

# Drugs to Watch 2019

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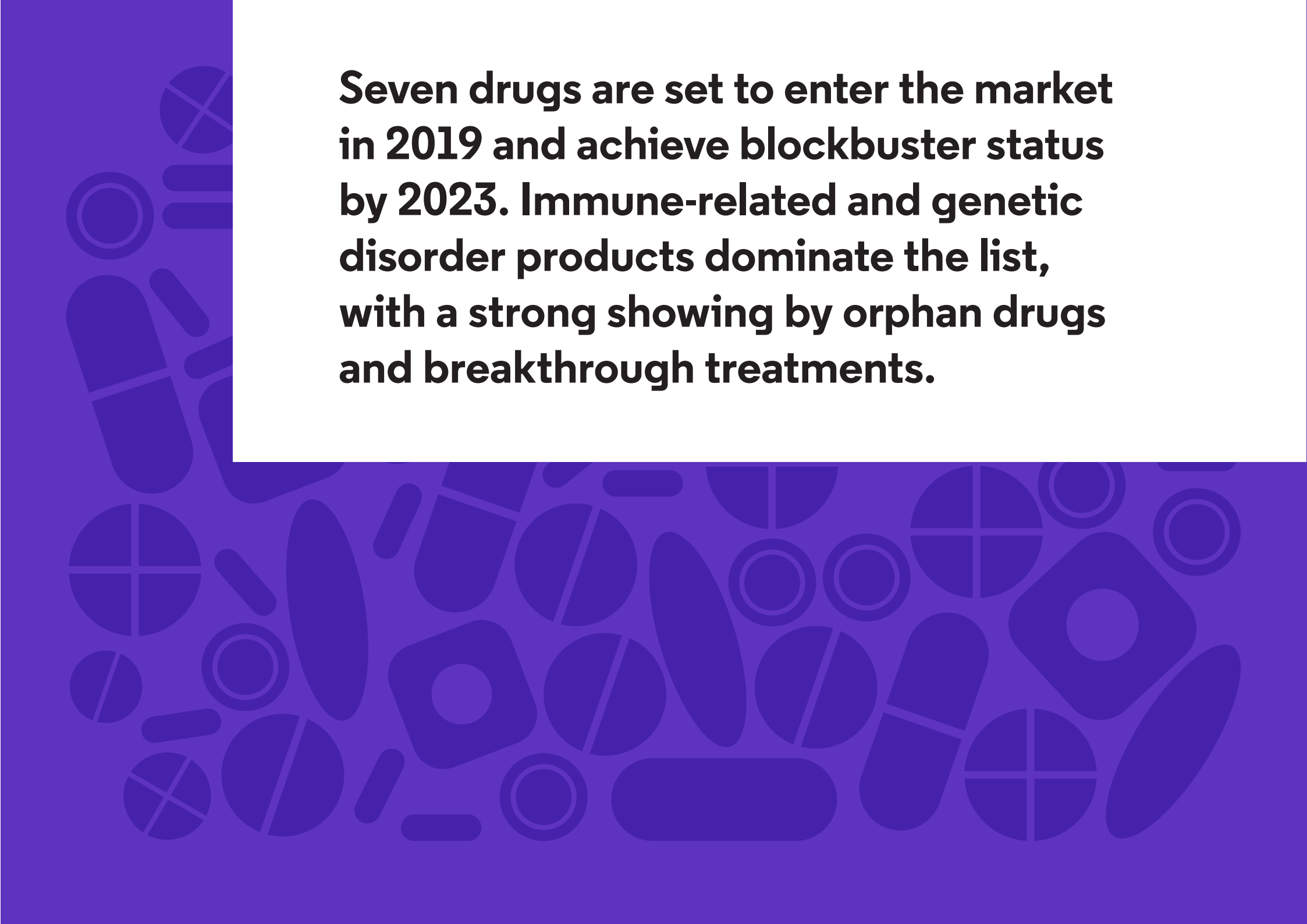
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The background of the slide is a solid purple color. It is decorated with numerous white icons of various pills and capsules, including round tablets with cross-hatches, oval capsules, and square tablets, scattered across the entire surface. A white rectangular box is positioned in the upper right quadrant, containing the main text.

**Seven drugs are set to enter the market in 2019 and achieve blockbuster status by 2023. Immune-related and genetic disorder products dominate the list, with a strong showing by orphan drugs and breakthrough treatments.**

# Introduction

## Overview

Since 2013, the Cortellis™ Forecast team at Clarivate Analytics™ has applied the proprietary technologies, tools and techniques trusted by its global life sciences customers to produce the Drugs to Watch report, which this year features seven products.

Each report showcases drugs entering the market that year with the potential to become blockbusters within five years. Blockbuster is defined by the common \$1 billion USD annual sales milestone.

The report is produced using a range of information, analytics and expertise available in Cortellis. This year's report additionally features the Cortellis Analytics – Drug Timeline & Success Rates analytic tool.

The Cortellis Drugs to Watch 2019 report examines the seven treatments that made the list, along with the competition they will face as they enter the market.



# Trends

**There are common elements among this cohort of seven drugs, clustered in three categories.**

First is diverse competition. The drugs highlighted in this report will face a variety of competitive landscapes in the markets they aim to enter – ranging from a single strong opponent to a plethora of different agents, each with its own strengths and weaknesses. The market dynamics will be discussed for each therapy.

Second is dominant therapeutic areas. The list almost fully comprises agents (six out of seven) targeting diseases characterized by genetic disorder and/or excessive immune response (including autoimmunity). The ability to not only define but also to manipulate such underlying mechanisms of disease states attests to the astonishing progress of medical and scientific knowledge in recent decades.

Notably, this year's list contains no cancer drugs. However, this may not reflect a downward trend in the research focus on cancer. Rather, it may highlight the increasing range of new oncology treatments in development, resulting in a smaller potential market share for each one, thus lessening the likelihood of any particular

drug becoming a blockbuster. It may also reflect the expansion into new oncology indications for established cancer drugs that, because they are already launched, do not fall within the remit of this analysis.

Third is mass versus niche clinical impact. It would appear that the opportunity to develop fast-follower treatments with limited differentiation addressing extremely high prevalence conditions has been tapped out. Instead, companies are investing more in rare diseases, unmet needs and conditions with current treatments hampered by safety, efficacy, convenience or other issues. This year's line-up of predicted blockbusters features a high proportion of therapies addressing such targets, with the seven drugs between them holding:

- Nine U.S., four EU and one Japanese Orphan Drug designations
- Four U.S. Breakthrough Therapy designations
- Two EU PRIME designations
- One U.S. Regenerative Medicine Advanced Therapy designation
- One Japanese Sakigake designation



# Treatments

(By therapeutic area with regulatory designations)

## Genetic disorders

**Zolgensma (onasemnogene abeparvovec):** Corrects the genetic defect underlying spinal muscular atrophy. The drug will face immediate competition from first-in-class Spinraza (nusinersen), which has been available in the U.S. since 2016 and the EU since 2017. (Orphan Drug & Breakthrough Therapy)

**LentiGlobin (betibeglogene darolentivec):** Corrects the defect causing beta thalassemia, a blood disorder that causes life-threatening anemia. Its only immediate competition will be donor stem cell transplant, which carries significant patient risks. (Orphan Drug & Breakthrough Therapy)

## Genetic disorders and excessive immune response/autoimmunity

**Ultomiris (ravulizumab):** Treats paroxysmal nocturnal hemoglobinuria, a rare, potentially fatal blood disorder. As a next-generation follow-on to Alexion's blockbuster Soliris (eculizumab) with non-inferiority and more convenient dosing, there will be market share opportunity. (Orphan Drug; U.S. Approval December 2018)

## Excessive immune response/autoimmunity

**Upadacitinib:** Treats rheumatoid arthritis. It will face significant competition from the well-established biological agents Humira, Enbrel, Simponi, Remicade and Cimzia, plus biosimilar versions of Humira and Enbrel.

**Skyrizi (risankizumab):** Treats psoriasis. It will compete with different treatment modalities such as topicals, light treatments and systemic medicines, including entrenched biological agents and biosimilar biologicals.

**AR-101:** Reduces peanut allergy. It will be first-in-class with no competition expected soon. (Breakthrough Therapy)

## Chronic disease complication

**Roxadustat:** Treats anemia in patients with chronic kidney disease. With long-standing competitors suffering setbacks related to cardiovascular events and tumors, there is opportunity to gain market share.



# The Cortellis team predicts seven new drugs will launch in 2019 and achieve blockbuster sales of more than \$1 billion by 2023

Name(s)	Developer(s)	Indication	Mechanism of action	Route of administration	Current status	2019 Sales forecast	2023 Sales forecast
<b>Upadacitinib</b> (ABT-494)	AbbVie	Rheumatoid arthritis	JAK1 selective inhibitor	Oral	Filed U.S. December 2018 Filed EU December 2018 Phase 2b/3 Japan	\$53M	\$2.20B
<b>Zolgensma</b> (onasemnogene abeparvovec; AVXS-101)	AveXis (a Novartis subsidiary)	Spinal muscular atrophy	Survival motor neuron (SMN) gene therapy	Intravenous infusion	Filed U.S. 3Q18 Filed EU 3Q18 Filed Japan 3Q18	\$449M	\$2.09B
<b>Roxadustat</b> (FG-4592; AZD-9941; ASP-1517)	AstraZeneca/ FibroGen/Astellas	Anemia in chronic kidney disease patients on dialysis	Hypoxia-inducible factor-prolyl hydroxylase (HIF-PH) inhibitor	Oral	Approved China December 2018 Filed Japan October 2018 Phase 3 U.S. and EU	\$30M	\$1.97B
<b>Ultomiris</b> (ravulizumab; ALXN-1210)	Alexion	Paroxysmal nocturnal hemoglobinuria	Complement inhibitor (humanized monoclonal antibody [mAb])	Intravenous infusion	Approved U.S. December 2018 Filed EU June 2018 Filed Japan December 2018	\$170M	\$1.93B
<b>Skyrizi</b> (risankizumab; BI-655066; ABBV-066)	Boehringer Ingelheim/AbbVie	Psoriasis	Anti-IL-23 p19 subunit (mAb)	Subcutaneous injection	Filed U.S. April 2018 Filed EU May 2018 Filed Japan May 2018	\$132M	\$1.74B
<b>AR-101</b>	Aimmune Therapeutics	Peanut allergy	Oral desensitization immunotherapy	Oral	Filed U.S. December 2018 Phase 3 EU	\$35M	\$1.17B
<b>LentiGlobin</b> (betibeglogene darolentivec)	bluebird bio	Beta-thalassemia in transfusion-dependent patients	Beta globin gene therapy (via hematopoietic stem cell transplant)	Intravenous infusion	Filed EU October 2018 Phase 3 U.S.	\$11M	\$1.12B

# How they got here: Regulatory status for Cortellis Drugs to Watch 2019

Name	Indication	U.S.	EU	Japan	China
Upadacitinib	Rheumatoid arthritis	Priority Review			
	Other indications	Breakthrough Therapy (atopic dermatitis) Orphan Drug (Crohn's disease) Orphan Drug (juvenile idiopathic arthritis [JIA], excluding systemic JIA) Orphan Drug (systemic JIA)			
Zolgensma	Spinal muscular atrophy	Breakthrough Therapy Orphan Drug Fast Track Priority Review	Orphan Drug PRIME	Sakigake designation	
Roxadustat	Anemia in chronic kidney disease in patients on dialysis				Priority Review
Ultomiris	Paroxysmal nocturnal hemoglobinuria	Orphan Drug Priority Review	Orphan Drug	Orphan Drug	
	Other indications	Orphan Drug (atypical hemolytic uremic syndrome)			
Skyrizi	Psoriasis				
	Other indications	Orphan Drug (pediatric Crohn's disease)			
AR-101	Peanut allergy	Breakthrough Therapy Fast Track Priority Review requested			
LentiGlobin	Beta-thalassemia in transfusion- dependent patients	Breakthrough Therapy Orphan Drug Fast Track	Orphan Drug PRIME Accelerated Assessment		
	Other indications	Orphan Drug (sickle cell disease) Fast Track (sickle cell disease) Regenerative Medicine Advanced Therapy (sickle cell disease)	Orphan Drug (sickle cell disease)		



# Methodology

**Data for this report were compiled from Cortellis, the suite of life sciences intelligence solutions from Clarivate Analytics. Cortellis includes the broadest and deepest range of sources of intelligence across the R&D lifecycle, including annual filings, drug pipelines, clinical trials, patents, chemistry, deals, conferences and company announcements.**

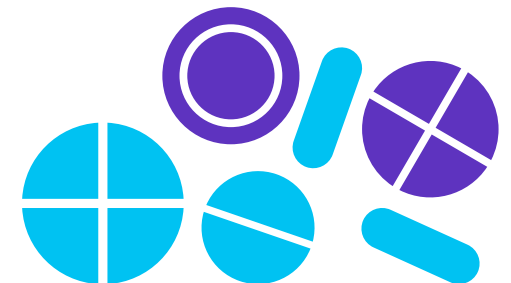
Drugs in phase 2 or phase 3 trials, at pre-registration or registration stage, or already launched early in 2019 were selected for analysis; drugs launched prior to 2019 were excluded. The dataset was then filtered for drugs that had total forecast sales of \$1 billion or more in 2023. This filtering process produced a list of drugs which was then manually reviewed to determine whether these products were likely to go to market in 2019, based on factors such as the company's expected approval or launch dates.

Following this manual review, seven drugs to watch for 2019 were determined. Each drug was subsequently researched and evaluated in its individual context, including 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 used included SWOT analyses compiled by Cortellis editors, biopharma company press releases and other publications (e.g., annual filings), peer-reviewed publications and Cortellis sales data (sourced from Refinitiv I/B/E/S).

New this year, the team leveraged Cortellis Analytics – Drug Timeline & Success Rates, an analytic tool that provides a reliable and accurate way to forecast drug development milestones. The tool applies statistical modeling and machine learning to forecast the timeline and probability of success for a drug, enabling improvements in pipeline forecasting and R&D investment decisions.

Please note that Cortellis analysts generated the data shown in this report on March 5, 2019 and the data were correct as of that time.



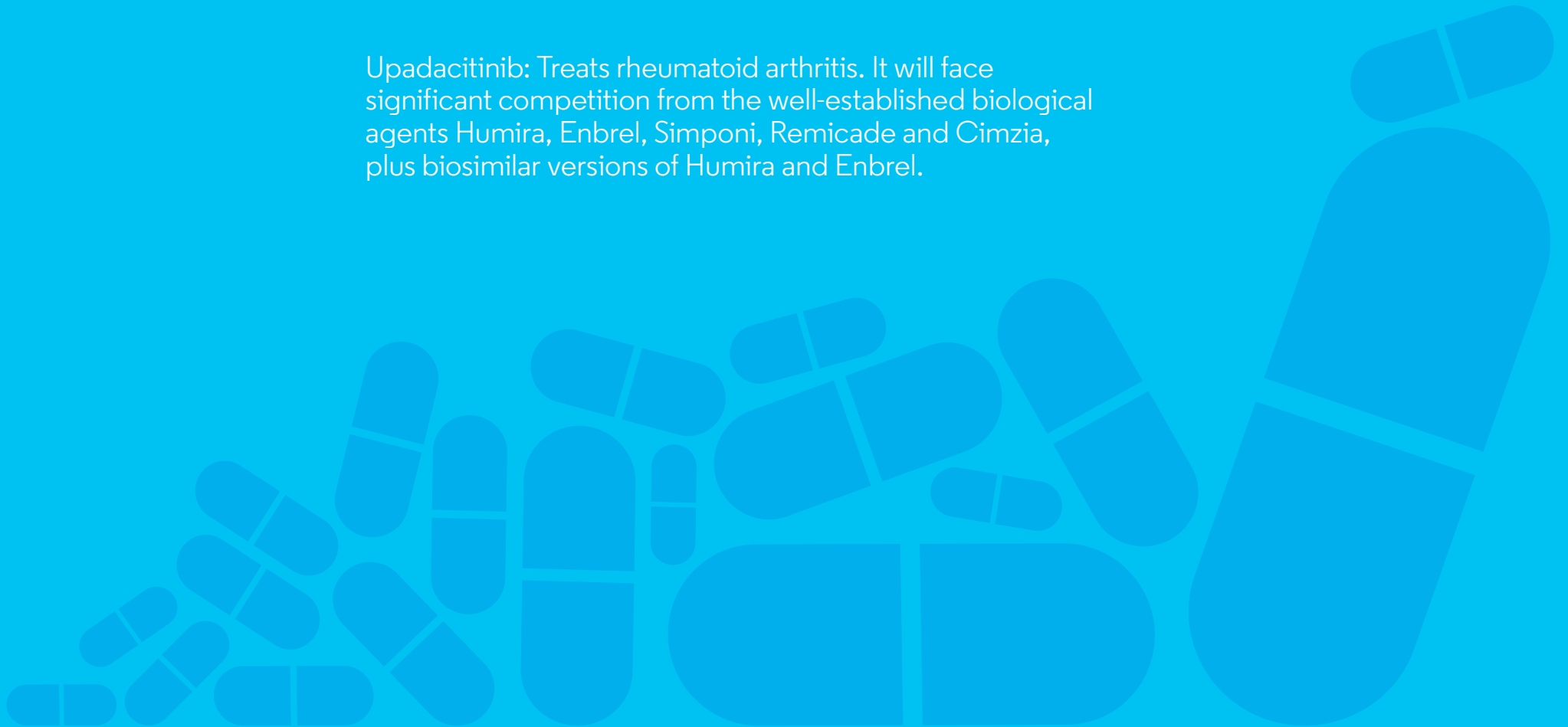
# Introducing the Cortellis Drugs to Watch 2019



# Upadacitinib

## for rheumatoid arthritis

Upadacitinib: Treats rheumatoid arthritis. It will face significant competition from the well-established biological agents Humira, Enbrel, Simponi, Remicade and Cimzia, plus biosimilar versions of Humira and Enbrel.



  
**\$2.20B**

Upadacitinib expected sales in 2023

**Rheumatoid arthritis is a chronic, progressive and debilitating autoimmune condition in which the immune system attacks joint linings, resulting in pain, swelling and stiffness. Damage can also occur in the heart, lungs, skin, eyes, kidneys and blood vessels. More general symptoms include fatigue, loss of appetite and weight loss. The triggers of the disease are unclear and there is no cure. However, treatments can reduce symptoms and prolong time between flare-ups. Rheumatoid arthritis affects between 0.3% and 1% of the worldwide population.**<sup>1,2,3</sup>

## Upadacitinib

AbbVie's upadacitinib is an orally dosed inhibitor of an intracellular target called JAK1. Dysfunction in the regulation of the JAK family of molecules is implicated in the aberrant production of pro-inflammatory mediators that are involved in the pathogenesis of rheumatoid arthritis, and inhibition of JAK proteins is an established method of controlling the symptoms of this disease.<sup>3</sup>

Upadacitinib was filed for approval in the U.S. and EU in December 2018, and accepted for U.S. Priority Review in February 2019.<sup>4</sup> Cortellis forecasts a 95% probability of approval in each region, with U.S. approval forecast for August 2019 and EU approval in October 2019. Sales forecasts for upadacitinib for 2023 are \$2.20 billion.

The filings for upadacitinib were based on data from the phase 3 SELECT trial program.<sup>4</sup> The SELECT trials produced significant efficacy in moderate to severe rheumatoid arthritis in different patient cohorts, highlights of which are noted below.

- SELECT-NEXT: In patients not responding adequately to conventional synthetic disease-modifying anti-rheumatic drugs (DMARDs)<sup>5</sup>
- SELECT-BEYOND: In patients not adequately responding to or intolerant of biologic DMARDs<sup>6</sup>
- SELECT-MONOTHERAPY: In patients switching from methotrexate monotherapy after inadequate responses<sup>7</sup>
- SELECT-COMPARE: In combination with methotrexate in patients with inadequate responses. Superiority to AbbVie's long-established rheumatoid arthritis drug Humira (adalimumab) was shown<sup>8</sup>
- SELECT-EARLY: In methotrexate-naïve patients<sup>9</sup>

Phase 3 trials of upadacitinib are also underway in ulcerative colitis, psoriatic arthritis, Crohn's disease and atopic dermatitis. Phase 2 development is ongoing in ankylosing spondylitis and a registration-enabling trial is planned for giant cell arteritis.

## Milestone forecasts for upadacitinib



Source: Cortellis Analytics – Drug Timeline & Success Rates

## The rheumatoid arthritis market

Launch of upadacitinib is anticipated in 2019, assuming approval is granted, but the drug would be a late entrant into a crowded market dominated by biological agents – many of which are recommended for use ahead of newer agents.<sup>10</sup>

The biologicals include ones that inhibit the pro-inflammatory mediator tumor necrosis factor (TNF), such as Humira, Enbrel (etanercept; Amgen/Pfizer/Takeda), Simponi (golimumab) and Remicade (infliximab; both Johnson & Johnson/Merck & Co/Mitsubishi Tanabe), and Cimzia (certolizumab pegol; UCB/Astellas). The American College of Rheumatology guidelines on rheumatoid arthritis treatment recommend these drugs as second-line therapy options after DMARDs.<sup>10</sup> Biosimilar versions of Humira (2017 sales of \$18.77 billion) entered the EU market in 2018 and are set to launch in the U.S. in 2023 – creating additional pressures in this already complex market.<sup>11,12,13</sup>

Also recommended ahead of newer agents are the non-TNF biologicals such as Actemra (tocilizumab; Roche/Chugai), Orencia (abatacept; Bristol-Myers Squibb/Ono) and Rituxan (rituximab; Roche/Biogen), which are positioned as alternatives to the TNF biologicals or after TNF inhibitor therapy failure.<sup>10</sup>

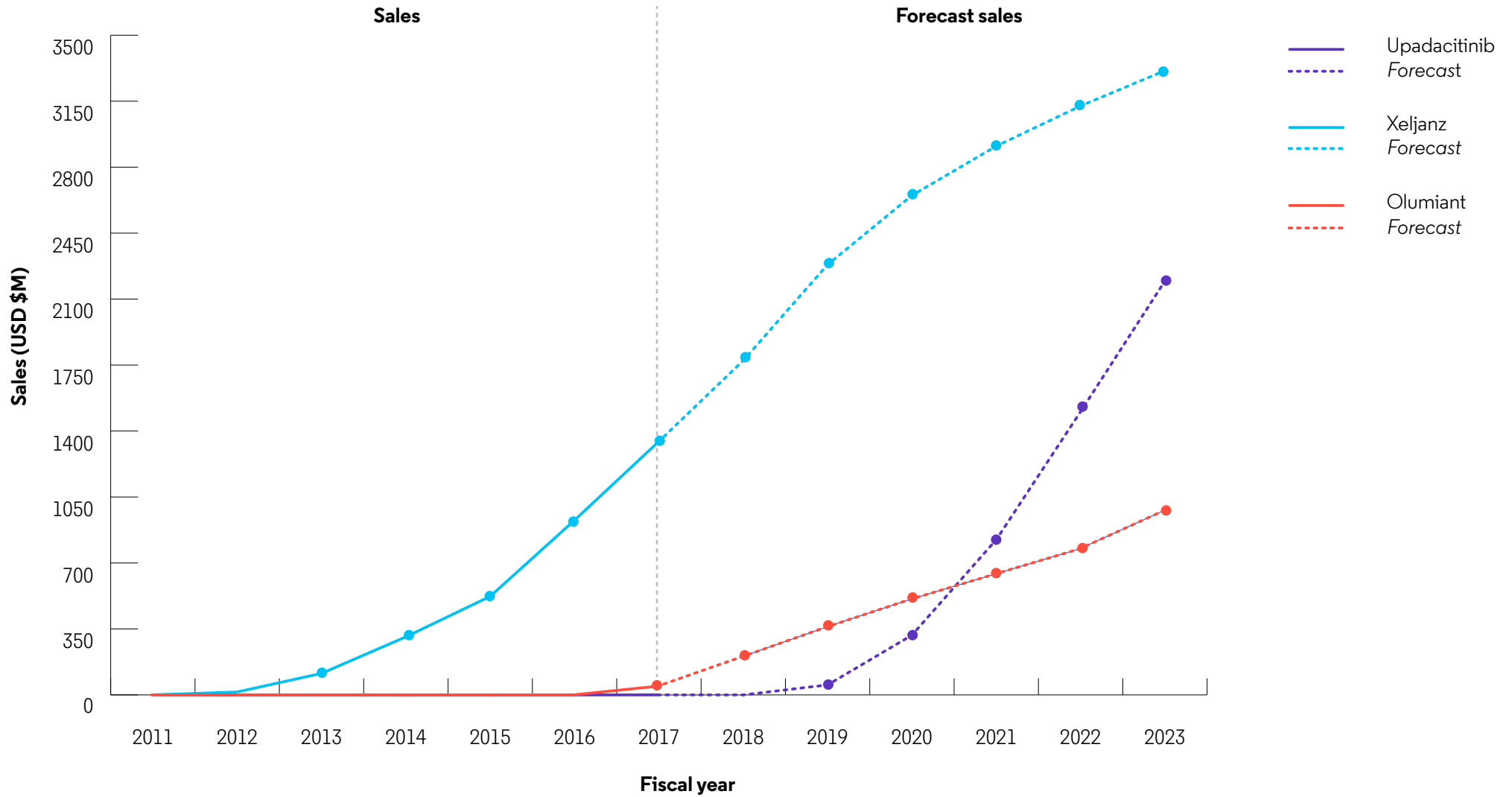
Upadacitinib will also face direct competition from other JAK inhibitors. First-in-class Xeljanz (tofacitinib; Pfizer) is a broad-spectrum JAK family inhibitor that has shown comparable efficacy to Humira. The American College of Rheumatology recommends it in the event of biological therapy failure.<sup>14,15</sup> Xeljanz sales in 2017 were \$1.35 billion, with forecast sales rising to \$3.31 billion in 2023.

Eli Lilly and Incyte's Olumiant (baricitinib), which is selective for JAK1/JAK2 and has shown superior efficacy to Humira, entered the EU and Japanese markets in 2017 and the U.S. in 2018.<sup>16</sup> Sales of Olumiant were \$46 million in 2017, with sales of \$977 million forecast for 2023 – approximately half those of upadacitinib.

Olumiant faces a number of challenges: for example, it has a black-box warning on its label more extensive than the Xeljanz one. Additionally, although Olumiant is available in the EU and elsewhere as 2-mg and 4-mg doses (the 4-mg dose is the most commonly used, outside the U.S.), the FDA has only approved the 2-mg dose. This decision was based on safety concerns with the 4-mg dose.<sup>17,18,19,20,21</sup> However, it was the 4-mg dose that showed superiority to Humira in the RA-BEAM trial, and thus the FDA's refusal to approve that dose is a significant blow to Olumiant, but also a potential opportunity for upadacitinib.<sup>22</sup>

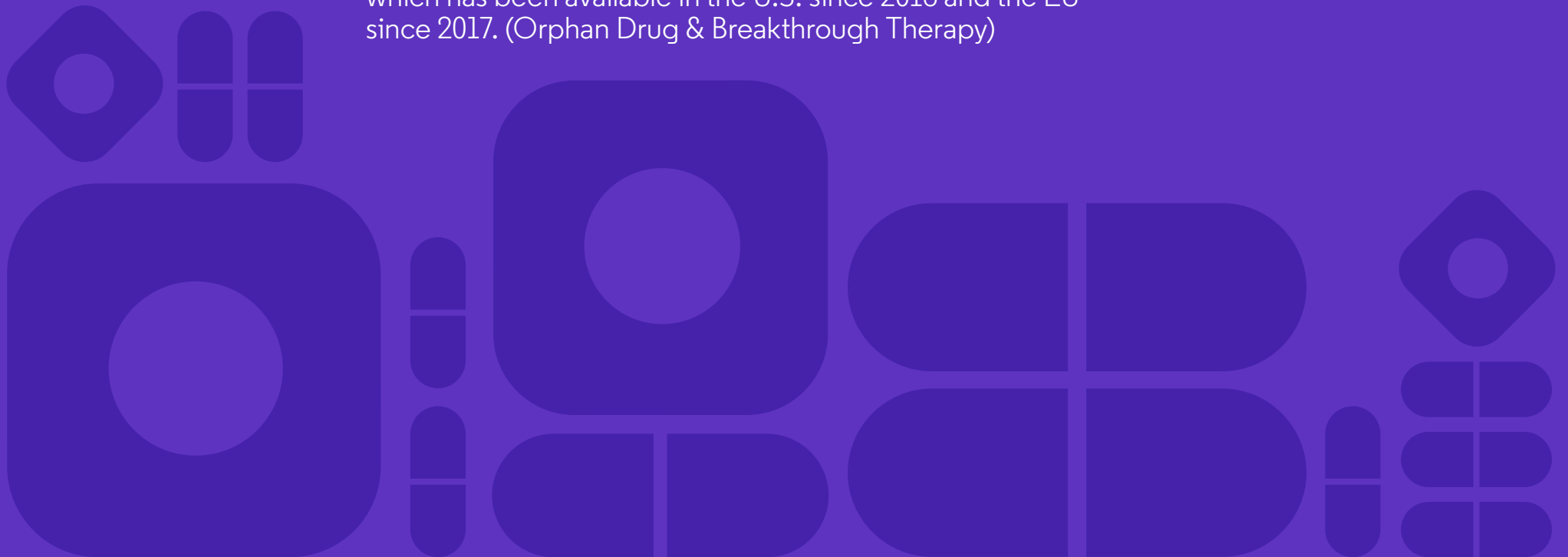


## Sales and sales forecasts for upadacitinib, Xeljanz and Olumiant



# Zolgensma for spinal muscular atrophy (SMA)

Zolgensma (onasemnogene abeparvovec): Corrects the genetic defect underlying spinal muscular atrophy. It will face immediate competition from first-in-class Spinraza (nusinersen), which has been available in the U.S. since 2016 and the EU since 2017. (Orphan Drug & Breakthrough Therapy)





  
**\$449M**

Zolgensma expected sales in 2019

  
**\$1.47B**

Zolgensma expected sales in 2021

  
**\$2.09B**

Zolgensma expected sales in 2023

**Spinal muscular atrophy (SMA) is a muscle-wasting condition predominantly affecting babies and children with lethal potential most often in early childhood. Approximately one in 8,000 to one in 11,000 people are affected. SMA is caused by SMN1 gene mutations, which block production of the survival motor neuron (SMN) protein that is essential for the transmitting of motor signals from the brain to the muscles. Without the SMN protein, motor neurons die. As a result, those affected have muscle weakness and wasting that creates difficulty moving, breathing and swallowing.**<sup>23,24,25</sup>

**In addition to SMN1, humans also possess the similar gene SMN2. The majority of SMN protein made by SMN2 is non-functional and cannot compensate for deficiencies in SMN protein caused by SMN1 mutations. However, depending on how much functional protein is produced by the SMN2 gene, it can delay the condition's onset and reduce its severity.**

**SMA is classified by age of onset and severity, with the most common variety, type I, evident at or within a few months of birth and most often causing early childhood death from respiratory failure. Type II is evident from 6 months to 12 months of age with patients possibly living into their 20s or 30s. Patients with type III (later childhood onset) and IV (adult onset) usually have normal life expectancies.**<sup>23,24,25</sup>

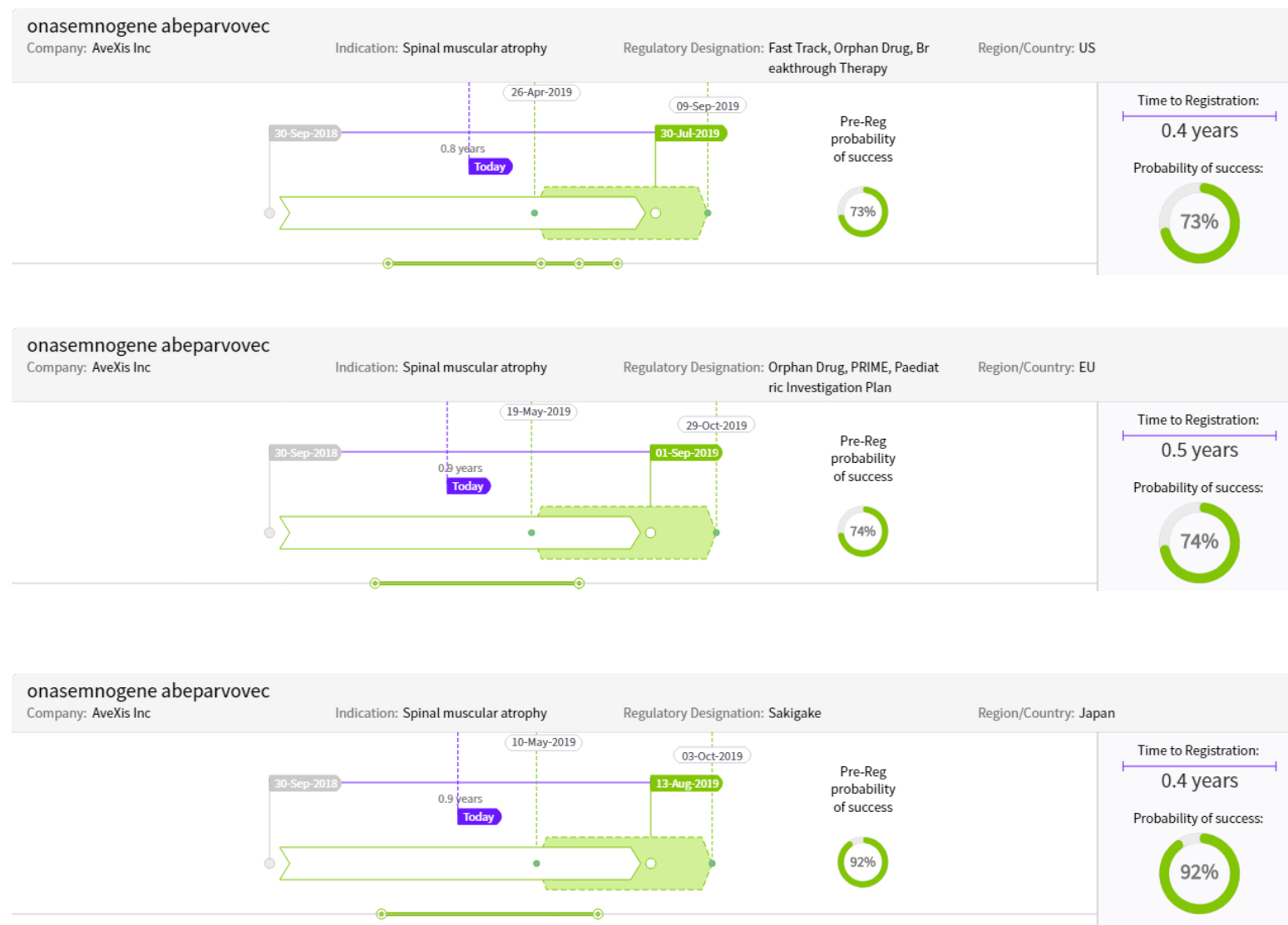
## Zolgensma

AveXis/Novartis's Zolgensma is an injectable gene therapy that uses a viral vector to introduce DNA for a functional SMN protein into a patient's cells. This enables the cells to make the missing SMN protein.<sup>26</sup> In the third quarter of 2018, AveXis filed Zolgensma for approval in the U.S., EU and Japan for the treatment of SMA type I.<sup>27,28,29</sup> The companies expect to launch the drug in the U.S. and Japan in the first half of 2019, and in the EU in the second half of 2019.<sup>30,31</sup> The approval probabilities in the U.S. and EU are both above 70%, and in Japan is above 90%. Sales of \$449 million are forecast for this year, rising to \$1.47 billion in 2021 and \$2.09 billion in 2023.

Zolgensma clinical studies have reported excellent survival results. In the pivotal phase 1 START trial, all 15 treated children with type I SMA were alive at 24 months. This is a sharp contrast to the death or permanently ventilated rate of 90% for natural disease progression. Also, initial data from the ongoing phase 3 pivotal STRIVE trial showed early and rapid improvements in motor function.<sup>28,31,32</sup>

Trials are also ongoing in other types of SMA, including the SPRINT trial for pre-symptomatic children less than 6 weeks old with type II, III and IV SMA, and the STRONG trial for symptomatic children between 6 months and 5 years with type II SMA. In addition, the planned REACH trial will assess the therapy in type II, III and IV SMA patients aged between 6 months and 18 years.<sup>28,33,34,35</sup>

## Milestone forecasts for Zolgensma



Source: Cortellis Analytics – Drug Timeline & Success Rates

## The spinal muscular atrophy market

Assuming Zolgensma is approved, it will face an interesting market dynamic. In December 2016, Ionis Pharmaceuticals and Biogen's Spinraza became the first ever U.S.-approved treatment for SMA, dramatically improving the prospects for patients with this condition. In June 2017, a similarly significant approval followed in Europe.<sup>36,37</sup> Spinraza sales were \$883 million in 2017, and are forecast to climb to \$2.26 billion in 2023. Spinraza is an antisense oligonucleotide that modifies translation from the SMN2 gene to SMN protein so as to increase functional SMN protein production.<sup>38</sup>

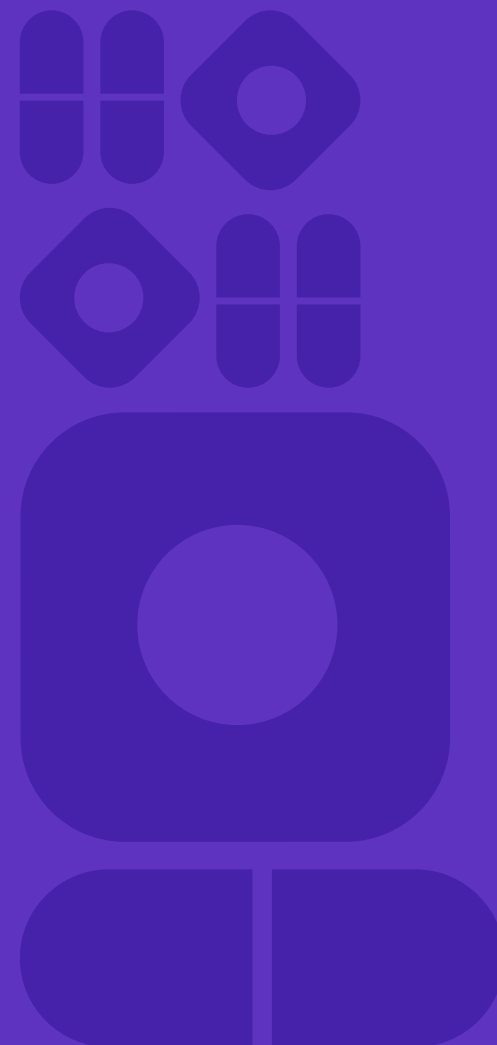
The competition between these two therapies is worth watching. While Zolgensma has currently only been filed for approval in SMA type I, Spinraza is approved for all SMA types. However, Zolgensma is given as a more convenient single one-time dose via an intravenous injection while Spinraza must be administered every four months into the cerebrospinal fluid via lumbar puncture (intrathecally).

AveXis is looking to broaden the use of Zolgensma into other SMA types with the trials described above. Although the STRONG and REACH trials use intrathecal administration rather than intravenous, the treatment is still via a single dose rather

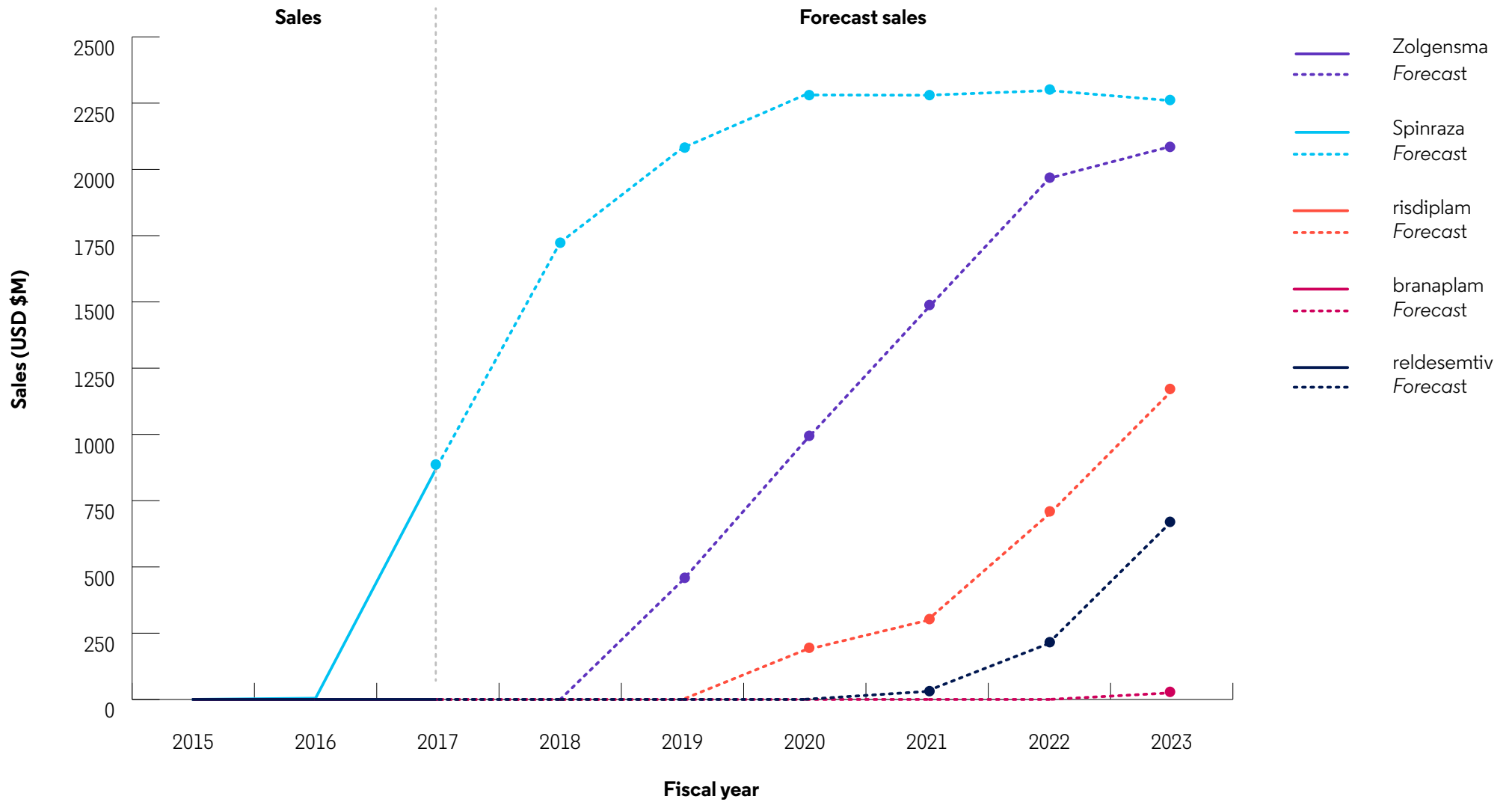
than regular ongoing administrations.<sup>28</sup> Filings for Zolgensma for SMA types II and III are expected in 2020.<sup>39</sup>

There are also a small number of other therapies in development that could compete with Zolgensma. Roche's risdiplam and Novartis's branaplam both act via modification of SMN2, like Spinraza. Risdiplam is in phase 2/3 development for type I SMA (FIREFISH) and for type II and III SMA (the SUNFISH trial), with a U.S./EU filing in support of a broad label in SMA types I, II and III planned for the second half of 2019. Sales of \$1.16 billion in 2023 are forecast for risdiplam. Branaplam is in phase 2 development for type I SMA, with filings expected in 2023 or later.

With a different mechanism of action, Cytokinetics and Astellas's reldesemtiv is in phase 2 development for types II, III and IV SMA. This oral drug acts on muscle fibers to increase their responsiveness to decreased neuronal stimulation. The forecast probability of U.S. market approval of reldesemtiv for SMA is 43%. The drug is also in development for other muscular dysfunction-related conditions. Forecast sales for reldesemtiv in 2023 are \$667 million.



## Sales and sales forecasts for Zolgensma, Spinraza, risdiplam, branaplam and reldesemtiv



# Roxadustat for anemia in chronic kidney disease (CKD)

Roxadustat: Treats anemia in chronic kidney disease. With longstanding competitors suffering setbacks from links to cardiovascular events and tumors, there is opportunity to gain market share.





200M

People worldwide suffering from chronic kidney disease (CKD)



\$1.97B

Roxadustat expected sales in 2023

**In patients with chronic kidney disease (CKD), the kidneys do not produce enough of the hormone erythropoietin, which is essential for red blood cell production. Many patients with kidney disease are also deficient in the iron that is required for red blood cells, for example due to blood lost during kidney dialysis. As a result, anemia is often present in kidney disease and worsens as kidney disease progresses. Most patients whose CKD has progressed to kidney failure have associated anemia. It is estimated that CKD affects 200 million people worldwide.**<sup>40,41,42</sup>

## Roxadustat

AstraZeneca/FibroGen/Astellas's roxadustat is a first-in-class inhibitor of hypoxia-inducible factor-prolyl hydroxylase (HIF-PH); prolyl hydroxylase is an enzyme that breaks down hypoxia-inducible factor, which is involved in erythropoietin production and iron mobilization. By inhibiting HIF-PH, roxadustat preserves hypoxia-inducible factor which is then able to stimulate the production of erythropoietin and mobilization of iron, and thus promote red blood cell production and function.<sup>43,44</sup> Sales forecasts for the drug for 2023 are \$1.97 billion.

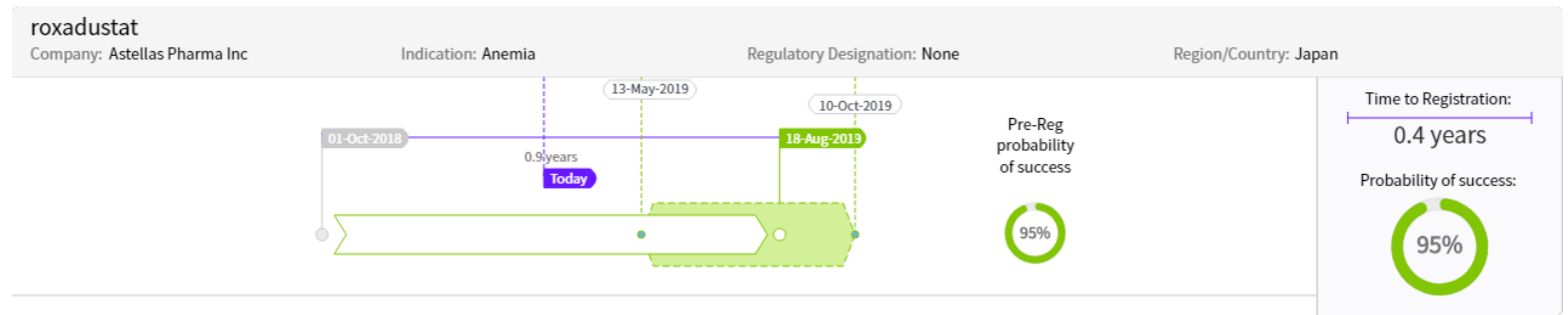
Roxadustat was approved in December 2018 in China for the treatment of CKD-related anemia in patients dependent on kidney dialysis. Launch is expected in the second half of 2019, and approval for use in patients not on dialysis is expected in mid-2019.<sup>45,46</sup>

The drug is under regulatory review in Japan, where a filing for anemia in CKD patients on dialysis was submitted in October 2018.<sup>47</sup> A U.S. filing is expected in the third quarter of 2019.<sup>45</sup> Cortellis forecasts a 95% probability of approval in Japan, with approval forecast in August 2019. In the U.S. and EU, the probabilities of regulatory filings are 95%, with 94% probabilities of approval if filed; the overall probabilities of progression from phase 3 to approval are 89% in both the U.S. and EU.

Approval of the drug in China was based on data from the phase 3 FGCL-4592-806 study in which roxadustat was non-inferior to the erythropoiesis-stimulating agent (ESA) epoetin alfa in producing an increase in hemoglobin levels from baseline to weeks 23 to 27 in patients on dialysis. Roxadustat also increased transferrin, maintained serum iron, and attenuated decreases in transferrin saturation versus epoetin alfa. In the FGCL-4592-808 trial in patients not on dialysis, roxadustat produced a greater change from baseline in hemoglobin levels compared with placebo.<sup>48</sup>

Roxadustat has also met its primary endpoints in the pivotal U.S. phase 3 ROCKIES trial in patients on dialysis, and in the European phase 3 ALPS and pivotal global phase 3 OLYMPUS trials in patients not on dialysis.<sup>49,50</sup>

## Milestone forecasts for roxadustat



Source: Cortellis Analytics – Drug Timeline & Success Rates

## The anemia in chronic kidney disease market

The market dynamic that roxadustat will encounter is an interesting one, as the main competing therapies, the ESAs, are well entrenched but not without significant drawbacks. Although these agents were introduced several decades ago, there are growing concerns over their safety, following the emergence of evidence of an association with greater risks of cardiovascular events and tumors.<sup>44,51,52</sup>

Due to these risks, patients receiving ESAs are often co-medicated with various other agents, including antihypertensive and anticoagulant drugs. Intravenous iron is also often needed alongside ESAs, due to their propensity to decrease iron levels during the correction of hemoglobin, causing functional iron deficiency.<sup>44,47</sup>

In contrast to the injectable ESAs, oral HIF-PH inhibitors such as roxadustat are expected to be able to avoid the inconvenient and expensive need for these co-medications due to their reduced cardiovascular side effect profile, and furthermore they may indeed have cardiovascular benefits. In clinical studies, no signals or trends to suggest roxadustat treatment is associated with cardiovascular events or thrombosis have been reported. In the phase 2 trial program, no exacerbations in hypertension were seen, and indeed significant reductions in mean arterial blood pressure were noted. Data also suggested

that roxadustat may lower cholesterol. As dyslipidemia and hypertension are also highly prevalent in CKD patients and are major cardiovascular risk factors in this population, data confirming improved cardiovascular outcomes, both relative to ESAs and also more generally, would represent a significant commercial advantage for roxadustat.<sup>44,47,49,53,54,55</sup>

Pooled safety data for roxadustat, including major adverse cardiovascular event (MACE) outcomes from trials such as ROCKIES, are expected in the first half of 2019, and are data to watch out for.<sup>49</sup>

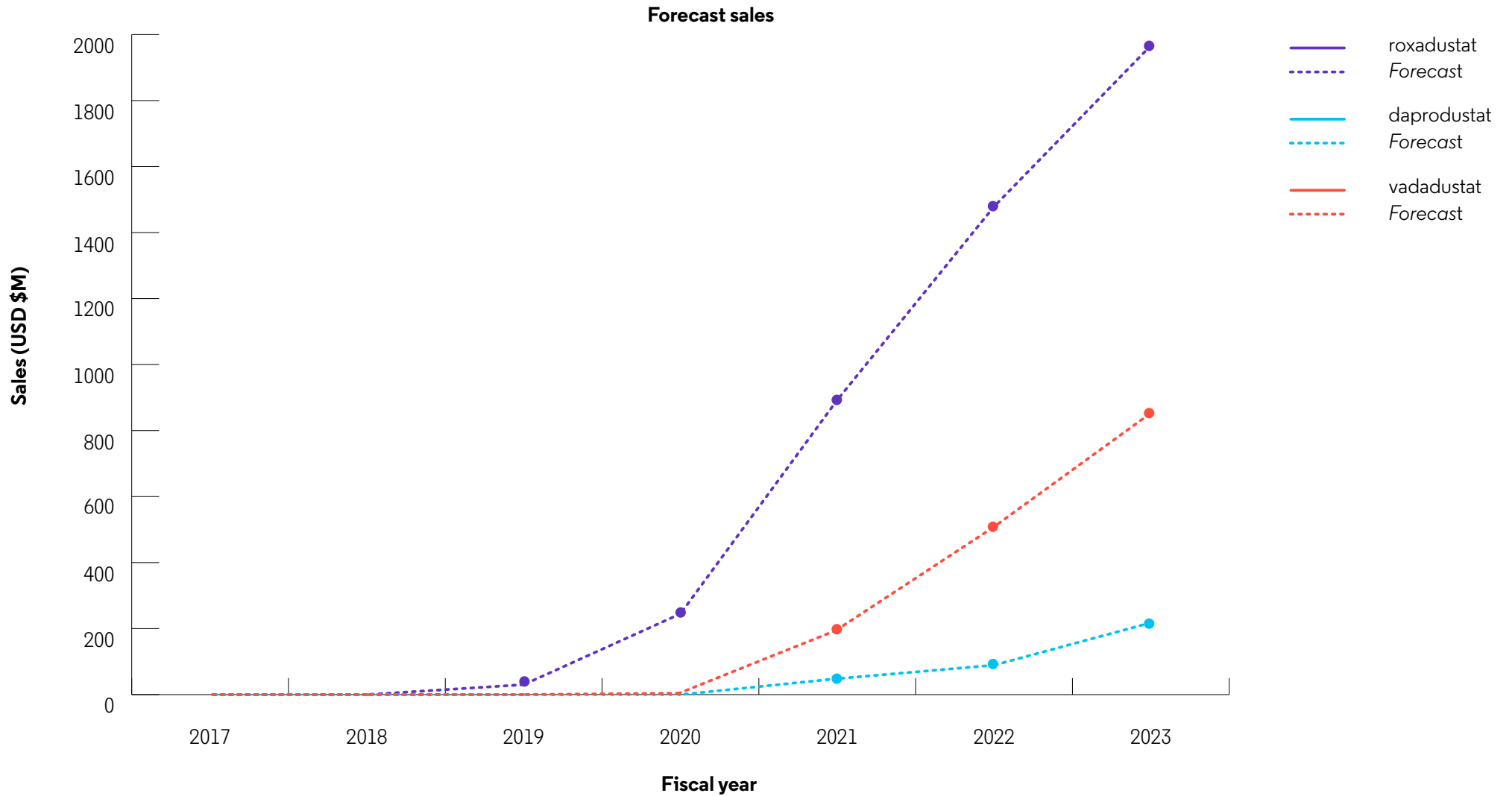
Roxadustat potentially faces competition from other HIF-PH inhibitors currently in clinical development, such as GlaxoSmithKline's daprodustat and vadadustat from Akebia Therapeutics, Mitsubishi Tanabe and Otsuka. Phase 3 trials of daprodustat began in various CKD anemia settings in 2016, with positive data from Japanese trials reported in 2018 (from the 204716 and 201754 studies) and a filing in that region planned in 2019. Data from phase 3 trials in the U.S. and Europe (ASCEND-ND and ASCEND-D) are expected in 2020. The forecast likelihood of this drug achieving approval is 90% in Japan (with approval expected in 2020), and over 75% in the U.S. and Europe (approval expected in 2021). Sales forecasts for daprodustat are \$218 million in 2023.

Vadadustat entered phase 3 development in the U.S. and Europe for anemia in non-dialysis-dependent CKD (the

PRO2TECT trial) and in dialysis-dependent CKD (INNO2VATE) in 2015 and 2016, respectively, with filings in those regions expected in 2019. Japanese phase 3 trials for anemia in non-dialysis-dependent (study MT-6548-J01) and dialysis-dependent (study MT-6548-J02) CKD began in 2017 and 2018, respectively. The forecast likelihood of vadadustat achieving approval is over 80% in the U.S. and Europe, and 90% in Japan (expected approval 2021 in all three regions). Sales of vadadustat are forecast to be \$850 million in 2023.



## Sales and sales forecasts for roxadustat, daprodustat and vadadustat



# Ultomiris

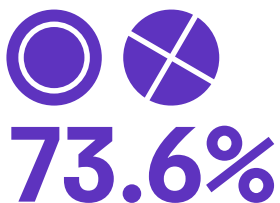
## for paroxysmal nocturnal hemoglobinuria (PNH)

Ultomiris (ravulizumab): Treats paroxysmal nocturnal hemoglobinuria, a rare, potentially fatal blood disorder. As a next-generation follow-on to Alexion's blockbuster Soliris (eculizumab) with non-inferiority and more convenient dosing, there will be market share opportunity. (Orphan Drug; U.S. Approval December 2018)

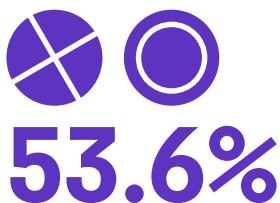




Ultomiris expected sales in 2023



In the 301 study, 73.6% of Ultomiris recipients were able to avoid blood transfusion



In the 301 study, 53.6% of Ultomiris recipients achieved normalization of their levels of lactate dehydrogenase

**Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired rare blood disorder, affecting between one and five people per million, which is chronic, progressive and fatal in approximately 50% of cases. Due to an acquired genetic defect, a patient's red blood cells become susceptible to destruction (hemolysis) by a substance called complement, resulting in thrombosis that can cause death or organ damage. Other symptoms include difficulty breathing and swallowing, severe anemia and fatigue, kidney disease and pain.**<sup>56,57,58,59,60</sup>

## Ultomiris

Alexion's Ultomiris is a next-generation follow-up to its blockbuster PNH drug Soliris. Both Soliris and Ultomiris are humanized monoclonal antibodies that bind to the complement component C5 and inhibit its cleavage into C5a and C5b, thereby blocking formation of the complement complex C5b-9, which is a mediator of hemolysis. However, Ultomiris is designed to be longer acting than Soliris, and is thus dosed only every eight weeks, instead of every two for Soliris.<sup>61,62</sup>

Ultomiris received regulatory approval from the FDA for adult patients with PNH in December 2018, just six months after the drug was filed, and two months ahead of the FDA's target date for the completion of Priority Review. It was launched in the U.S. in January 2019, making it the first of the 2019 Drugs to Watch to reach the market. In the EU and Japan, approval of the drug is pending, following acceptance of regulatory filings in 2018.<sup>63,64</sup>

U.S. approval of Ultomiris was based on data from two phase 3 trials that showed non-inferiority to Soliris. In the 301 study in complement inhibitor-naïve patients, 73.6% of Ultomiris recipients were able to avoid blood transfusion, and 53.6% achieved normalization of their levels of lactate dehydrogenase – a marker of cell damage and destruction. The 302 trial confirmed Ultomiris's non-inferiority in patients switching from Soliris therapy to Ultomiris.<sup>65,66</sup>

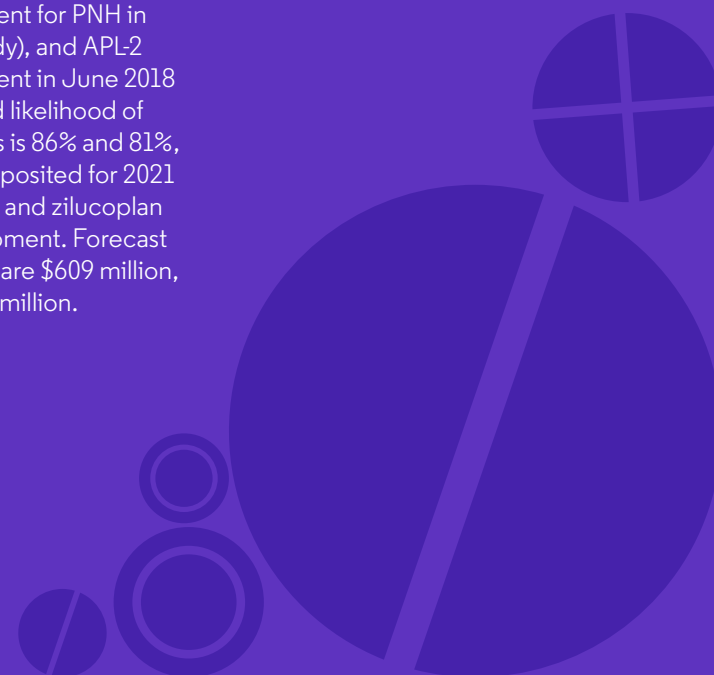
## The paroxysmal nocturnal hemoglobinuria market

Soliris entered the U.S. market in 2007 as the first ever drug approved for PNH.<sup>67</sup> In the TRIUMPH trial it showed hemoglobin stabilization in 49% of patients versus 0% with placebo, and an 85.8% decrease in lactate dehydrogenase relative to placebo.<sup>68</sup> Pooled data from the TRIUMPH, SHEPHERD and X03-001 studies showed a reduction of 85% in thrombotic events – the most common cause of mortality in PNH patients.<sup>69</sup>

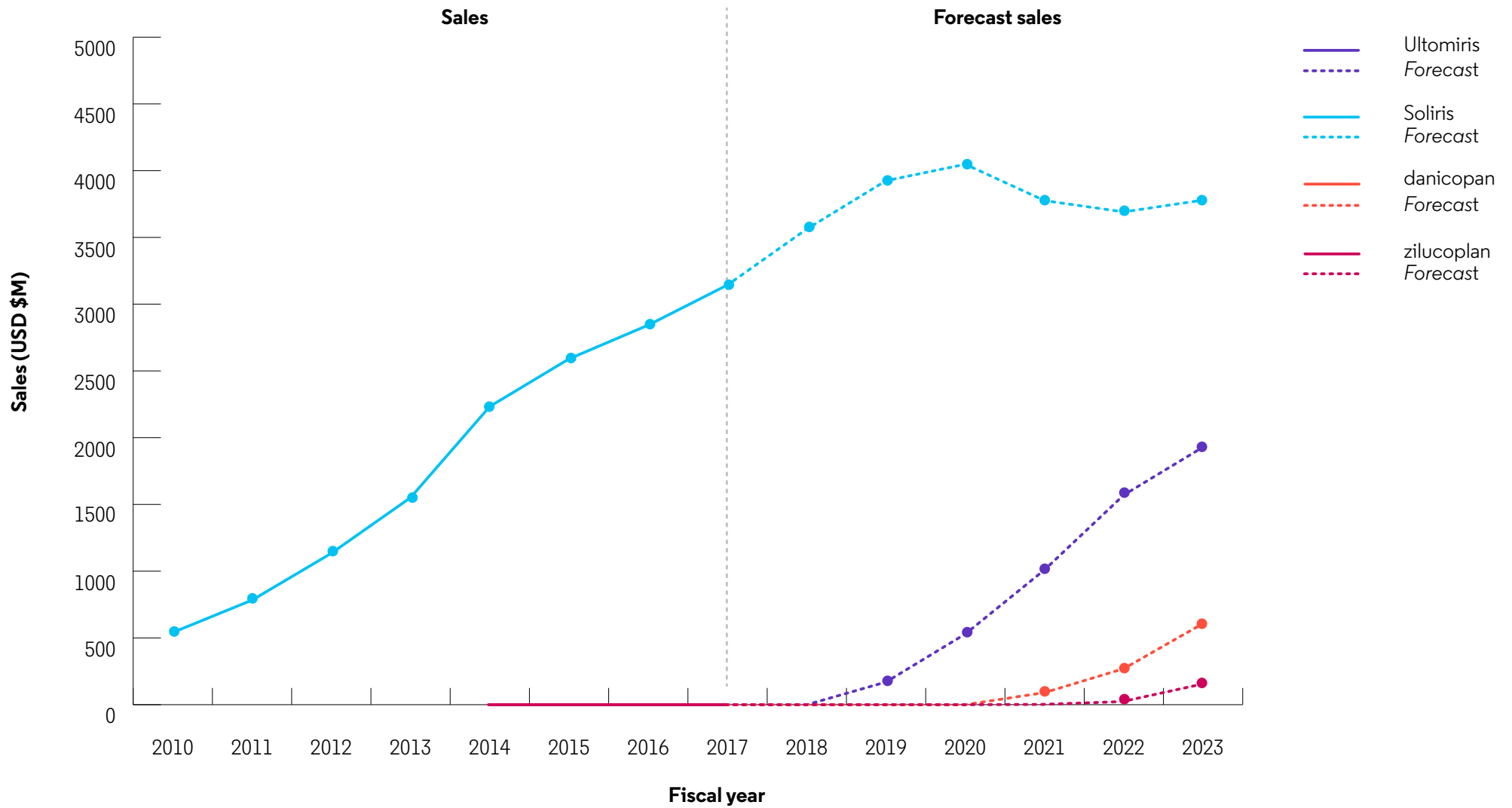
Although PNH is a very rare disease, Soliris leveraged ultra-orphan drug pricing<sup>70</sup> to achieve blockbuster sales, with 2017 sales of \$3.14 billion, and \$3.78 billion forecast for 2023. Ultomiris's non-inferiority to Soliris and its greatly improved dosing convenience should position it well with regard to taking market share from its predecessor. Sales of \$1.93 billion are forecast for Ultomiris in 2023. The clinical data demonstrating the non-inferiority of Ultomiris in patients switching from Soliris therapy will also allow Alexion to promote the movement of patients from Soliris to

Ultomiris; this is a strategic approach given that biosimilar versions of Soliris are in development. Soliris is also approved for a number of other indications, including atypical hemolytic uremic syndrome (aHUS). Ultomiris is in clinical development for this indication, with positive phase 3 data from the Ultomiris aHUS-311 trial reported in January 2019, and filings in the U.S., EU and Japan expected soon.<sup>66,71</sup>

There is also potential competition in the PNH development pipeline from other complement inhibitors, for example Akari Therapeutics's Coversin (nomacopan), Apellis's APL-2, Achillion's danicopan and Ra Pharmaceutical's zilucoplan. Coversin entered phase 3 development for PNH in March 2017 (the AK581 study), and APL-2 entered phase 3 development in June 2018 (PEGASUS). The forecasted likelihood of approval of these two drugs is 86% and 81%, respectively, with approval posited for 2021 for both agents. Danicopan and zilucoplan are both in phase 2 development. Forecast sales in 2023 for danicopan are \$609 million, and for zilucoplan are \$154 million.



## Sales and sales forecasts for Ultomiris, Soliris, danicopan and zilucoplan



# Skyrizi for psoriasis

Skyrizi (risankizumab): Treats psoriasis. It will compete with different treatment modalities, such as topicals, light treatments and systemic medicines, including entrenched biological agents and biosimilar biologicals.



  
**\$1.74B**

Skyrizi expected sales in 2023

**Psoriasis is a condition in which the process of replacing skin cells is abnormally increased, leading to a build-up of cells on the skin surface that form itchy and painful scales and plaques. It results from T lymphocytes and neutrophils in the immune system attacking healthy skin cells, although it is not clear what the trigger for this is. Psoriasis prevalence varies widely across the globe, although in most developed countries it is between 1.5% and 5%.<sup>72,73</sup>**

## Skyrizi

Boehringer Ingelheim and AbbVie's Skyrizi is a monoclonal antibody that inhibits the pro-inflammatory cytokine IL-23. It was filed for U.S. approval for moderate to severe plaque psoriasis in April 2018, and for EU approval in that setting in May 2018. Also in May 2018, approval for Skyrizi was filed in Japan for plaque psoriasis, psoriatic arthritis, pustular psoriasis and erythrodermic psoriasis. A 95% probability of approval is forecast by Cortellis in all regions, with U.S., EU and Japanese approval expected to take place in the first half of 2019. Forecast sales for Skyrizi in 2023 are \$1.74 billion.

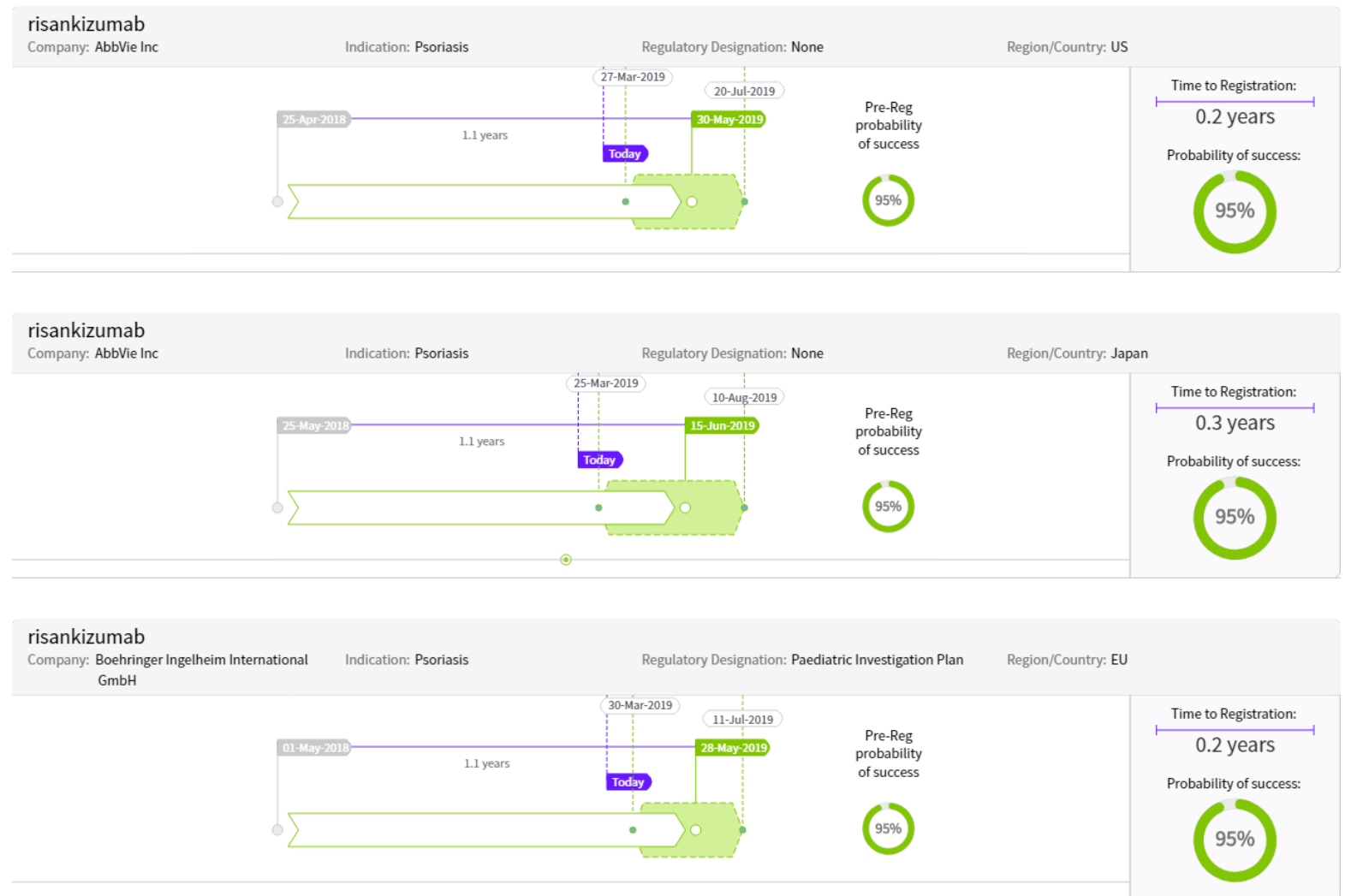
The regulatory filings were based on data from the phase 3 ultIMMA-1, ultIMMa-2, IMMvent and IMMhance trials.<sup>74,75,76</sup> The primary endpoints of ultIMMA-1 and ultIMMA-2 were a 90% improvement in the Psoriasis Area and Severity Index (PASI 90) and a static Physician Global Assessment (sPGA) score of clear or almost clear (sPGA 0/1). In ultIMMA-1, PASI 90 was achieved at week 16 by 75% of Skyrizi recipients, versus 42% of patients taking competitor drug Stelara (ustekinumab; Johnson & Johnson), and 5% of patients on placebo. sPGA 0/1 was achieved by 88%, 63% and 8% of subjects in the three groups, respectively. In ultIMMA-2, the achievement rates for PASI 90 in the three groups were 75%, 48% and 2%, and for sPGA 0/1 were 84%, 62% and 5%.<sup>77</sup>

IMMvent was a similar trial that compared Skyrizi with Humira (AbbVie). At week 16, 72% of Skyrizi recipients met PASI 90, compared with 47% for Humira. The figures for sPGA 0/1 were 84% and 60%, respectively.<sup>77</sup>

IMMhance was a randomized withdrawal and re-treatment trial of Skyrizi versus placebo. After 16 weeks of treatment, PASI 90 was met by 73% and 2% of Skyrizi and placebo recipients, respectively, and sPGA 0/1 was met by 84% and 7%, respectively. Patients achieving sPGA 0/1 at week 28 were randomized to Skyrizi maintenance therapy or withdrawal; withdrawal patients relapsing after week 32 were retreated with Skyrizi. sPGA 0/1 was maintained to 52 weeks by 87% of the maintenance group, and 61% of the withdrawal group.<sup>78</sup>

In addition to psoriasis, Skyrizi is also in trials for psoriatic arthritis, asthma, Crohn's disease and ulcerative colitis. Approvals in additional areas such as these will be useful in the marketing of the drug, as many of its competitors are approved across multiple disease indications.

## Milestone forecasts for Skyrizi



Source: Cortellis Analytics – Drug Timeline & Success Rates



# Skyrizi PASI 90 and sPGA 0/1 data

Trial	Endpoints	Skyrizi	Stelara	Humira	Placebo
<b>ultIMMA-1</b>	PASI 90	75%	42%	n/a	5%
	sPGA 0/1	88%	63%	n/a	8%
<b>ultIMMA-2</b>	PASI 90	75%	48%	n/a	2%
	sPGA 0/1	84%	62%	n/a	5%
<b>IMMvent</b>	PASI 90	72%	n/a	47%	n/a
	sPGA 0/1	84%	n/a	60%	n/a
<b>IMMhance (treatment phase)</b>	PASI 90	73%	n/a	n/a	2%
	sPGA 0/1	84%	n/a	n/a	7%

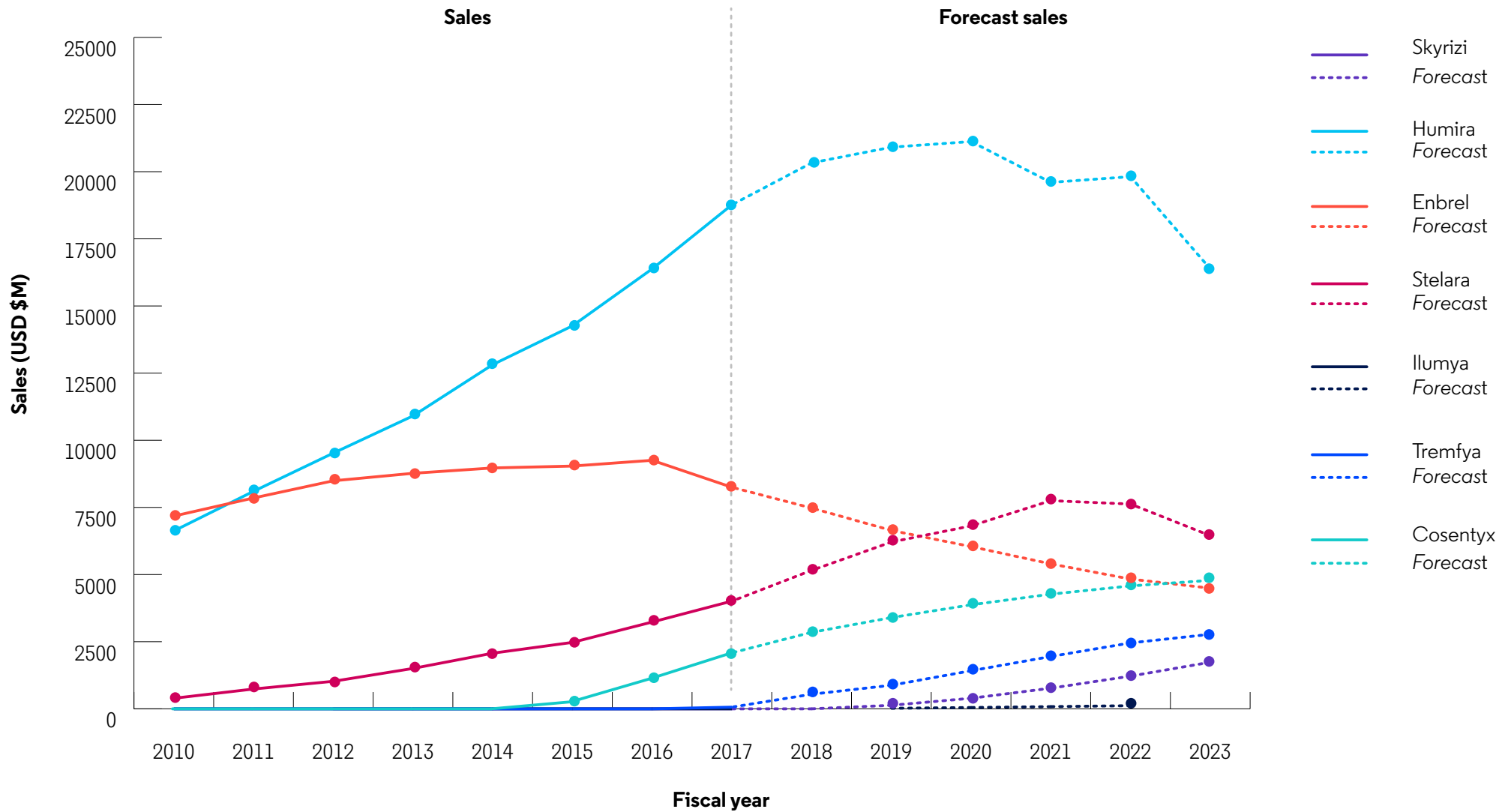
## The psoriasis market

Numerous different treatment modalities exist in the market that Skyrizi is hoping to enter, including topical treatments, light therapies and systemic medicines. Over-the-counter topical medications such as salicylic acid and coal tar have long traditions of use. Prescription topical agents are also commonly used, such as corticosteroids, retinoids and vitamin D analogs. Various types of light therapy are available, which are commonly used due to their safety, efficacy, cost-effectiveness, and lack of systemic toxicities and immunosuppressive effects. When it comes to non-biological systemic agents, methotrexate is the most commonly used medication worldwide for moderate to severe psoriasis, as it is inexpensive and has a long history of use. Otezla (apremilast; Celgene), an oral anti-inflammatory, may also be preferred ahead of injectable biologics for mild to moderate psoriasis.<sup>72,79,80,81,82,83,84</sup>

In the realm of biological systemic agents, the TNF inhibitors Humira and Enbrel are leading drugs in the field. Biosimilar versions of these two agents are available, the lower cost of which may drive preferential use over other, more expensive branded biologics.<sup>85,86</sup> In the IL-23-inhibitor class, there is Stelara, the first-in-class IL-12/IL-23 inhibitor, plus the IL-23 inhibitors Ilumya (tildrakizumab; Sun Pharmaceutical/Almirall) and Tremfya (guselkumab; Johnson & Johnson).<sup>87,88,89,90</sup> Competing with these is the IL-17 inhibitor Cosentyx (secukinumab; Novartis), which was superior to Stelara in the CLEAR trial; targeting IL-17 rather than the upstream molecules TNF and IL-23 is expected to have more specific effects, fewer side effects and a faster onset of efficacy.<sup>91,92,93,94,95</sup>



## Sales and sales forecasts for Skyrizi, Humira, Enbrel, Stelara, Ilumya, Tremfya and Cosentyx



# AR-101 for peanut allergy

AR-101: Reduces peanut allergy. It will be first-in-class with no competition expected soon. (Breakthrough Therapy)





AR-101 expected sales in 2023

**Peanut allergy is one of the most common food allergies, affecting approximately 6 million people in the U.S. and Europe alone. Such allergies are potentially life threatening, and unlike many food allergies, patients allergic to peanuts often do not outgrow the condition; approximately 80% of peanut allergies persist lifelong.**<sup>96,97,98,99</sup>

## AR-101

Tiny exposures to peanuts can trigger severe or fatal responses, with peanut allergy being responsible for most of the deaths from food allergies. Peanuts are also present in a wide range of foods, thus making them difficult to avoid. At least one study has shown that more than 50% of patients over a five-year period suffered adverse reactions to accidentally encountered peanuts. To make matters worse, there is currently no approved treatment: the only options are avoidance of peanuts and self-injection with epinephrine in the event of a reaction to exposure.<sup>96,99,100,101,102</sup>

Aimmune's AR-101 is an oral drug containing defined amounts of peanut protein. It is designed to be given in increasing quantities over a number of months so as to induce peanut tolerance in patients by desensitizing them to peanut protein, thus protecting them from the risks associated with accidental peanut exposure. Maintenance dosing is used after the initial dosing regime in order to maintain tolerance.<sup>103</sup>

A regulatory filing for U.S. approval of AR-101 in children and adolescents aged from 4 to 17 years was submitted in December 2018, with a request for Priority Review. The filing was based on data from the PALISADE, ARC004 (a follow-on trial to PALISADE) and RAMSES studies. However, Aimmune reported in February 2019 that the FDA has initially determined that the drug, as an allergenic extract, is exempt from the PDUFA process; this determination may mean that instead of expedited review because of AR-101's Breakthrough Therapy designation, the filing may instead be given a 12-month target period. Discussions are underway between the FDA and the company regarding the review timeline.<sup>104</sup> The current forecast likelihood of U.S. approval is 95% with approval expected in November 2019, although this may be influenced by the outcome of the discussions. An EU filing is expected in the first half of 2019.<sup>105</sup>

The one-year phase 3 PALISADE trial enrolled patients who experienced dose-limiting reactions to 100 mg or less of peanut protein (approximately one third of a peanut). After induction and maintenance dosing, 67.2% of AR-101 recipients aged from 4 to 17 years were able to tolerate a challenge dose of 600 mg of peanut protein (approximately two peanuts), compared with 4% of placebo recipients. Tolerance of 1000 mg was achieved by 50.3% and 2.4% of AR-101 and placebo recipients, respectively. Symptom severity was also reduced with AR-101 compared with placebo. The RAMSES study confirmed the safety profile of the drug.<sup>105,106,107,108</sup>

## The peanut allergy market

Although a number of studies in recent years have shown the promise of oral immunotherapy for inducing food allergen tolerance, AR-101 has the potential to be the first approved therapy in this field.<sup>97,99</sup> Sales of \$1.17 billion are forecast for AR-101 in 2023.

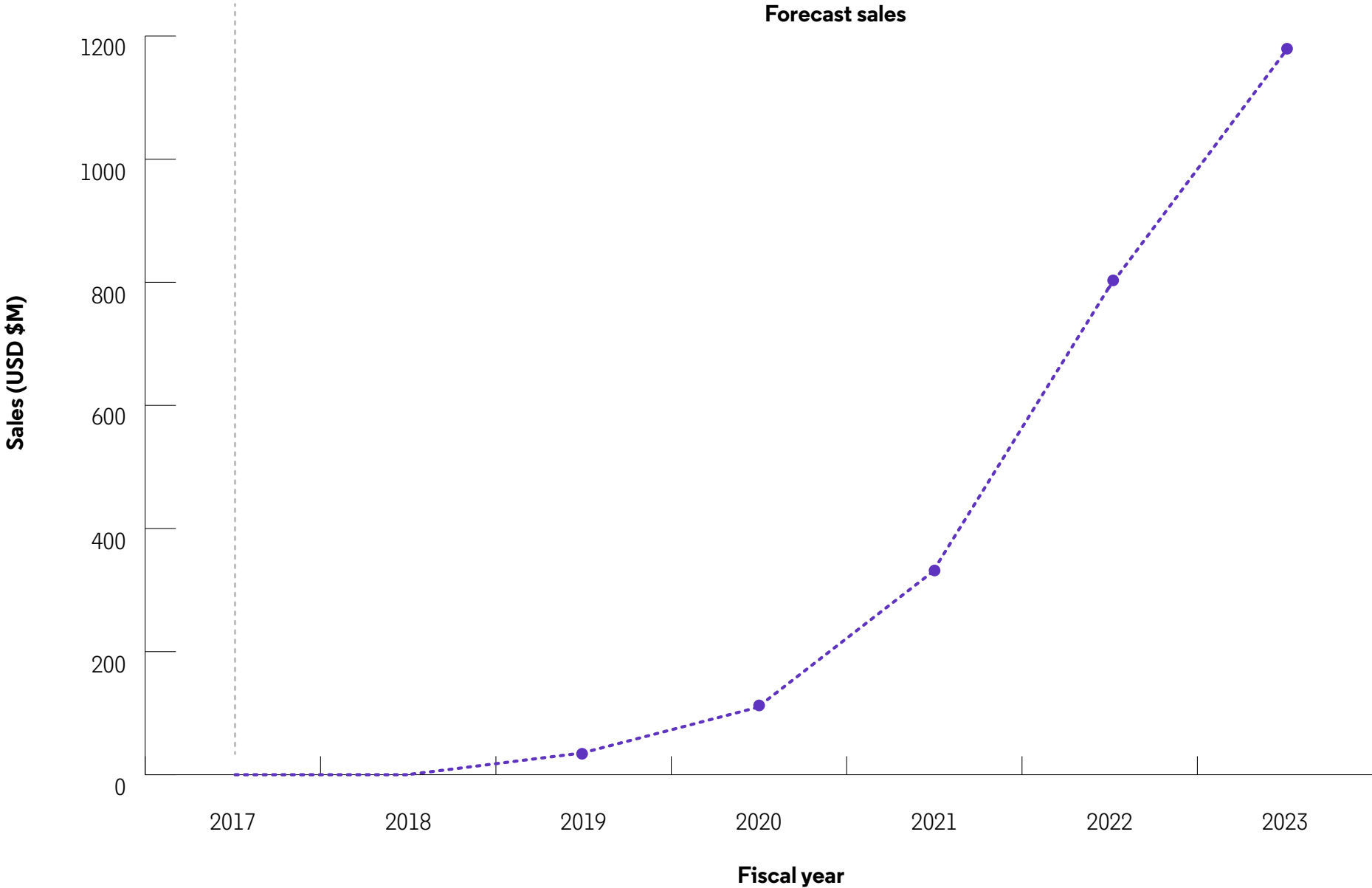
Broadening the eligible patient age range for AR-101 would further increase its market appeal. Expansion into a younger pediatric population is the most likely option, as the PALISADE trial failed to show significant efficacy in adults, with 41.5% of AR-101 recipients tolerating the 600-mg challenge, compared with 14.3% of placebo recipients.<sup>107</sup> Younger children are particularly vulnerable to the risks of food allergies due to the difficulty of self-monitoring food contents compared with older children and adults, and the large proportion of their time spent in childcare/school settings away from parental supervision. In December 2018, the phase 3 POSEIDON trial began in children aged between 1 and 3 years.<sup>109,110</sup>

AR-101 may face competition from other peanut desensitization therapies that are currently in development. For example, DBV Technologies filed its Viaskin Peanut transdermal therapy for U.S. approval for children aged 4 to 11 years in October 2018, but withdrew the filing in December 2018 after discussions with the FDA regarding the insufficiency of the manufacturing procedure and quality control data in the filing; resubmission of the application is planned.<sup>111,112</sup> The forecast likelihood of approval of Viaskin Peanut in the U.S. is 26%.

Also in development are ProTA Therapeutics's probiotic and peanut oral immunotherapy (PPOIT), and Camallergy's oral peanut immunotherapy (CA-002), both of which are expected to enter phase 3 trials in the near term.



Sales and sales forecasts for AR-101



# LentiGlobin for beta thalassemia

LentiGlobin (betibeglogene darolentivec): Corrects the defect causing beta thalassemia, a blood disorder that causes life-threatening anemia. Its only immediate competition will be donor stem cell transplant, which carries significant patient risks. (Orphan Drug & Breakthrough Therapy)







LentiGlobin expected sales in 2023

**Beta thalassemia is a genetic disorder in which beta globin, one half of the hemoglobin complex, is reduced or lacking, thus resulting in hemolysis and life-threatening anemia. The stimulating effect of anemia on erythropoietin results in bone deformities, as well as growth and metabolic complications. The more severe cases of beta thalassemia may require lifelong regular blood transfusions, without which most patients would die in early childhood. However, repeat transfusions can cause iron overload, which must be treated with iron chelation therapy in order to prevent widespread organ damage. The incidence of the disease varies across the world, with approximately 60,000 symptomatic people born annually.**<sup>113,114,115,116</sup>

**Transplantation with donor (allogeneic) hematopoietic stem cells (HSC) is an option for patients with transfusion-dependent beta thalassemia, although this is a procedure with significant risks, including treatment-related mortality, infections, graft failure and graft-versus-host disease. It is therefore generally reserved for younger patients with tissue-matched donors, such as a sibling.**<sup>117,118,119</sup>

## LentiGlobin

bluebird bio's LentiGlobin therapy provides an alternative take on the transplant option. Instead of using donor cells, the patient's own cells are harvested, genetically modified to produce functional beta-globin, and then re-introduced back into the patient, thus correcting the disease.<sup>120,121</sup>

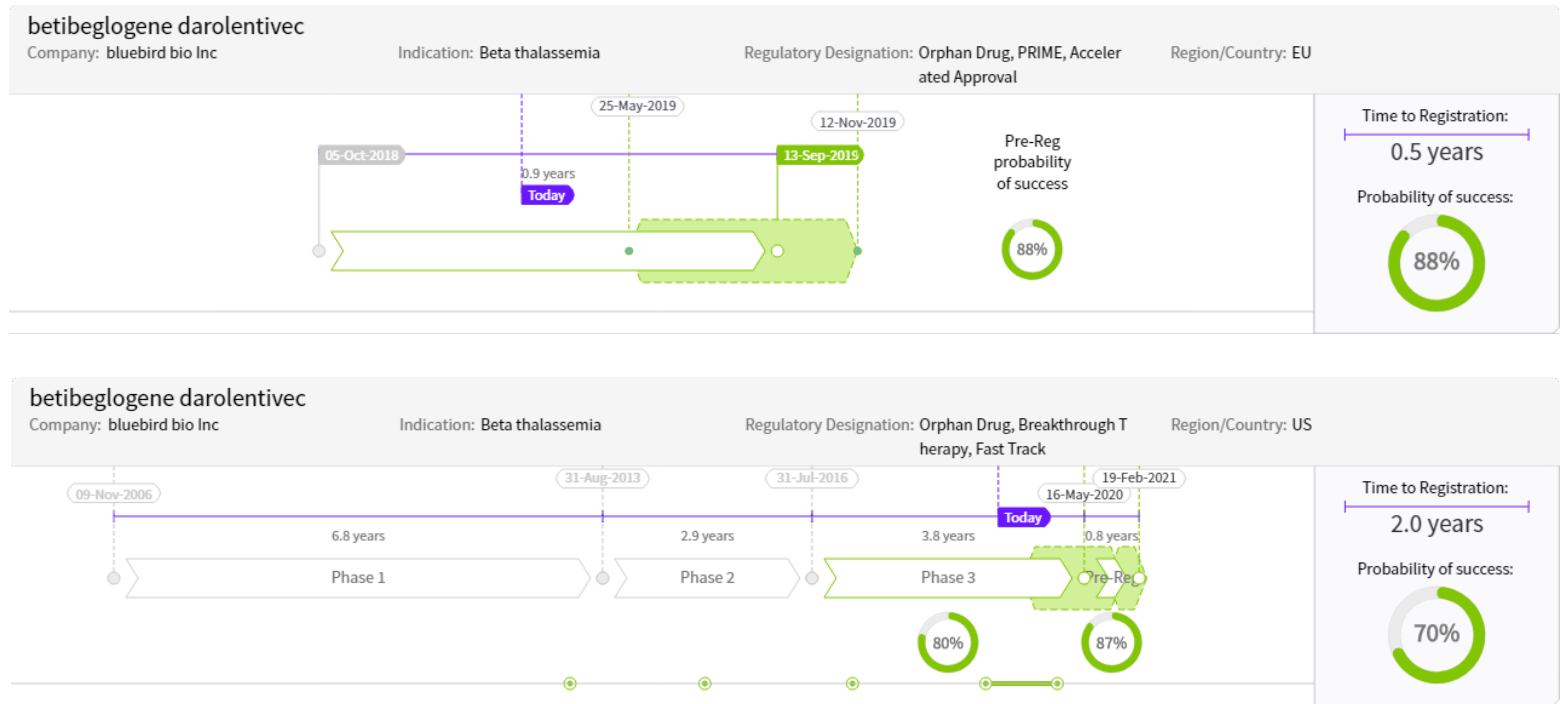
There are a number of potential mutations to the beta globin gene. Mutations that allow reduced production of beta globin are termed beta+, while those that prevent any beta globin production from that gene are termed beta0. A patient with a beta0 mutation on both copies of the gene (homozygous beta0) has no beta globin.<sup>122</sup>

The initial regulatory pathway for LentiGlobin in transfusion-dependent beta thalassemia has focused on patients with non-beta0/beta0 genotypes, that is patients who have some residual production of beta globin. In October 2018, the drug was accepted for regulatory review in the EU for non-beta0/beta0 adolescents and adults, based on data from the completed phase 1/2 HGB-204 (Northstar) and ongoing phase 1/2 HGB-205 trials, plus available data from the ongoing phase 3 HGB-207 (Northstar-2) and long-term follow-up LTF-303 studies.<sup>119</sup>

Interim data from Northstar and HGB-205, published in April 2018, showed that 12 of the 13 non-beta 0/beta 0 patients had become independent of regular transfusions; the median time since the last transfusion was 27 months, with a range of between 11 months and 42 months.<sup>123,124</sup>

The forecast likelihood of approval of LentiGlobin is 88% in the EU (expected in November 2019) and 70% in the U.S. (expected in February 2021). Sales forecasts for LentiGlobin in 2023 are \$1.12 billion.

## Milestone forecasts for LentiGlobin



Source: Cortellis Analytics – Drug Timeline & Success Rates

## The beta thalassemia market

If approved, LentiGlobin would enter a market in which there is a high unmet need. As discussed above, currently the only curative treatment is HSC transplantation, which is limited by donor availability and the considerable risks entailed in the use of allogeneic cells.<sup>125</sup>

The broader the range of approved indications for LentiGlobin, the greater its penetration into this under-served market. The therapy has initially been filed for use in adults and adolescents with a non-beta0/beta0 genotype, but development is also ongoing in beta0/beta0 patients. The Northstar and HGB-205 trials enrolled patients of all genotypes, and the phase 3 HGB-212 (Northstar-3) study, which began in July 2017, is treating beta0/beta0 patients.<sup>126</sup> The interim data published in April 2018 from Northstar and HGB-205 showed that median transfusion volume was decreased by 73% in the nine beta0/beta0 patients, with three patients becoming able to stop transfusions altogether.<sup>123,124</sup> Data from these trials, plus Northstar-3, are expected to form the basis of later filings for use of LentiGlobin in beta0/beta0 subjects.<sup>125</sup>

Sickle cell disease, another condition caused by a mutation in the beta globin gene, is also being assessed as a therapeutic indication for LentiGlobin, with a phase 3 trial planned for 2019. Success in this setting could further broaden the market opportunity for LentiGlobin.<sup>127</sup>

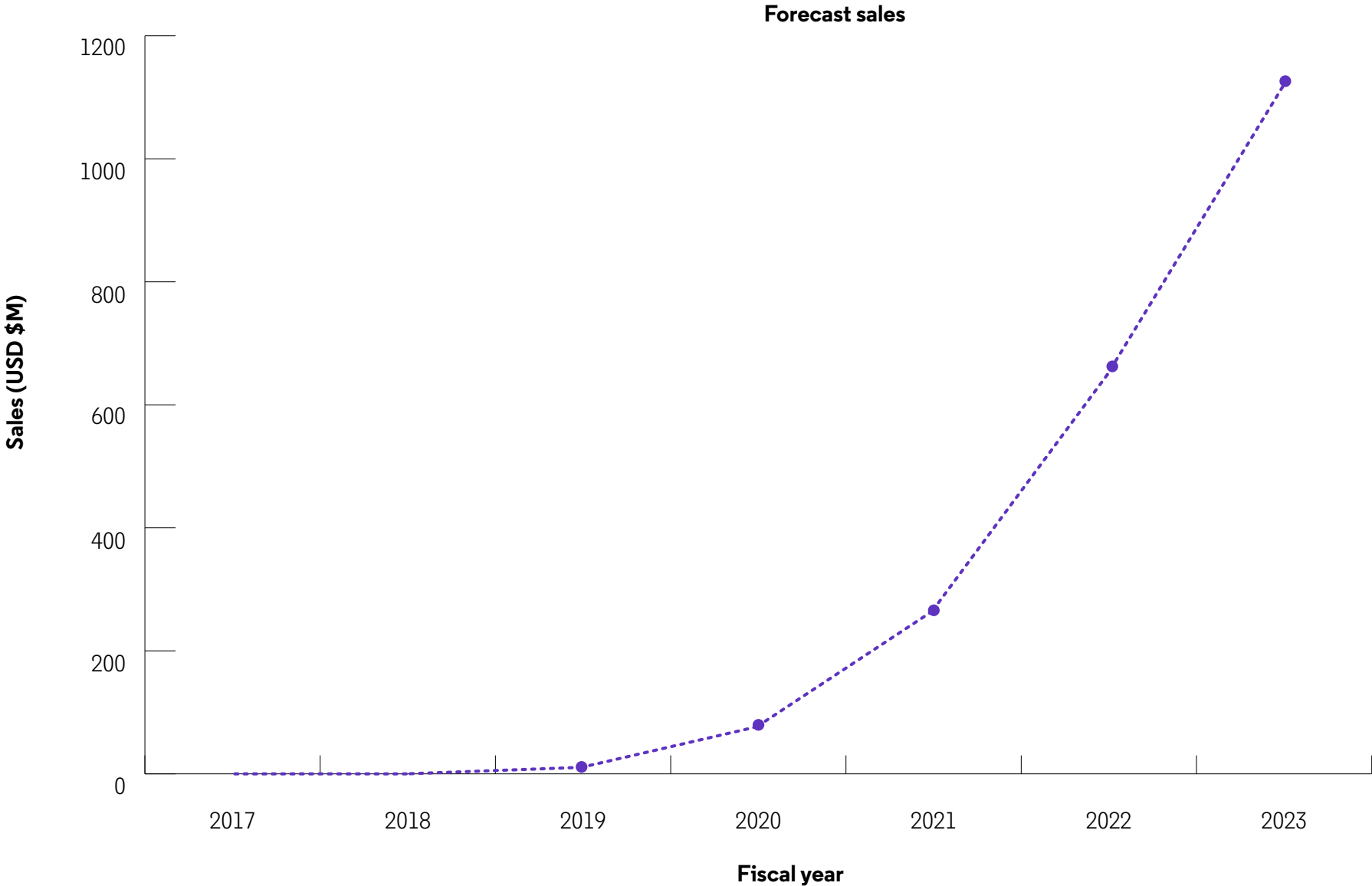
There are a number of genetically modified HSC therapies in the development pipeline that could become competitors to LentiGlobin. Like LentiGlobin, Orchard Therapeutics's OTL-300 aims to correct the beta globin gene, and is currently being assessed in the phase 2 TIGET-BTHAL trial. The forecasted likelihood of EU approval of OTL-300 is 70%, with approval expected in 2023.

Other genetically modified HSC potential competitors for LentiGlobin have a different mechanism of action; rather than correcting the beta globin gene, these therapies instead disrupt the BCL11A gene that causes the switch in early life from fetal to adult hemoglobin production, thus promoting the retention of fetal hemoglobin and restoring red blood cell function.<sup>128,129</sup> Examples include Vertex and CRISPR Therapeutics's

CTX-001, which entered phase 1/2 development for beta thalassemia (study CTX001-111) and sickle cell disease (CTX001-121) in July and November 2018, respectively,<sup>129,130,131</sup> and Sangamo and Bioverativ's ST-400 that entered phase 1/2 development for beta thalassemia in May 2018 (study ST-400-01).<sup>132</sup>

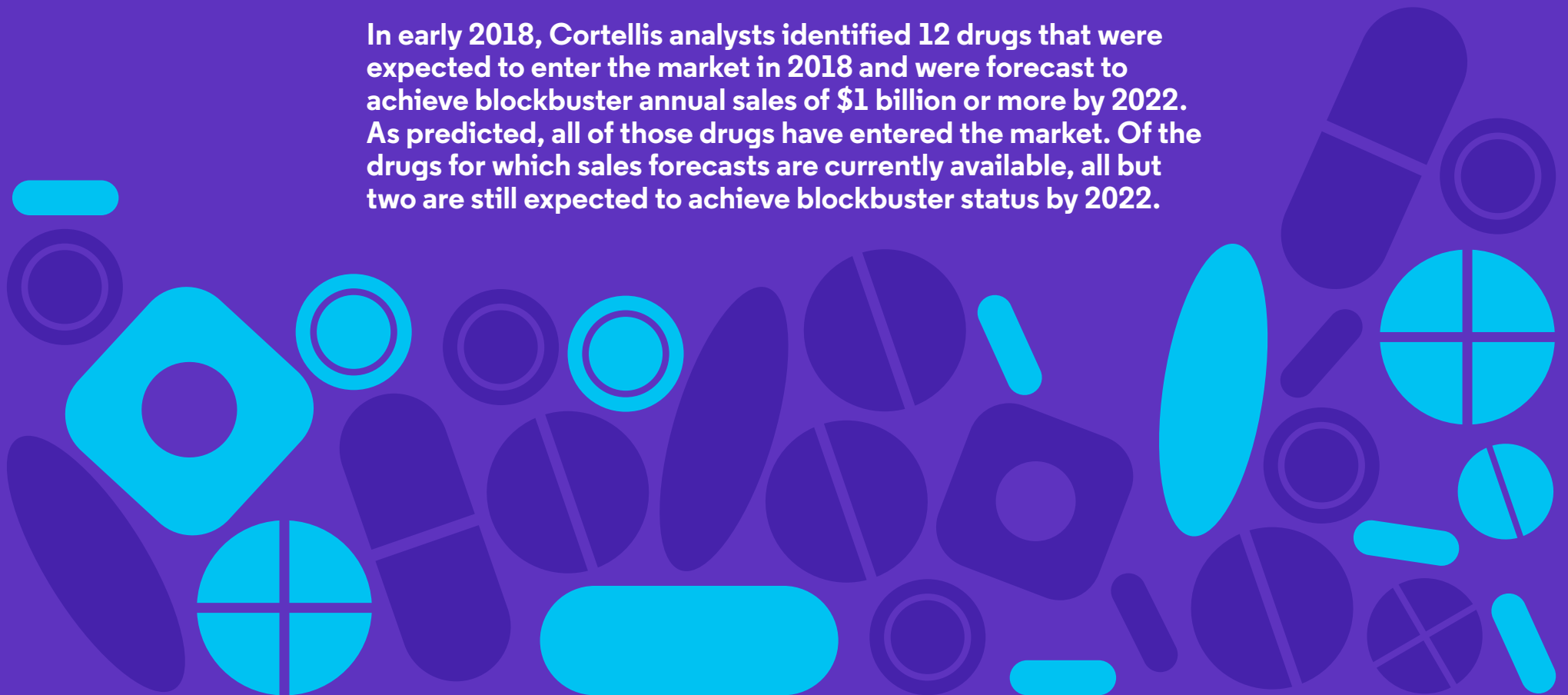


Sales and sales forecasts for LentiGlobin



# Drugs to Watch 2018 – Where are they now?

In early 2018, Cortellis analysts identified 12 drugs that were expected to enter the market in 2018 and were forecast to achieve blockbuster annual sales of \$1 billion or more by 2022. As predicted, all of those drugs have entered the market. Of the drugs for which sales forecasts are currently available, all but two are still expected to achieve blockbuster status by 2022.



The HIV drug Biktarvy (bictegravir + emtricitabine + tenofovir alafenamide fumarate; Gilead) currently has forecast sales that place it ahead of all the other 2018 Drugs to Watch. The drug was made available in the U.S. in February 2018<sup>133</sup>, approved in the EU in June 2018, and by July 2018 was launched in a number of EU countries.<sup>134</sup> It was filed for approval in Japan in December 2018.<sup>135</sup> The October 2018 updates to the U.S. and European HIV treatment guidelines that added Biktarvy to the list of recommended first-line therapies have contributed to the significantly increased forecast sales for this agent. Forecast sales for the drug in 2022 are currently \$6.03 billion, compared with forecasts of \$3.72 billion at this time last year. Gilead expects the drug to become the number one regimen for treatment-naïve HIV, and the most successful HIV launch in history, helping cement Gilead's leading position in the market.<sup>134,136,137</sup>

Hemlibra (emicizumab; Roche/Chugai) had entered the U.S. market for hemophilia A in adult and pediatric patients with factor VIII inhibitors by the time the 2018 Drugs to Watch report was published, becoming the first new agent in this disease setting in close to 20 years.<sup>138</sup> In October 2018, Hemlibra was additionally approved in the U.S. for hemophilia A without factor VIII inhibitors, thereby significantly broadening its market.<sup>139</sup> Approval in the EU for patients with inhibitors was granted in February 2018.<sup>140</sup> In Japan, the drug was launched in May 2018 for patients

with inhibitors and approved in December 2018 for patients without inhibitors.<sup>141,142</sup> Current 2022 forecast sales stand at \$2.79 billion.

Ozempic (semaglutide; Novo Nordisk) sales of \$3.47 billion in 2022 were forecast early last year, and are similar a year later, at \$3.62 billion. The drug was launched in the U.S. into a crowded type 2 diabetes market in February 2018<sup>143</sup> and was also approved in the EU that month.<sup>144</sup> In March 2018, it was approved in Japan.<sup>145</sup>

The only cancer drug on the 2018 Drugs to Watch list, Erleada (apalutamide; Johnson & Johnson), was launched in the U.S. in February 2018 as the first FDA-approved agent for non-metastatic castration-resistant prostate cancer<sup>146</sup> and has 2022 forecast sales of \$1.58 billion. It was approved in the EU in January 2019, and filed for Japanese approval in March 2018.<sup>147,148</sup>



Sales of the shingles vaccine Shingrix (GlaxoSmithKline) to distributors began in December 2017,<sup>149</sup> and in March 2018, the drug was approved in the EU and Japan,<sup>150</sup> setting it on course to becoming the leading shingles vaccine.

For the rare disorder polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults, potential best-in-class Onpattro (patisiran; Alnylam) was approved in the U.S. as expected in August 2018 and was launched immediately.<sup>151</sup>

In October 2018, the drug was launched in its first EU market,<sup>152</sup> and it was filed for approval in Japan in September 2018.<sup>153</sup>

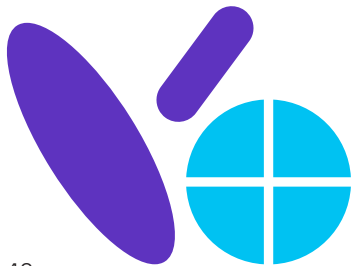
Becoming the first cannabis-derived therapeutic in the U.S., Epidiolex (cannabidiol; GW Pharmaceuticals) was launched in the U.S. in November 2018 for seizures associated with Lennox-Gastaut or Dravet syndromes;<sup>154</sup> an EU filing was accepted for review in February 2018, with a decision expected soon.<sup>155</sup> In the migraine prevention market, Aimovig (erenumab; Amgen/Novartis) was the first of a new class of treatments to be approved and was then launched in the U.S. in May 2018;<sup>156, 157</sup> by October 2018, launch was also underway in the EU.<sup>158</sup>

In hereditary angioedema, Takhzyro (lanadelumab; Shire), a novel, more convenient treatment, was approved and launched in the U.S. in August 2018<sup>159,160</sup> and is set to dominate the market. In November 2018, the drug was also approved in Europe.<sup>161</sup> As anticipated, first-in-class Orilissa (elagolix; AbbVie) was launched in the U.S. for endometriosis pain in August 2018.<sup>162</sup> Steglatro (ertugliflozin; Pfizer/Merck & Co) was launched for type 2 diabetes in the U.S. in January 2018,<sup>163</sup> and in March 2018, the drug was approved in Europe.<sup>164</sup> Finally, in opioid dependence, Sublocade (buprenorphine; Indivior) was launched in the U.S. in March 2018 as the first once-monthly formulation of buprenorphine for use in this setting.<sup>165</sup>



# Looking ahead

The launches of the 12 Drugs to Watch in 2018 are making significant impacts on their various markets, and it will be of great interest to watch the progress throughout 2019 of this year's seven Drugs to Watch. Covering a wide range of conditions, and with the recurring themes of genetic modification and immune-modulation, they represent a fascinating snapshot of the cutting-edge development that characterizes the medical life sciences industry.





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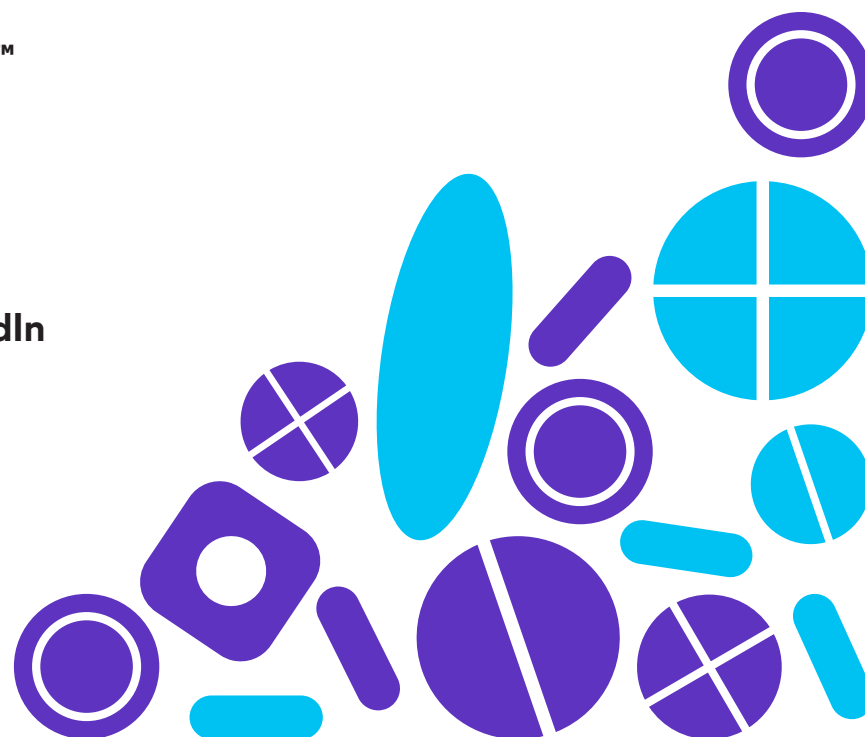
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