designation created in 2012 to accelerate the development of products that showed substantial improvement over existing therapies for serious and life-threatening diseases.

Fast track designation: fast track is a process designed to facilitate the development, and expedite the review of drugs to treat serious conditions and fill an unmet medical need.

Orphan drug: a drug developed specifically to treat a rare medical condition, the condition itself being referred to as “orphan disease.”

Priority review: a priority Review designation means FDA’s goal is to take action on an application within 6 months.

Top 12 to watch

Analysis of 12 new drugs forecast to enter the market in 2018 and achieve blockbuster sales of over \$1 billion by 2022

RANK	DRUG	DISEASE	2018	2019	2020	2021	2022	COMPANY (HQ)
1	Hemlibra (emicizumab)*,†, ,¶,‡‡	Hemophilia A with factor VIII inhibitors	496	1,457	2,356	3,362	4,002	Roche (Switzerland)/Chugai (Japan)
2	Biktarvy (tenofovir alafenamide + emtricitabine + bictegravir)**,¶, ††	HIV infection	896	2,282	3,387	4,296	3,716	Gilead (U.S.)
3	Ozempic (semaglutide)*	Type 2 diabetes	260	862	1,576	2,583	3,469	Novo Nordisk (Denmark)
4	Erleada (apalutamide)¶,**	Non-metastatic CRPC	25	500	1,200	1,600	2,000	Johnson & Johnson (U.S.)
5	Shingrix (Zoster vaccine recombinant, adjuvanted)§§	Shingles	242	537	879	1,202	1,368	GlaxoSmithKline (UK)
6	Patisiran §, ,¶,‡‡	Hereditary TTR amyloidosis	83	373	726	1,104	1,212	Alnylam (U.S.)/Genzyme (U.S.)
7	Epidiolex (plant-derived cannabidiol)‡, ,¶,**	Dravet syndrome and Lennox-Gastaut syndrome	19	266	645	936	1,191	GW Pharmaceuticals (UK)
8	Aimovig (erenumab)*,‡‡	Migraine	115	361	685	941	1,170	Amgen (U.S.)/Novartis (Switzerland)
9	Lanadelumab *,†, ,¶,‡‡	Hereditary angioedema	74	350	629	902	1,153	Shire (Ireland)
10	Elagolix ¶, **,‡‡	Endometriosis	57	268	549	896	1,152	AbbVie (U.S.)
11	Steglatro (ertugliflozin)**	Type 2 diabetes	220	482	769	1,024	1,087	Pfizer (U.S.)/Merck (U.S.)
12	Sublocade (once-monthly buprenorphine)‡,¶,**	Opioid dependence	121	308	439	634	1,072	Indivior (UK)

Data were obtained from the Cortellis Competitive Intelligence database, accessed March 05, 2018 (Source: Thomson Reuters I/B/E/S). Forecasts are in U.S.\$ million. CRPC=castration-resistant prostate cancer.

TTR=transthyretin. *=biological drug. †=Breakthrough Therapy designation. ‡=Fast Track designation. §=RNA interference. | =Orphan Drug designation. ¶=Priority Review. **=small molecule. ††=novel integrase inhibitor. ‡‡=first-in-class. §§= vaccine.

In the HIV market, early 2018 already saw the launch of Gilead's **Biktarvy**, an HIV triplet therapy containing the novel, once-daily integrase inhibitor bictegravir plus tenofovir alafenamide and emtricitabine. This launch is expected to help the business claw back market share from GlaxoSmithKline's (GSK) HIV regimens based on the once-daily integrase inhibitor Tivicay (dolutegravir), cementing Gilead's leading position in the market.

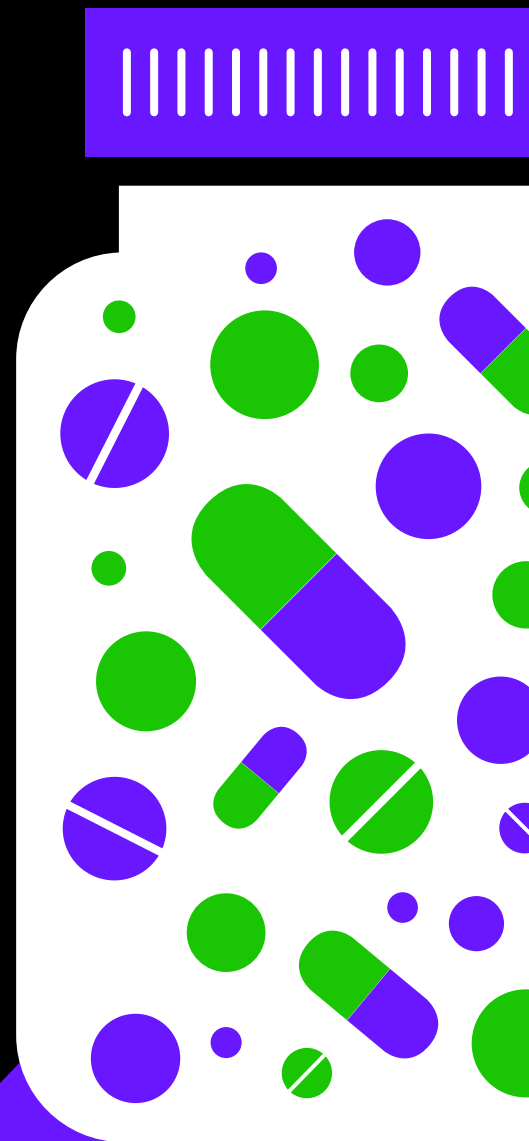
The crowded type-2-diabetes market is set to gain two new entrants in 2018, Novo Nordisk's **Ozempic** (semaglutide) and Pfizer/Merck's **Steglatro** (ertugliflozin). These treatments are forecast to perform well due to their superior efficacy and safety versus competitor products.

In the area of orphan diseases (which, as defined in the U.S., are rare diseases affecting fewer than 200,000 people), three first-in-class drugs have blockbuster potential. Roche/Chugai are launching **Hemlibra** (emicizumab) for the treatment of hemophilia A with factor VIII inhibitors. For treatment of hereditary angioedema, Shire is on track to launch **lanadelumab**. Alnylam and Genzyme are also forecast to launch **patisiran** for treatment of hereditary transthyretin amyloidosis. Each of these orphan drugs is set to become the new standard of care in its respective disease area.

First-in-class **Aimovig** (erenumab), from Amgen/Novartis, will contribute to the transformation of the migraine market. AbbVie's first-in-class **elagolix** could become the first new oral treatment option for endometriosis-associated pain in more than a decade.

A major development for Johnson & Johnson is **Erleada** (apalutamide), which has become the first FDA-approved treatment for non-metastatic castration-resistant prostate cancer. GW Pharmaceuticals' **Epidiolex** (plant-derived cannabidiol) is positioned to be the first FDA-approved cannabidiol-based drug for seizures associated with the rare childhood epilepsy indications Lennox-Gastaut syndrome and Dravet syndrome.

The only vaccine to make the list is GSK's **Shingrix** (Zoster vaccine recombinant, adjuvanted), which is set to become the market leading shingles vaccine. Indivior's **Sublocade** (once-monthly buprenorphine) provides a welcome addition to the armamentarium of treatments available to combat opioid addiction, which was declared a public health emergency in late 2017 by the U.S. government.¹



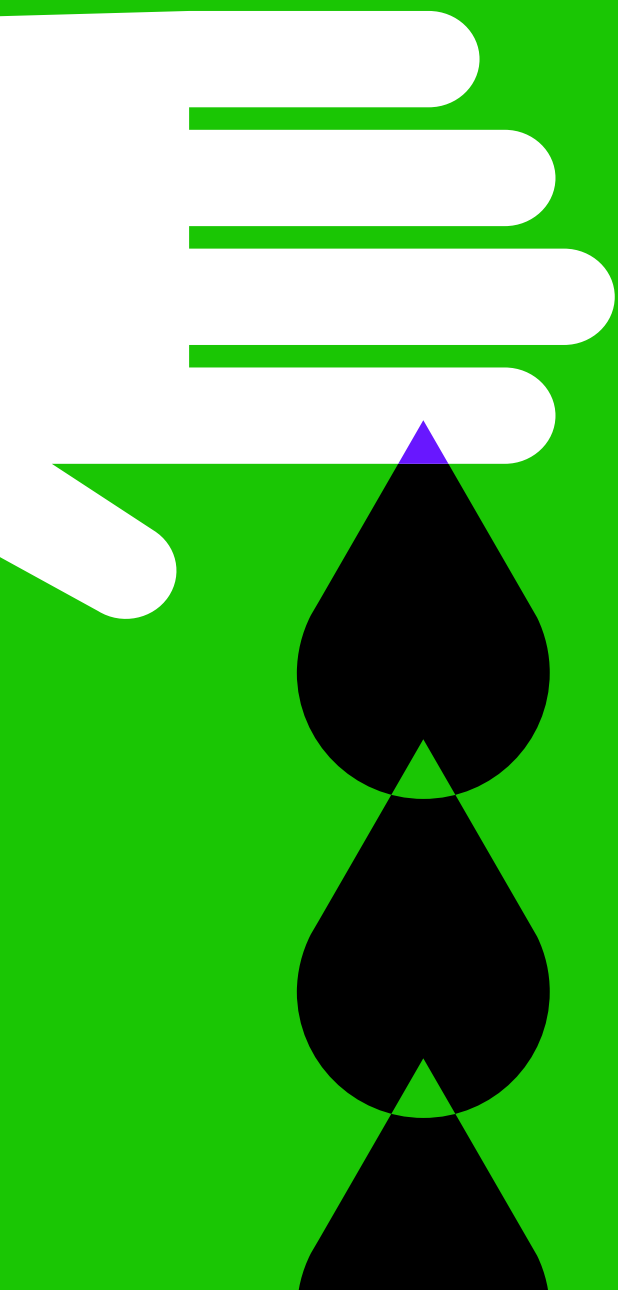
Methodology



Data for this report were compiled from the Cortellis database, from Clarivate Analytics, the premier source of life sciences competitive intelligence information and analytics. The Cortellis database covers and includes data gathered from diverse sources, including annual filings, drug pipelines, clinical trials, patents, chemistry, deals, conferences, and company announcements.

Using the advanced search functions, drugs in phase 2 or phase 3 trials, at pre-registration or registration stage, or already launched early in 2018 were selected. From the results, drugs in those stages of development but already launched prior to 2018 were excluded and the dataset was then filtered for drugs that had total forecast sales of \$1 billion or more in 2022. This filtering process produced a list of 28 drugs, which were then manually reviewed to determine whether these products were likely to go to market in 2018, based on factors such as the company's expected approval or launch date.

Following this manual review, 12 "Drugs to Watch" for 2018 were selected. Each drug was subsequently researched and evaluated in its individual context, covering clinical trial results, regulatory status, the market for each drug (including analysis of competitor drugs) and regulatory designations (e.g., Orphan Drug, Priority Review). Sources for these data included specialist SWOT analyses compiled by Cortellis editors, pharmaceutical company press releases and other publications (e.g., annual filings), peer-reviewed publications and competitor sales (obtained via the Cortellis database).



01.

Hemlibra for hemophilia A with factor VIII inhibitors

Hemophilia A is one of the most common congenital severe bleeding disorders, which globally affects around 350,000 people. The disorder is the result of a deficiency in the clotting protein factor VIII and therapy to prevent or treat bleeding is via recombinant factor VIII replacement.²

However, as a consequence of treatment, up to 30% of patients with severe hemophilia A can develop antibodies (i.e., inhibitors) to factor VIII, which bind to factor VIII and impair its clotting action. Factor VIII inhibitors are the most serious and challenging complication of hemophilia treatment, increasing morbidity and mortality since bleeds no longer respond to standard factor replacement therapy.³

Hemlibra expected sales

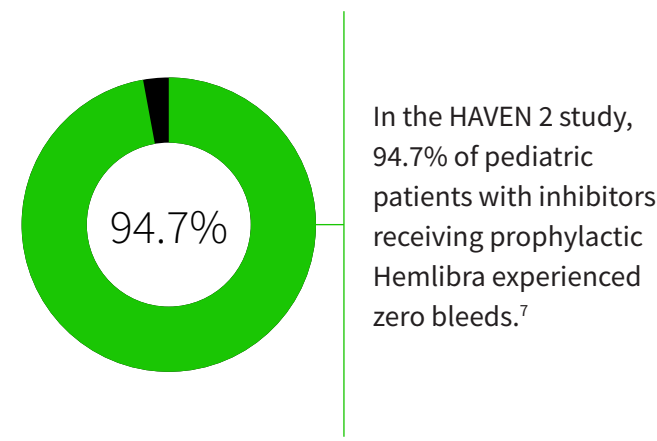
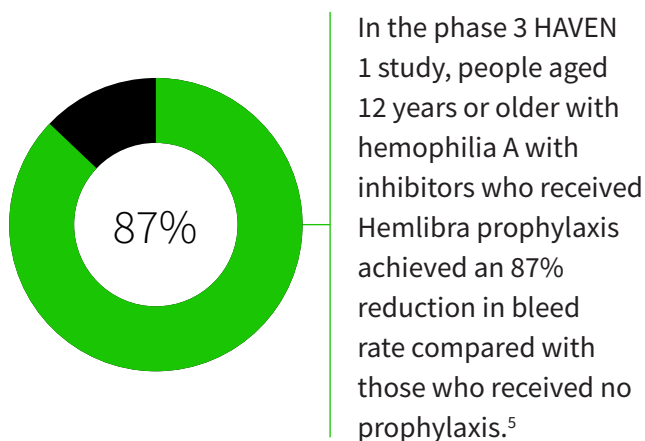


Hemlibra

A novel approach to treating hemophilia A, Roche/Chugai's once-weekly Hemlibra (emicizumab) is a bispecific antibody that simultaneously binds to both factor IXa and factor X, bringing them into spatially appropriate position to mimic the function of factor VIII. Although launched in the U.S. in late 2017 for hemophilia A with inhibitors, the Prescription Drug User Fee Act (PDUFA) action date for approval of Hemlibra's June 2017 filing had been set for February 2018.⁴ However, with Priority Review, Breakthrough Therapy, and Orphan Drug designations, the FDA approved Hemlibra almost three months earlier in November 2017, which led to a product launch in late December 2017.⁵

Nevertheless, Hemlibra is one to watch in 2018 when promotion begins in full force and launches occur elsewhere. In February 2018, the European Medicines Agency (EMA) approved Hemlibra⁶, and launches in both Europe and Japan are expected in 2018. Sales of \$496 million have been forecast for 2018, reaching blockbuster status in 2019 with \$1.457 billion and increasing steeply to \$4.002 billion in 2022.

Hemlibra has been approved for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children with hemophilia A developing factor VIII inhibitors.⁵ This makes Hemlibra the first agent to be approved in close to 20 years in this disease setting, which is currently dominated by Shire's Feiba (a prothrombin coagulant complex) and Novo Nordisk's NovoSeven (coagulation factor VIIa [recombinant]). Data from the HAVEN study have supported approval.



The hemophilia market

From 2018, both Feiba and NovoSeven are expected to see significant sales losses due to competition from Hemlibra. However, the biggest impact is likely to come from regulatory approval for use of Hemlibra in the broader population of patients living with hemophilia A without inhibitors, with HAVEN 3 data released in November 2017 showing superiority of Hemlibra in this setting versus standard factor VIII prophylaxis.⁸ Additionally, less frequent every-four-week dosing will drive sales, with HAVEN 4 data indicating clinically meaningful bleeding control consistent with other HAVEN trials for this dosing approach.⁹

Most patients living with hemophilia have to regularly infuse their treatment two to three times per week.¹⁰ Frequent intravenous administration can lead to patient dissatisfaction and non-adherence to treatment, and there is therefore a substantial need for long-acting treatments. Since its launch in 2014, Bioverativ's first long-acting recombinant factor VIII replacement therapy Eloctate has taken significant market share from Shire's long-term market-leading recombinant factor VIII replacement therapy Advate.

Eloctate is forecast to be a blockbuster in 2018, achieving \$1.153 billion sales, while Advate sales are declining from a peak of \$2.360 billion in 2013. Despite this decline, Advate is forecast to generate \$1.795 billion worth of sales in 2018, retaining market-leader status. However, sales are forecast to decline further thereafter.

Shire's own long-acting recombinant factor VIII replacement therapy Adynovate was launched in late 2015. However, sales of the drug are on par with other recently launched long-acting agents, with sales of Adynovate over the next five years not expected to exceed \$600 million.

Hemlibra will challenge standard-of-care factor VIII replacement therapy with its novel action, impressive efficacy and potential monthly dosing. Despite a black box warning (the FDA's strictest warning for potentially serious side effects) due to thrombotic events, the treatment is set to lead the market from 2020 onwards.

↑ ELOCTATE (BIOVERATIV)
\$1.153B
expected sales in 2018

↓ ADVATE (SHIRE)
\$1.795B
expected sales in 2018

↓ ADYNOVATE (SHIRE)
\$600M
sales over next five years not expected to exceed this number

02.

Biktarvy

for HIV infection

According to the World Health Organization (WHO), an estimated 37 million people globally are living with HIV of whom approximately 21 million are receiving antiretroviral therapy, which targets steps in the viral life cycle.¹¹ While antiretroviral therapy does not cure HIV infection, it suppresses viral replication and allows an individual's immune system to strengthen and regain the capacity to fight off infections, making HIV a chronic disease requiring life-long therapy. Expanding access to antiretroviral treatment is at the heart of a new set of targets for 2020, issued by the WHO, which aim to end the AIDS epidemic by 2030.¹¹

Biktarvy

Gilead's new single-tablet HIV treatment, Biktarvy, was launched in early 2018. This once-daily tablet contains the new integrase inhibitor bictegrovir, plus the nucleoside reverse transcriptase inhibitor tenofovir alafenamide and the nucleoside reverse transcriptase inhibitor emtricitabine. A U.S. regulatory filing had been submitted in June 2017 and Biktarvy was approved as expected in mid-February 2018 and launched shortly thereafter;¹² an EU marketing-authorization application was filed in July 2017.¹³



Biktarvy virological suppression, similar to therapy regimens containing Tivicay

The HIV market

Medication adherence is vital for HIV drugs to effectively suppress viral load (i.e., the amount of HIV in the blood), and simplicity and durability of treatments therefore define the HIV market. Since Gilead's 2006 launch of the first single-tablet once-daily triple regimen, Atripla (emtricitabine/efavirenz/tenofovir disoproxil), followed by Complera (emtricitabine/rilpivirine/tenofovir disoproxil) and Stribild (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil), the company has been gaining market share from the previous market leader, GSK.

However, the 2014 launch of GSK's Triumeq (dolutegravir/lamivudine/abacavir) enabled GSK to claw back market share from Gilead. This drug was the first single-pill regimen not to contain tenofovir disoproxil (which can cause bone toxicity). Triumeq also had superior viral suppression versus Atripla and did not require the use of a second drug to boost the levels of the integrase inhibitor component, Tivicay (dolutegravir).

In response, Gilead launched several safer, best-in-class regimens containing tenofovir alafenamide. These regimens, including Genvoya (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide), launched in 2015, and Odefsey (rilpivirine/emtricitabine/tenofovir alafenamide) and Descovy (emtricitabine/tenofovir alafenamide), launched in 2016, helped Gilead regain market share. Both Genvoya and Odefsey were featured in our 2016 Drugs to Watch report.

In January 2018, GSK launched Juluca (dolutegravir/rilpivirine), which contains its best-in-class integrase inhibitor Tivicay plus rilpivirine.

Compared with GSK's Tivicay, Gilead's competitor integrase inhibitor Vitekta (elvitegravir) has disadvantages, such as the requirement for boosting with ritonavir to increase its level to allow for once-daily dosing. However, Gilead's new drug, bictegravir, has shown equivalent safety and efficacy to Tivicay, and like Tivicay, is a true once-per-day integrase inhibitor and does not require combination with a boosting agent.

In previously untreated patients infected with HIV-1 and in virologically suppressed adults who switched to Biktarvy, the drug has demonstrated high rates of virological suppression (~93%) similar to therapy regimens containing Tivicay. No treatment-emergent resistance has been associated with Biktarvy through 48 weeks in phase 3 trials.¹⁴

With the entry of the generic version of tenofovir disoproxil in December 2017, potential launches of generic versions of Atripla and Truvada (tenofovir disoproxil/emtricitabine) in the short term, and GSK's increasing market share for its Tivicay-based regimens, Gilead is likely to heavily promote Biktarvy. Physicians may also support a true once-daily combination of best-in-class tenofovir alafenamide and an integrase inhibitor non-inferior to Tivicay.

Sales of \$896 million are expected for Biktarvy in 2018, quickly rising to blockbuster sales of \$2.282 billion in 2019 and forecast to be \$3.716 billion in 2022. This sales trajectory is comparable to those figures for Triumeq, which had sales of \$1.115 billion in 2015 (its first full year in the market after launch). Anticipated sales for Triumeq in 2018 (i.e. five years after launch) are \$3.684 billion.

Biktarvy expected sales





03.

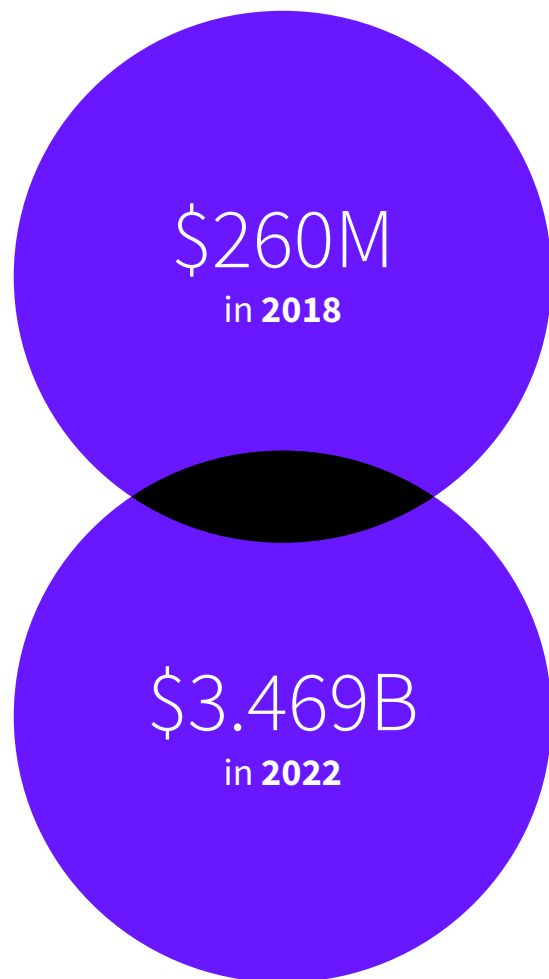
Ozempic for type 2 diabetes

The hormone insulin, which is produced by the pancreas, is responsible for controlling the amount of glucose in the blood. Diabetes is a chronic disease that occurs either when the pancreas does not produce insulin (type 1) or when the pancreas does not produce enough insulin or the body's cells do not react to insulin (type 2). Approximately 90% of patients with diabetes are living with type 2 diabetes.¹⁵

More than 425 million adults are living with diabetes globally. By 2045, this number is projected to rise to 629 million. In 2017, diabetes caused at least \$727 billion in health expenditure.¹⁶

Diabetes is a major cause of blindness, kidney failure, heart attacks, stroke and lower limb amputation.¹⁵ But the risk factors related to these complications can be reduced through effective control of blood sugar levels.

Ozempic expected sales



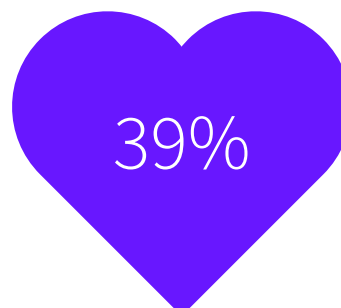
Ozempic

One class of medication that is used to treat type 2 diabetes is known as glucagon-like peptide-1 (GLP-1). GLP-1 treatments help stimulate the body's own insulin release, limit how much sugar gets into the blood from the liver and slow down how quickly food leaves the stomach.¹⁷

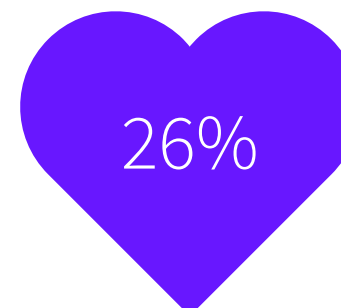
As predicted in the Drugs to Watch 2017 report, Novo Nordisk's weekly GLP-1 analog Ozempic (semaglutide) was approved for treatment of type 2 diabetes that year based on positive data from the SUSTAIN program. However, the late approval in December 2017 delayed the expected year-end launch to February 2018.

In the SUSTAIN trial, Ozempic demonstrated superiority in blood glucose and weight control over existing options, including Januvia (sitagliptin), Bydureon (controlled-release exenatide) and Lantus (insulin glargine).¹⁸⁻²⁰ Like Novo Nordisk's market-leading GLP-1 analog Victoza (liraglutide), Ozempic has demonstrated a positive cardiovascular effect, reducing stroke risk by 39% and myocardial infarction risk by 26%.²¹

STROKE RISK
REDUCED BY



MYOCARDIAL INFARCTION
RISK REDUCED BY

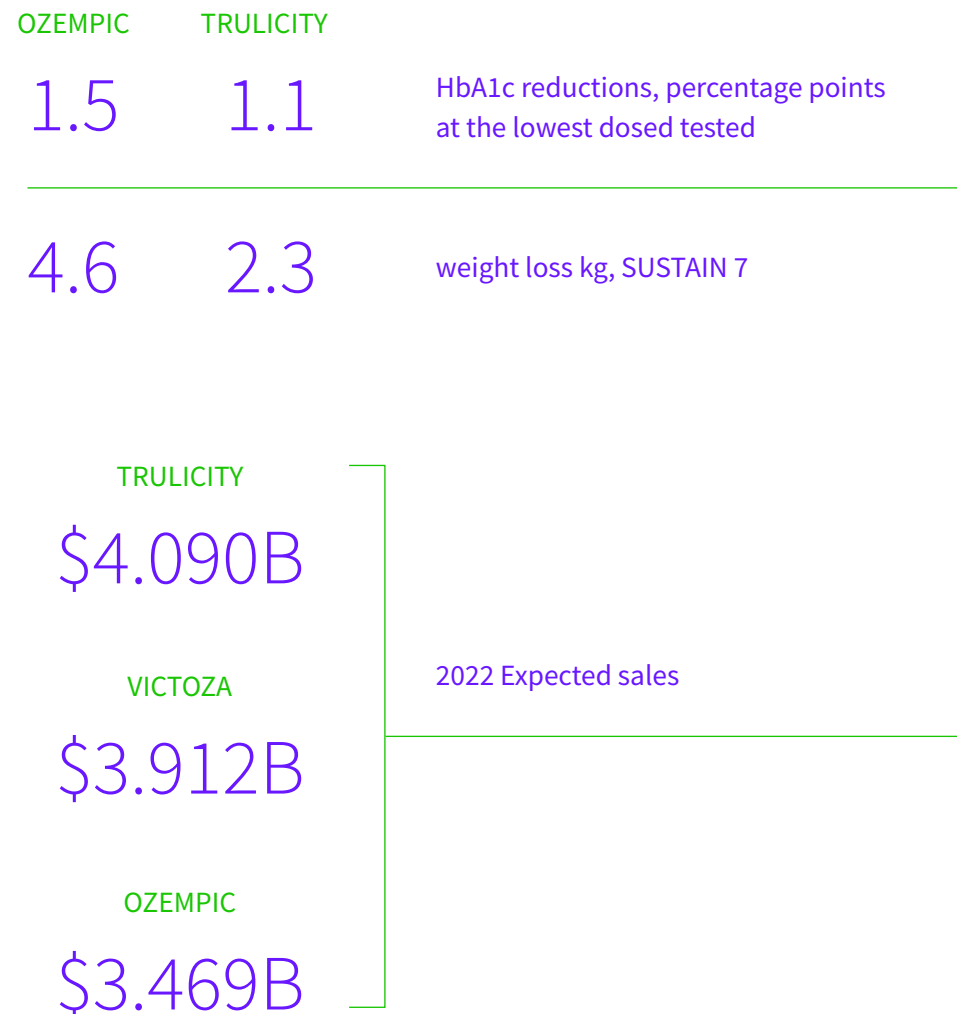


The GLP-1 market

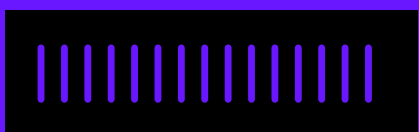
Once-daily Victoza has lost market share to longer acting, weekly GLP-1 analogs, particularly Eli Lilly's Trulicity (dulaglutide), but data released in 2017 from SUSTAIN 7 showed that Ozempic achieved greater HbA1c reductions (i.e., a measure of average blood sugar levels over weeks/months) compared with Trulicity (1.5 versus 1.1 percentage points at the lowest doses tested).²² Data from the SUSTAIN 7 study also showed that patients treated with Ozempic had doubled the weight loss versus patients treated with Trulicity (4.6 kg versus 2.3 kg).²²

Cardiovascular outcomes for Trulicity are being assessed in the REWIND study,²³ and data are expected from 2018 onwards. With a positive cardiovascular effect already demonstrated for Ozempic, it will put pressure on Trulicity and help Novo Nordisk regain market share, although Trulicity is anticipated to lead the GLP-1 market by 2022, with forecasts of \$4.090 billion for Trulicity, \$3.912 billion for Victoza and \$3.469 billion for Ozempic.

Injectable GLP-1 analogs are commonly used after therapy with oral drugs has failed. However, Novo Nordisk's once-daily oral formulation of semaglutide (assessed in the PIONEER program²⁴) could be a game-changing development for the treatment of type 2 diabetes. Availability of an oral GLP-1 formulation could result in earlier switching from small-molecule oral antidiabetic medications to GLP-1 analogs, which are viewed as more efficacious and have a proven cardiovascular benefit. Semaglutide is also being assessed for treatment of obesity (in view of its weight loss effects) and non-alcoholic steatohepatitis (i.e., fatty liver disease) and thus presents a competitive threat to a range of drugs on the market.



04.



Erleada for prostate cancer

Prostate cancer is the most common cancer in the U.S. and the third most common cause of cancer death in U.S. men. More than 164,000 men will be diagnosed with prostate cancer in 2018 and about one man in 41 will die of prostate cancer.²⁵

Male sex hormones, known as androgens, are required for normal growth and function of the prostate. Androgens are also necessary for prostate cancers to grow. Hormone therapy for prostate cancer—also called androgen suppression therapy or androgen deprivation therapy—can block the production and use of androgens. When the disease continues to progress despite androgen deprivation, it is considered to be castration resistant.²⁶

24.3 months

metastasis-free survival extension,
compared to placebo

72%

reduction in risk of distant
metastasis or death

Erleada expected sales



\$25M
in 2018

\$2.000B
in 2022

Erleada and the market for CRPC treatments

The castration-resistant prostate cancer (CRPC) market is dominated by oral next-generation anti-androgens Zytiga (abiraterone; Johnson & Johnson) and Xtandi (enzalutamide; Pfizer/Astellas), which are approved for CRPC that has metastasized (i.e. spread to other parts of the body). However, until February 2018, no FDA-approved treatment options were available for men with non-metastatic CRPC until the spread of the cancer could be confirmed by radiographic assessment.

While Zytiga and Xtandi battle to expand their market share, including the market for patients with non-metastatic disease, Johnson & Johnson's second-generation oral anti-androgen treatment, Erleada (apalutamide), became the first to be approved in that setting in mid-February 2018.²⁷ This approval came two months ahead of its April 2018 PDUFA date and only four months after its new drug application (NDA) filing in October 2017, which had been granted Priority Review.

The NDA submission for Erleada was based on data from the pivotal phase 3 SPARTAN trial. Trial results showed that the drug significantly extended metastasis-free survival by 24.3 months compared with placebo, with a 72% reduction in risk of distant metastasis or death.²⁸

Xtandi has also shown positive data in non-metastatic CRPC in the PROSPER trial, with an increase in metastasis-free survival of 21.9 months and a 71% reduction in the risk of developing metastases or death,²⁹ and Xtandi was filed for U.S. approval in this setting in January 2018.³⁰ Erleada, however, has first-mover advantage, having been launched in February 2018 shortly after approval, and is forecast to see blockbuster sales from 2020 onwards.

Besides non-metastatic CRPC, Erleada also has potential applications in other clinical settings, including metastatic hormone-sensitive prostate cancer (assessed in the TITAN trial³¹), in high-risk localized/locally advanced prostate cancer (assessed in the ATLAS trial³²), and in combination with Zytiga for treatment of metastatic CRPC in men who have not yet received chemotherapy, which are contributing to its blockbuster potential.

05.

Shingrix

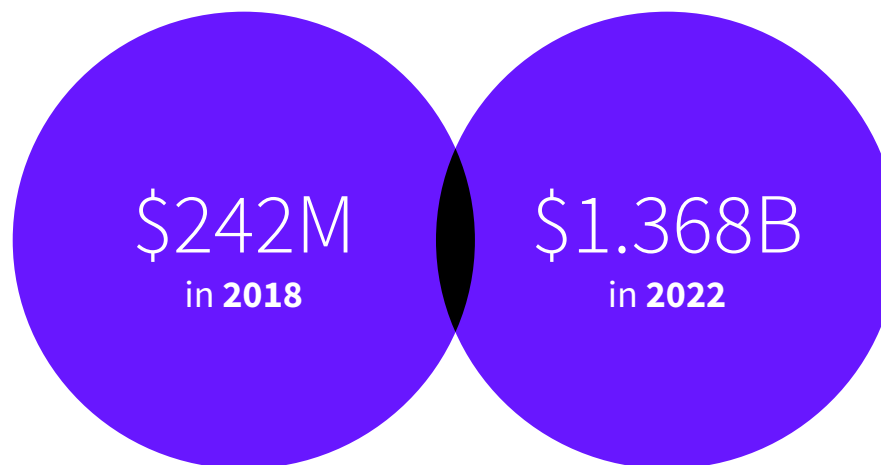
for herpes zoster
(shingles) infection

One in three people in the U.S. will develop shingles, also known as herpes zoster, in their lifetime.³³ Shingles are caused by the varicella zoster virus, the same virus that causes chickenpox. After a person recovers from chickenpox, the virus stays dormant in the body. It remains unclear why the virus can reactivate years later, causing shingles.³³



97.2%
risk reduction in adults aged 50 years or older versus placebo in the phase 3 ZOE-50 trial

89.8%
risk reduction in adults aged 70 years or older versus placebo in the ZOE-70 trial



Shingrix
expected sales

Shingrix and the shingles vaccine market

Following FDA approval in October 2017, GSK's Shingrix (Zoster vaccine recombinant, adjuvanted) is set to enter the market in early 2018 and will be the first new shingles vaccine in more than a decade.³⁴ Shingrix is anticipated to quickly take market share from Zostavax (shingles vaccine [live]; Merck), previously the only FDA-approved shingles vaccine.

In the phase 3 ZOE-50 trial, Shingrix reduced the risk of shingles by 97.2% in adults aged 50 years or older versus placebo.³⁵ In the ZOE-70 trial, Shingrix reduced the risk of shingles by 89.8% in adults aged 70 years or older compared with placebo. By contrast to Zostavax, for which protection against shingles wanes over time, GSK's vaccine offers lasting protection.³⁶ Shingrix can also provide protection for those who have previously received Zostavax. Although Zostavax is more convenient, requiring one dose versus two for Shingrix, the U.S. Centers for Disease Control and Prevention made a formal recommendation in January 2018 to use Shingrix over Zostavax in adults aged 50 years or older in view of Shingrix's superior efficacy.³⁷ Within two years of its launch, Shingrix is expected to replace Zostavax as the market-leading shingles vaccine, with 2019 forecasts of \$537 million for Shingrix and \$492 million for Zostavax (decreasing from a peak of \$765 million in 2014). Shingrix sales are forecast to exceed the \$1 billion mark from 2021 onwards.



06.

Patisiran for hereditary transthyretin-mediated amyloidosis

Transthyretin amyloidosis is a slowly progressive condition characterized by the buildup of abnormal deposits of a protein called amyloid (amyloidosis) in the body's organs and tissues.³⁸
In most cases, the condition is inherited. The exact prevalence of the disease is unknown, but it is less common among Americans of European descent, where it affects about one in 100,000 people. The cardiac form of transthyretin amyloidosis is more common among people with African ancestry, affecting between 3% and 3.9% of African Americans and approximately 5% of people in some areas of West Africa.³⁸

Patisiran and the market for transthyretin amyloidosis treatments

In December 2017, shortly after reporting top-line data, Alnylam completed its NDA submission for patisiran, an intravenously administered RNA interference (RNAi) therapeutic targeting the transthyretin gene.³⁹ Together with Sanofi, Alnylam filed for EU approval that same month.⁴⁰

Patisiran was filed for treatment of patients with debilitating hereditary transthyretin-mediated amyloidosis. If successful, patisiran will be the first FDA-approved RNAi therapeutic. The FDA granted patisiran Priority Review with a PDUFA date in August 2018, and Fast Track and Breakthrough Therapy designations.⁴¹ The FDA also expanded patisiran's Orphan Drug designation from transthyretin familial amyloid polyneuropathy to the broader indication of hereditary transthyretin-mediated amyloidosis.⁴²

In the EU, the EMA granted accelerated assessment.⁴³ Launch of this treatment in both the U.S. and the EU is expected later in 2018, putting patisiran on track to become the standard of care for hereditary transthyretin-mediated amyloidosis.

The current standard of care for this disease is liver transplantation but the risks of surgery, acute liver rejection and increased risk of infection make it an option only in patients in good clinical condition who can tolerate the intervention.

Vyndaqel (tafamidis, Pfizer), a first-in-class anti-amyloid therapy, is currently the only approved anti-amyloid treatment for transthyretin familial amyloid polyneuropathy. However, this therapy is limited to treatment for early-stage disease, and is not yet approved in the U.S.⁴⁴

Patisiran expected sales



Competitor drugs, expected sales in 2022



Patisiran has potential to be a best-in-class treatment. In the APOLLO phase 3 trial in patients with transthyretin familial amyloid polyneuropathy (including those with cardiac symptoms), patisiran showed significant improvement of neurological impairment (with a 34-point difference in the mNIS+7 scale [a composite measure of neurological impairment] at 18 months), improved quality of life and reduced disease symptoms and disability with an encouraging safety profile.⁴⁵

Treatment benefit was better than with Ionis' potential competitor inotersen, an antisense drug that inhibits transthyretin. In the phase 3 NEURO-TTR study, inotersen showed a 19.7-point treatment benefit compared with placebo at month 15.⁴⁶ Additionally, inotersen was associated with safety signals, including cases of severe thrombocytopenia.

Inotersen was filed for approval ahead of patisiran in November 2017, in both the U.S. and EU.^{47,48} While it is likely to be the first of the two to be approved (PDUFA date is in July 2018), patisiran is set to reap the greatest revenue due to its superior efficacy and safety. In 2019, the first full year following launch, patisiran sales of \$373 million are forecast, rising to \$1.212 billion in 2022. Inotersen sales are forecast at \$106 million in 2019 and \$533 million in 2022. Vyndaqel sales of \$170 million are forecast for 2022.

07. Epidiolex

for Dravet syndrome and Lennox-Gastaut syndrome



Epilepsy is a chronic disorder of the brain that affects people of all ages. About 50 million people worldwide have epilepsy, making it one of the most common neurological diseases globally.⁴⁹ However, two rare forms of epilepsy exist, Dravet syndrome and Lennox-Gastaut syndrome, which affect people during childhood.

Lennox-Gastaut syndrome is a form of severe epilepsy and is characterized by multiple types of seizures and intellectual disability. People with Lennox-Gastaut syndrome begin having frequent seizures in early childhood, usually between the ages of 3 and 5 years. More than three-quarters of affected individuals have tonic seizures, which cause the muscles to stiffen (contract) uncontrollably.⁵⁰

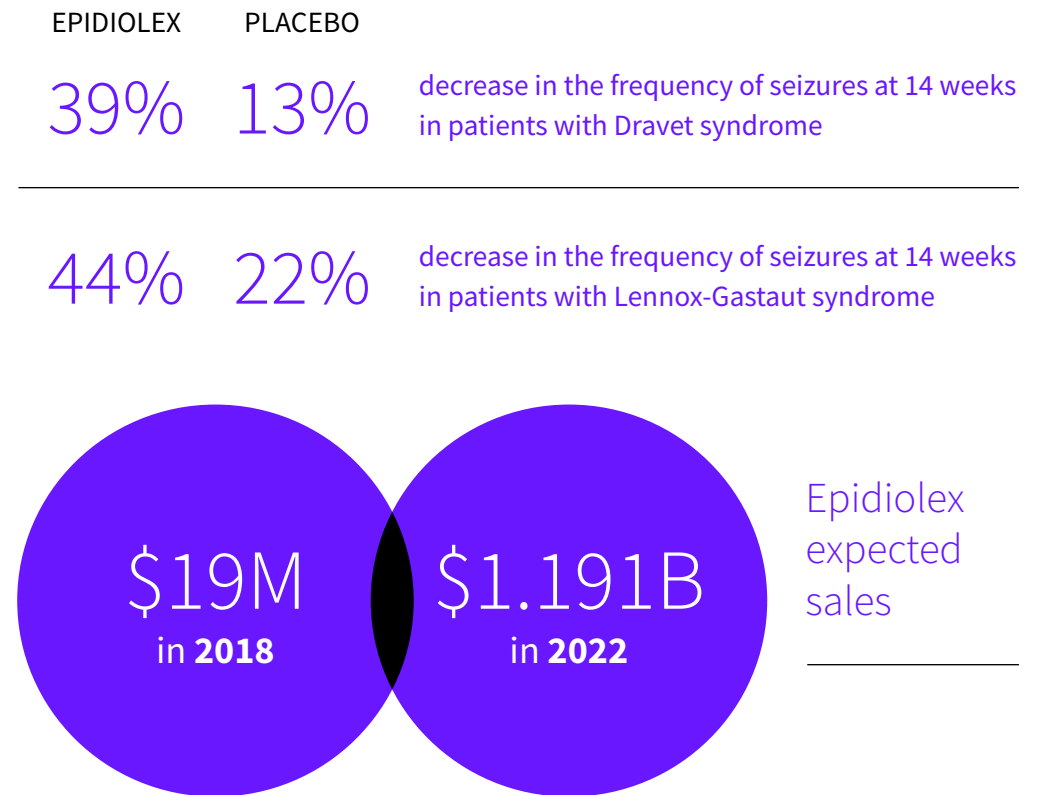
Dravet syndrome is another severe form of epilepsy. It appears during the first year of life with frequent febrile seizures (fever-related seizures).⁵¹

Epidiolex and the epilepsy market

Following a NDA submission in June 2017, GW Pharmaceuticals' Epidiolex (plant-derived cannabidiol) has the potential to become the first cannabinoid-based anti-epileptic medication. The FDA has granted a Priority Review with a PDUFA date in June 2018.⁵² A marketing authorization application for the drug was also submitted in December 2017.⁵³ Efficacy data have been compelling in both disease settings, supporting the possibility of approval.

In patients with Dravet syndrome, a disease for which there are no FDA-approved therapies, Epidiolex treatment led to a 39% decrease in the frequency of seizures at 14 weeks versus 13% for patients in the placebo group.⁵⁴ In patients with Lennox-Gastaut syndrome, a disease highly resistant to treatment, Epidiolex treatment led to a 44% reduction in frequency of seizures at 14 weeks versus 22% for patients in the placebo group.⁵⁵

However, if approved Epidiolex will likely encounter bureaucratic barriers to distribution and political hurdles associated with cannabis-derived medicines, particularly in the U.S. where strict guidelines for use of medicinal cannabis exist.⁵⁶ Within five years of launch, sales of Epidiolex are anticipated to reach \$1.191 billion. Epidiolex is worth looking out for as it could pave the way for future cannabis-derived therapeutics in the U.S.

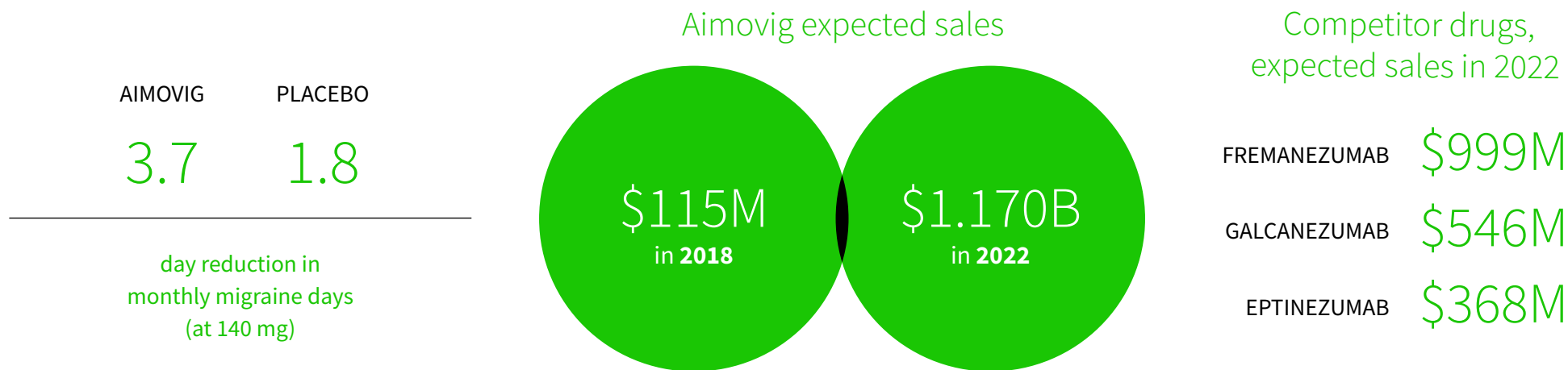


08.

Aimovig for migraine

Migraine is characterized by recurrent headaches that cause moderate to severe pain. The disorder is the third most common disease in the world with an estimated global prevalence of 14.7%. Migraine is responsible for 2.9% of all years of life lost to disability and is the leading cause of disability among all neurological disorders.^{57,58} In terms of treatment satisfaction, fewer than 50% of patients with migraine are satisfied with their current treatment.⁵⁸





Aimovig and the market for migraine treatments

After little movement for many years, the migraine-prevention market is about to undergo a transformation with several new drugs, known as calcitonin gene-related peptide (CGRP) receptor inhibitors, poised to enter the market from 2018 onwards. CGRP, a neuropeptide, has been shown to be released during migraine attacks and may play a causative role in induction of migraine attacks.⁵⁹

Aimovig (erenumab) has the potential to be the first-to-market CGRP inhibitor and become a blockbuster drug. Aimovig, a once-monthly subcutaneously administered monoclonal antibody, was assessed in the ARISE and STRIVE trials for the prevention of episodic migraine. STRIVE data showed a significant 3.7-day reduction in monthly migraine days (at 140 mg) versus 1.8 days for placebo.⁶⁰ Following a Biologics License Application (BLA) submission in May 2017, a PDUFA date for May 2018 was set and, with the robust data, approval is likely.⁶¹

A first-to-market advantage will be crucial for Aimovig since competition from two other subcutaneously administered monoclonal antibodies targeting CGRP is not far behind.

Both Eli Lilly's galcanezumab (once-monthly dosing) and Teva's fremanezumab (once-monthly or quarterly dosing) filed for U.S. approval in October 2017.^{62,63} Alder's intravenously administered monoclonal antibody, eptinezumab (quarterly dosing), is in phase 3 development but has shown excellent 100% response rates in some patients and is expected to be filed in 2018.⁶⁴

Aimovig is anticipated to become the market leader in the CGRP class, with forecasts of \$1.170 billion in 2022, followed by fremanezumab at \$999 million (which has preferable quarterly dosing). 2022 sales for galcanezumab are forecast at \$546 million and eptinezumab at \$368 million. However, eptinezumab is forecast to increase to \$946 million in 2023 due to strong data.

Other oral CGRP inhibitors of note include Allergan's atogepant and Biohaven's rimegepant, which could be launched in the medium-term and disrupt the market due to their differentiated oral dosing.

A stylized graphic of lips in shades of green, positioned on the left side of the page. The lips are rendered with a gradient from dark green to bright green, and are set against a background of concentric, wavy green shapes that create a ripple effect.

09.

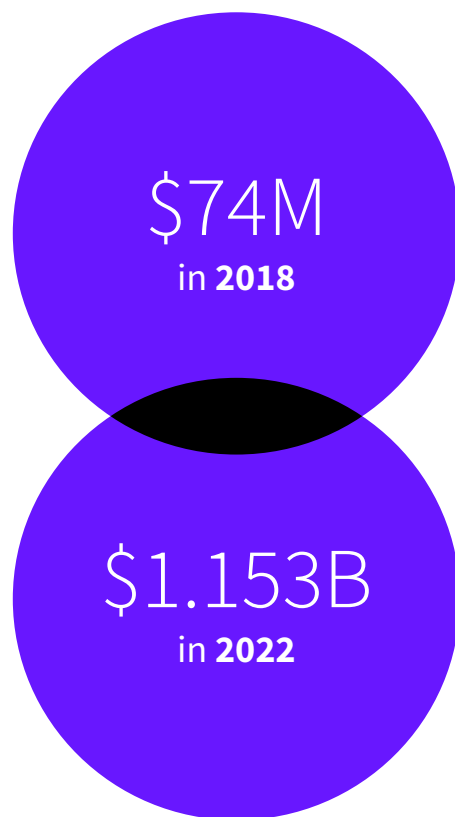
Lanadelumab

for hereditary
angioedema

Hereditary angioedema is a rare genetic disorder caused by excessive production of bradykinin, a vasodilatory mediator and enhancer of vascular permeability.⁶⁵ The disorder is characterized by recurrent episodes of severe swelling (angioedema). The most common areas of the body to develop swelling are the limbs, face, intestinal tract and airway. Minor trauma or stress may trigger an attack but swelling often occurs without a known trigger. About one in 50,000 people is affected by the disease.⁶⁵



Lanadelumab expected sales



Lanadelumab and the market for hereditary angioedema treatments

Shire’s novel drug that prevents angioedema, lanadelumab (a fully human monoclonal antibody which inhibits plasma kallikrein), could enter the market in late 2018. Regulatory filings were submitted in the U.S. and EU in February 2018 with Priority Review and accelerated assessment granted in the U.S. and EU, respectively.^{66,67}

Shire’s Cinryze (C1 esterase inhibitor [human]) is the dominant brand for prevention of angioedema attacks, but one of its main drawbacks is its intravenous administration. The first subcutaneous product to prevent attacks of angioedema was CSL Behring’s Haegarda, launched in mid-2017 and also a C1 esterase inhibitor. However, despite Haegarda’s first-mover advantage, lanadelumab is set to dominate the market for first-line prevention of angioedema attacks in patients with hereditary angioedema and significantly increase the use of such prophylactic medications due to its superior efficacy and more convenient dosing.

In the phase 3 HELP study, lanadelumab significantly reduced the mean frequency of angiodema attacks in patients with hereditary angiodema by 87% versus placebo.⁶⁸ These findings compare favorably to the 84% and 54% reductions in attacks reported for Haegarda⁶⁹ and Cinryze⁷⁰, respectively.

While both Haegarda and Cinryze require twice-weekly dosing, lanadelumab is dosed once every two weeks with potential for once-monthly dosing. Lanadelumab also has a smaller injection volume than Haegarda, allowing for more rapid injection, thereby giving it a competitive edge that will see blockbuster revenue.

Sales of Cinryze are expected to decline from \$665 million in 2018 to \$283 million in 2022. Meanwhile lanadelumab is forecast to start out with modest sales of just \$74 million in 2018, increasing to \$1.153 billion in 2022.

10.

Elagolix for endometriosis



The tissue lining the uterus is known as the endometrium. Endometriosis occurs when this tissue grows outside of the uterus.⁷¹

Any woman in the reproductive period of her life can be affected and the disorder affects around 10% of women in the reproductive-age group.^{72,73} Endometriosis is associated with dysmenorrhea (painful periods), non-menstrual pelvic pain, dyspareunia (painful intercourse) and infertility.⁷⁴

Elagolix and the endometriosis market

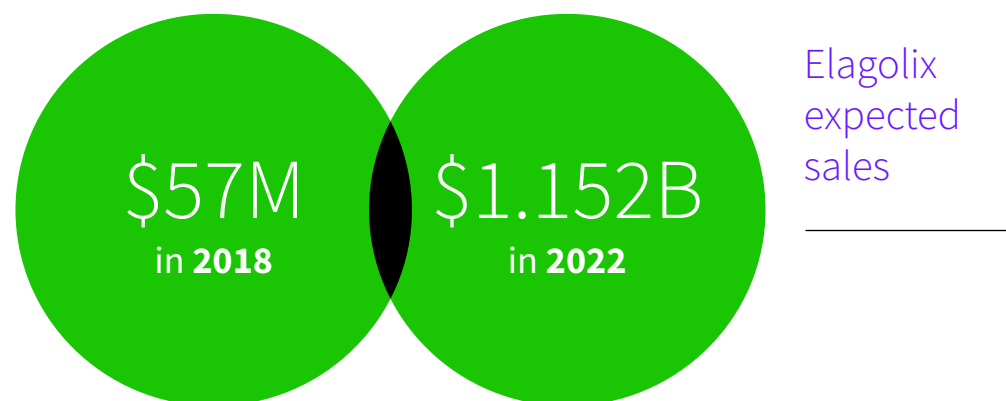
Estrogen plays an essential role in the pathophysiology of endometriosis. AbbVie’s elagolix is a first-in-class oral gonadotropin-releasing hormone (GnRH) antagonist, which acts to reduce levels of estrogen as well as other sex hormones such as progesterone. Elagolix was filed for approval in the U.S. in September 2017 for the management of endometriosis with associated pain.⁷⁵

The FDA accepted the filing for elagolix with a Priority Review and a decision is expected in the second quarter of 2018. Endometriosis has no cure and requires symptomatic treatment and a life-long management plan, which includes oral contraceptives, progestins, danazol, opioids and GnRH agonists (Lupron; AbbVie). Many of these treatments are used off-label, are inconveniently administered, and are associated with side-effects such as weight gain, bone loss and menopause-like side-effects (for Lupron).⁷⁶ Elagolix has been assessed in two replicate phase 3 trials (Violet PETAL and Solstice).

The therapy showed significant reductions at both month three and month six in the proportion of women complaining of menstrual pain (76.9% at six months) and non-menstrual pain (62.2% at six months, respectively) versus placebo-treated patients (up to 25% and 40%, respectively).^{77,78} Elagolix also reduced proliferation of endometrial tissue at six months. Importantly, Elagolix caused fewer menopause-like side effects and had an acceptable effect on bone mineral density relative to Lupron.^{77,78}

Since endometriosis affects more than 170 million women worldwide,⁷⁹ even a modest market penetration will result in significant sales. \$1.152 billion worth of sales are forecast for 2022. In the mid-term, elagolix might see competition from Myovant’s relugolix, another oral GnRH antagonist currently in phase 3 development, which is forecast to be a blockbuster by 2024.

ELAGOLIX	PLACEBO	
76.9%	25%	reduction in the proportion of women complaining of menstrual pain at six months
62.2%	40%	reduction in the proportion of women complaining of non-menstrual pain at six months



11.

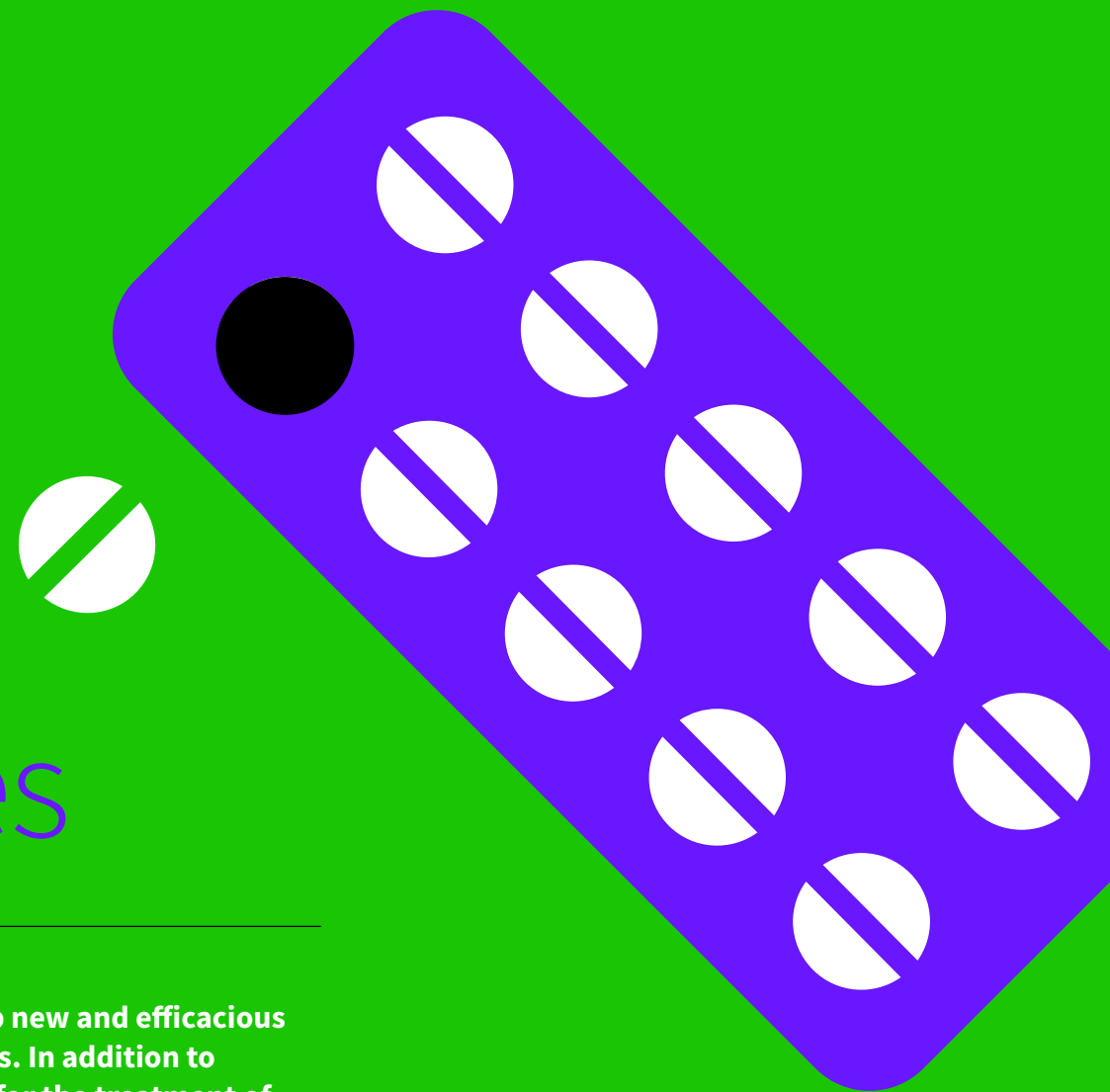
Steglatro

for type 2 diabetes

In view of the growing burden of type 2 diabetes, the race is on to develop new and efficacious treatments to help clinicians and their patients manage blood sugar levels. In addition to insulins and GLP-1 therapies, several other classes of drugs are available for the treatment of type 2 diabetes, including sodium glucose co-transporter-2 (SGLT-2) inhibitors.

SGLT-2's reduce the amount of glucose being absorbed in the kidneys so that it is passed out in the urine and reduce the amount of glucose in the blood.⁸⁰

In addition to the 2018 market entry of the potential GLP-1 analog blockbuster, Ozempic, a new SGLT-2 inhibitor, Steglatro (ertugliflozin), is also expected to launch in early 2018 for type 2 diabetes.



Steglatro and the type 2 diabetes market

Although SGLT-2 inhibitors are the newest oral treatment options for diabetes, Steglatro will be a late entrant to an increasingly crowded market and will compete with first-to-market Invokana (canagliflozin; Johnson & Johnson; launched in 2013), Farxiga (dapagliflozin; AstraZeneca; launched in early 2014) and Jardiance (empagliflozin; Boehringer Ingelheim; launched in late 2014).⁸¹

Steglatro does, however, have specific strengths that will help it gain market share, including significant HbA1C reductions in combination with Merck's DPP-4 market leader Januvia (sitagliptin) in the first-line setting as shown in the VERTIS SITA trial (HbA1C reductions of up to 1.7 versus 0.4 percentage points for the combination and placebo, respectively).⁸²

Steglatro is also efficacious as a monotherapy (see VERTIS Mono⁸³), in combination with metformin (see VERTIS MET trial⁸⁴), and combined with Januvia versus Januvia alone (see VERTIS Factorial trial⁸⁵). All of these studies showed significant weight loss and blood-pressure-lowering effects, which led to FDA approval of Steglatro as a monotherapy and in fixed-dose combinations with Januvia (as Steglujan) and metformin (as Segluromet) in December 2017.⁸⁶

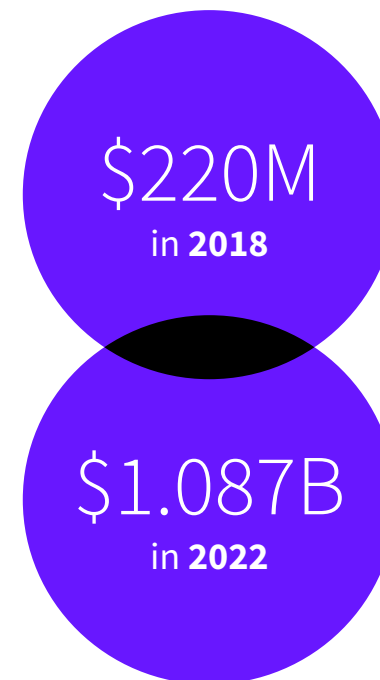
A cardiovascular outcomes study (VERTIS CV⁸⁷) for Steglatro is ongoing. Results of this study are expected in 2019.

Positive cardiovascular data are key to helping Steglatro consolidate a place among the other SGLT-2 inhibitors.

Cardiovascular benefits from Jardiance's paradigm-shifting EMPA-REG OUTCOME trial⁸⁸ were included in the label for Jardiance in December 2016. CANVAS data⁸⁹ for Invokana were filed in October 2017 and outcomes data from the DECLARE study⁹⁰ of Farxiga are also expected in 2019.

In 2016, Invokana was the market-leading SGLT-2 inhibitor and the only one with blockbuster sales (\$1.407 billion). However, cardiovascular benefits, among other strengths, are predicted to result in a rapid rise in sales of this drug class and Steglatro is expected to be a significant contributor. By 2022, Farxiga is forecast to lead the market (\$2.025 billion), followed by Jardiance (\$1.713 billion), and another novel class member sotagliflozin (a dual SGLT-1 and SGLT-2 inhibitor from Lexicon/Sanofi). Sotagliflozin is likely to be filed for approval in the first half of 2018 and could enter the market in 2019 and is forecast to generate 2022 sales of \$1.193 billion, followed by \$1.087 billion for Steglatro and \$652 million for Invokana. A decline in sales for Invokana could be a result of the amputations observed in the CANVAS trial, which led to a black box warning for this medicine.

Steglatro expected sales



Competitor drugs, expected sales in 2022

FARXIGA	\$2.025B
JARDIANCE	\$1.713B
SOTAGLIFLOZIN	\$1.193B
INVOKANA	\$652M



12.

Sublocade for opioid dependence

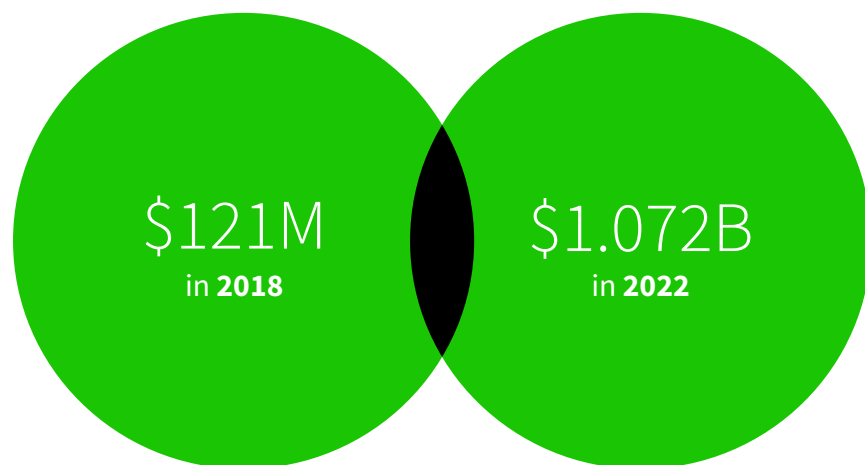
Opioids are a type of medicine often used to help relieve pain. This class of drugs includes the illegal drug heroin, synthetic opioids such as fentanyl, and pain relievers available legally by prescription, such as oxycodone (OxyContin), hydrocodone (Vicodin), codeine, morphine and many others.⁹¹

Regular use—even as prescribed by a doctor—can lead to dependence and, when misused, opioid pain relievers can lead to overdose and death. Opioid addiction, misuse and overdose are an ongoing and rapidly evolving public health crisis. Effective medications exist to treat opioid use disorders including methadone, buprenorphine and naltrexone.



abstinence rates in patients with opioid use disorder
(in phase 3 trial)

Sublocade expected sales



Sublocade and the market for medication-assisted treatment

Indivior’s Sublocade (once-monthly buprenorphine) was approved in November 2017, and is the first once-monthly formulation of buprenorphine. Following its launch in March 2018, this treatment could disrupt the market for medication-assisted treatment options to overcome opioid use.⁹²

The current standard of care for medication-assisted treatment is oral buprenorphine taken daily. Indivior’s Suboxone (buprenorphine and naloxone sublingual tablet) leads in this market, with other options including: Orexo’s Zubsolv (buprenorphine and naloxone sublingual tablet); BioDelivery Sciences’s Bunavail (buprenorphine and naloxone buccal film); oral methadone taken daily; Braeburn Pharmaceuticals/Titan’s Probuphine (a six-month subcutaneous sustained-release implant of buprenorphine); and Alkermes’ Vivitrol (a once-monthly naltrexone formulation). However, these drugs have several limitations such as the burden and inconvenience of the daily oral treatments, surgery for the implantable treatment option, and a detox period for Vivitrol, leaving space for novel options.

Sublocade is administered via subcutaneous injection once a month by a healthcare provider. The treatment does not require a detox period and so addresses the limitations of other treatment options.

In a phase 3 trial, patients with opioid use disorder who were treated with Sublocade had significantly higher abstinence rates than did those given placebo (42.7% versus 5.0%).⁹³ Presence of opioids in urine samples and self-reported opioid use was also lower among patients given Sublocade versus those given placebo.⁹⁴

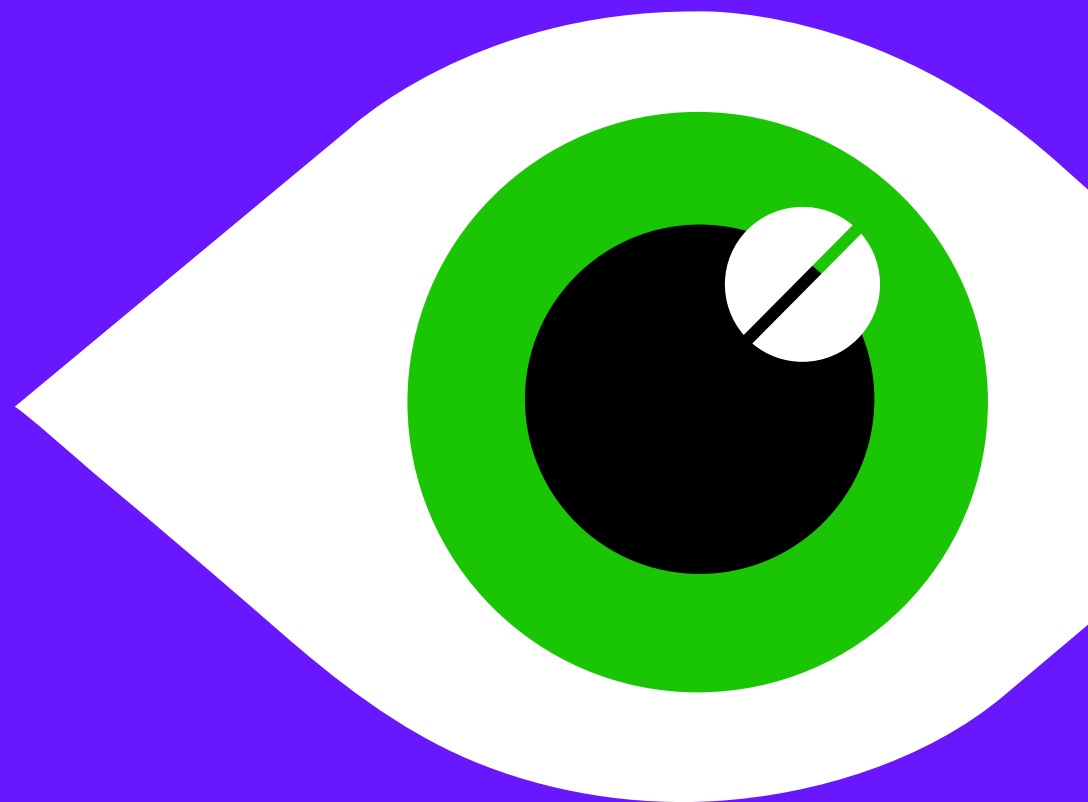
In view of the opioid crisis in the U.S., sales of Sublocade are forecast to reach blockbuster status in 2022 at \$1.072 billion, thereafter increasing further and significantly topping Suboxone’s peak sales of \$1.082 billion in 2013. Vivitrol has the second highest 2022 sales forecast at \$690 million.

A few more Drugs to Watch

A few additional therapies could enter the market in 2018 that are worth watching, especially if they receive accelerated approval.

Juno Therapeutics' CAR T-cell therapy, lisocabtagene maraleucel, is expected to be filed for diffuse large B-cell lymphoma in the second half of 2018 and has 2022 sales forecasts of \$2.221 billion.

Alexion's next-generation Soliris treatment, ravulizumab, for paroxysmal nocturnal hemoglobinuria, is expected to file for approval in the third quarter of 2018. This drug is forecast to generate \$2.199 billion of sales by 2022.



Drugs to Watch 2017 where are they now?

In January 2017, we highlighted eight drugs to enter the market in 2017 that could achieve blockbuster annual sales of \$1 billion or more by 2021. Of these eight drugs, seven entered the market as anticipated. One outlier was Ozempic. As predicted in the Drugs to Watch 2017 report, Ozempic was approved for treatment of type 2 diabetes that year on the basis of positive data from the SUSTAIN program. However, the late approval in December 2017 delayed the expected year-end launch to February 2018.

In our 2017 report we also made a special mention of Gilead's cancer drug Yescarta (axicabtagene ciloleucel), in view of the advance this treatment represented for the treatment of large B-cell lymphoma and for personalized cancer therapy in general. At the time, this drug was not forecast to reach blockbuster status by 2021, but is now forecast to achieve sales of more than \$1 billion by 2021.

Two of the drugs on the 2017 list of Drugs to Watch, Olumiant (baricitinib; Eli Lilly) and Bavencio (avelumab; Merck Serono/Pfizer), currently have anticipated sales short of blockbuster status. For Olumiant, these revised sales forecasts for Lilly's rheumatoid arthritis drug were a result of regulatory setbacks in the U.S. Despite receiving regulatory approval from European officials in 2017, the FDA issued a complete response letter citing dosing and safety data concerns.⁹⁵ For Bavencio, increasing competition in the immune checkpoint inhibitor class meant that Merck Serono and Pfizer's anti-PD-L1 (programmed cell death ligand 1) immunotherapy also has reduced sales forecasts for 2021. However, both Olumiant and Bavencio are predicted to exceed \$1 billion in sales in 2022.

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