

# Drug and Biologic Pipeline Update

September 2020



**ingenio**<sup>Rx</sup>  
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# IngenioRx's quarterly *Drug and Biologic Pipeline Update*

Welcome to the IngenioRx Drug and Biologic Pipeline Update. This publication will provide an overview of emerging new therapies. Because our goals are improving health, reducing waste, lowering the total cost of care (pharmacy and medical), and estimating future cost impact, we believe it's critical to carefully monitor the drug and biologic pipeline.

In this inaugural issue, we examine a new treatment that has just received U.S. Food and Drug Administration (FDA) approval, and two awaiting approval that have the potential for significant market impact. We also review the latest on emerging treatments for nonalcoholic steatohepatitis (NASH) – liver inflammation and damage caused by fat buildup in the liver – a category that has the potential to produce several blockbuster drugs. In addition, we look at several select agents with possibility for FDA approval through 2021. We also examine the effect of COVID-19 on FDA approvals.

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Unless otherwise noted, the information contained in this document was obtained from the Centers for Disease Control and Prevention ([cdc.gov](https://www.cdc.gov)), the Food and Drug Administration ([fda.gov](https://www.fda.gov)), [clinicaltrials.gov](https://clinicaltrials.gov), releases from pharmaceutical manufacturers, and UpToDate.com (registration required). Information in this document is accurate as of September 2, 2020.



# Top emerging new therapies

We expect these products to have significant impact on health plans and members.

## EVRYSDI™

**Product:**

Evrysdi (risdiplam)

**Indication:**

Spinal muscular atrophy, types 1, 2, and 3

**FDA approval date:**

August 7, 2020

**Therapeutic class:**

Survival motor neuron-2 (SMN2) splicing modifier

**Route of administration:**

Oral

**FDA designations:**

Priority, Fast track, Orphan, Breakthrough

**Manufacturer:**

Roche

**Condition:**

Spinal muscular atrophy (SMA) is a rare and often fatal genetic disease that affects muscle strength and movement due to the loss of nerve cells in the spinal cord. SMA can affect people at any stage of life and is the most common genetic cause of infant mortality, affecting approximately 1 in 10,000 infants.<sup>1</sup> There are five types of SMA, ranging in severity from type 0 as the most severe to type 4 as the least severe.<sup>2</sup> Patients with type 1, the most common form, usually do not live past age 2.<sup>1</sup>

**Role in treatment:**

Evrysdi™ is the third FDA-approved treatment option for SMA, and has a potential advantage as an oral therapy. Current FDA-approved therapies for SMA include Spinraza, which is injected into the spinal fluid, and Zolgensma, a gene therapy.

**Efficacy:**

The manufacturer is conducting clinical trials on Evrysdi, called FIREFISH and SUNFISH. In the FIREFISH manufacturer trial, 29% of infants with SMA type 1 were able to sit without support for at least five seconds after receiving risdiplam for one year. In the SUNFISH study, patients 2 to 25 years of age with SMA types 2 or 3 showed improvement from baseline in a motor function scale designed to measure changes in people with neurological disorders.

**Safety:**

No significant safety issues have been reported in the literature.

**Financial impact:**

Roche has announced the maximum price for Evrysdi (risdiplam) will be \$340,000 per year.<sup>3</sup> Evrysdi is projected to have peak U.S. sales of \$223M.<sup>4</sup> **Evrysdi approval is expected to result in a moderate increase in drug spend** (with greater impact in Medicaid than other business segments), largely due to competition from high-cost alternative treatments.<sup>5</sup>

**IngenioRx view:**

Evrysdi is the first oral treatment option approved for SMA. It has received approval to treat a broad range of SMA patients, from infants to adults. Evrysdi will likely compete most directly with Spinraza, including newly diagnosed and existing Spinraza users.

1 Spinal Muscular Atrophy Foundation website: *About SMA: Overview* (accessed August 2020): [smafoundation.org](http://smafoundation.org).

2 National Organization for Rare Disorders website: *Rare Disease Database: Spinal Muscular Atrophy* (accessed August 2020): [rarediseases.org](http://rarediseases.org).

3 Fidler B: *First oral drug for spinal muscular atrophy approved by FDA*. *BioPharma Dive* (August 7, 2020): [biopharmadive.com](http://biopharmadive.com).

4 Decision Resources Group, with adjustments for current pricing.

5 Decision Resources Group website: [insights.decisionresourcesgroup.com](http://insights.decisionresourcesgroup.com) (accessed July 2020; registration required).

# TANEZUMAB

**Product:**

Tanezumab

**Indication:**

Chronic pain due to moderate-to-severe osteoarthritis in patients who have experienced inadequate pain relief with other analgesics

**Estimated FDA approval:**

December 2020

**Therapeutic class:**

Nerve growth factor (NGF) inhibitors

**Route of administration:**

Subcutaneous (SC) injection

**FDA designations:**

Fast track

**Manufacturer:**

Pfizer and Eli Lilly

**Condition:**

Osteoarthritis (OA) is a degenerative joint disease that causes pain and swelling in the hands, hips, knees, spine, and other joints. With severity levels ranging from mild to severe, an estimated 30 million adults in the United States have OA, making it the most common cause of disability in adults.

**Role in treatment:**

Tanezumab would be the first FDA-approved, health care-administered monoclonal antibody approved for the treatment of OA. Current treatments include pain relievers, including opioids, intra-articular (IA) joint injections, and joint replacement surgery. However, tanezumab's role is unclear due to lingering and serious safety concerns that may outweigh any efficacy benefit.

**Efficacy:**

In two clinical trials, tanezumab 2.5 mg was slightly better than placebo, but no different than oral nonsteroidal anti-inflammatory drugs (NSAIDs) in relieving pain.

**Safety:**

Important safety signals emerged in clinical trials. In the placebo comparison trial, the incidence of rapidly progressive OA (RPOA) and number of joint replacement surgeries were higher with tanezumab-treated patients. In the 56-week NSAID comparison trial, tanezumab patients had a significantly higher rate of joint safety events — a composite measure including RPOA and fractures. RPOA occurred in 3.2% of tanezumab 2.5 mg patients, compared to 1.2% of NSAID-treated patients. Joint replacement surgeries were required for 5.3% of tanezumab 2.5 mg, versus 2.6% of NSAID-treated patients.

**Financial impact:**

Tanezumab is expected to be costlier than treatment alternatives, including certain generics. Projected domestic sales are estimated to reach \$2.93 billion by 2028.\* Safety concerns may prevent broad adoption. **Tanezumab approval could lead to a sizeable increase in medical spend, especially in the senior population.**

**IngenioRx view:**

Tanezumab would be the first FDA-approved monoclonal antibody for OA. Trials have identified important safety signals, which we are monitoring, that may limit tanezumab uptake. With its uncertain benefit-to-risk profile, it is unclear how tanezumab will be used in clinical practice. Despite limitations in efficacy and safety, physician and patient interest may be higher than expected because it is a nonopioid option.

\* Decision Resources Group website: [insights.decisionresourcesgroup.com](https://insights.decisionresourcesgroup.com) (accessed July 2020; registration required).

# ROXADUSTAT

**Product:**

Roxadustat

**Indication:**

Anemia of chronic kidney disease in both nondialysis-dependent (NDD) and dialysis-dependent (DD) patients

**Estimated FDA approval:**

December 20, 2020

**Therapeutic class:**

Hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI)

**Route of administration:**

Oral

**FDA designations:**

None

**Manufacturer:**

AstraZeneca and FibroGen

**Condition:**

Chronic kidney disease (CKD) occurs in patients with damaged kidneys and is estimated to affect approximately 37 million adults in the United States. Anemia due to CKD can occur when a patient's kidneys no longer make enough of the erythropoietin hormone that helps make red blood cells. These red blood cells contain hemoglobin (Hb) that carries oxygen throughout the body.

**Role in treatment:**

Roxadustat would be the second oral FDA-approved treatment option for anemia due to CKD. Oral iron supplementation is the only oral option currently available. Patients with low Hb typically use injectable erythropoiesis-stimulating agents (ESAs). Roxadustat's novel mechanism of action gives it a potential advantage to compete directly with injectable ESAs.

**Efficacy:**

Positive pooled results from six trials found roxadustat statistically superior to the placebo, and to the ESA epoetin alfa, in improving Hb levels over one year of therapy, with a treatment difference of 1.72 grams per deciliter (g/dL) for the placebo and 0.23 g/dL for ESA. The clinical impact of a 0.23 g/dL treatment difference is unclear. In a noninferiority trial, roxadustat was shown to be noninferior to the ESA darbepoetin alfa in improving Hb levels over 24 weeks.

**Safety:**

Cardiovascular safety trials are underway, comparing the rate of major adverse cardiovascular events (MACE) and all-cause mortality with roxadustat versus ESAs and a placebo.

**Financial impact:**

Analysts predict roxadustat pricing at approximately \$11,000, annually with projected U.S. sales of \$460 million by 2027.\* **The overall increase in drug spend from the new class of oral HIF-PHIs is expected to be sizeable,** particularly within the senior population where CKD is more prevalent, as well as within the NDD-CKD population, which, unlike dialysis patients, does not have established IV access due to dialysis and may welcome the oral dosing option.

**IngenioRx view:**

Roxadustat would be the second oral treatment with a novel mechanism of action for patients with anemia due to CKD. Oral roxadustat would compete directly with injectable ESAs. Without results from ongoing cardiovascular outcomes studies, the safety of roxadustat is unknown; we are monitoring safety issues for roxadustat as it approaches an approval date.

\* Decision Resources Group website: [insights.decisionresourcesgroup.com](https://insights.decisionresourcesgroup.com) (accessed July 2020; registration required).

In addition to the treatments listed previously, there are other important drugs and biologics scheduled to receive FDA approval within the next 18 months.

**\*\* Key:**

**BCMA:** B-cell maturation antigen

**CAR-T:** chimeric antigen receptor T-cell

**CKD:** chronic kidney disease

**HER2:** human epidermal growth factor receptor 2

**HIV:** human immunodeficiency virus

**IV:** intravenous

**SC:** subcutaneous

**Rolling submission:** when a drug company submits completed sections of its application for review instead of waiting until every section of the application is completed; decision date is assigned when the application is complete



Orphan drug/rare disease; potential high cost, but minimal impact on drug spend due to low prevalence of disease or utilization



Significant potential impact to overall incremental or new drug spend due to cost or prevalence of disease

## Other significant product approvals

We expect these drugs to reach the market in 2020 or 2021:\*

Drug or biologic manufacturer	Indication/route**	Place in therapy**	Estimated approval date	Impact on overall drug spend**
<b>Ryoncil™ (rexlemestrocel-L)</b> Mesoblast	Graft-versus-host disease (GVHD), acute, steroid refractory/IV	<b>First in class:</b> stem cell therapy for acute and steroid refractory GVHD	9/30/2020	
<b>Rolontis® (eflapegrastim)</b> Spectrum	Neutropenia/SC	<b>Addition to class:</b> long-acting analogue of granulocyte colony-stimulating factor; noninferior to pegfilgrastim in clinical trial	10/24/2020	
<b>Sutimlimab</b> Bioverativ	Cold agglutnin disease/IV	<b>Addition to class:</b> would be first FDA-approved treatment for this indication	11/13/2020	
<b>Lisocabtagene maraleucel</b> Bristol Myers Squibb	Diffuse large B-cell lymphoma/IV	<b>Addition to class:</b> would compete with Kymriah™ and Yescarta™	11/16/2020	
<b>Zokinvy™ (lonafarnib)</b> Eiger BioPharmaceuticals	Hutchinson–Gilford progeria syndrome; Progeroid laminopathies/oral	<b>First in class:</b> would be first FDA-approved treatment for these indications	11/20/2020	

\* As of September 2, 2020.



## Other significant product approvals (continued)

Drug or biologic manufacturer	Indication/route**	Place in therapy**	Estimated approval date	Impact on overall drug spend**
<b>Setmelanotide</b> Rhythm Pharmaceuticals	Obesity due to rare genetic disorders/SC	<b>First in class:</b> would be first FDA-approved treatment for these conditions	11/30/2020	
<b>Inclisiran</b> The Medicines Co.	Dyslipidemia; hypercholesterolemia/SC	<b>First in class:</b> can be given as add-on to statins or ezetimibe: administered twice in the first 90 days, followed by biannual injections thereafter	December 2020	
<b>Berotralstat</b> BioCryst	Hereditary angioedema attack prevention/oral	<b>Addition to class:</b> second-generation plasma kallikrein inhibitor; appears to have less efficacy than injectables	12/03/2020	
<b>Lumasiran</b> Alnylam	Hyperoxaluria, primary/SC	<b>First in class:</b> would be first FDA-approved treatment for this indication	12/03/2020	
<b>Margetuximab</b> MacroGenics	Breast cancer/IV	<b>Addition to class:</b> second-generation anti-HER2 monoclonal antibody; will compete with Herceptin and Perjeta	12/19/2020	
<b>Relugolix</b> Myovant	Prostate cancer/oral	<b>Addition to class:</b> first oral gonadotropin-releasing hormone inhibitor for prostate cancer	12/20/2020	



## Other significant product approvals (continued)

Drug or biologic manufacturer	Indication/route**	Place in therapy**	Estimated approval date	Impact on overall drug spend**
<b>Ansofaxine hydrochloride</b> Luye Pharma	Major depressive disorder/oral	<b>First in class:</b> serotonin-norepinephrine-dopamine triple reuptake inhibitor	12/26/2020	
<b>Dostarlimab</b> GlaxoSmithKline	Endometrial cancer/IV	<b>Addition to class:</b> would compete with Keytruda for microsatellite instability-high disease (MSI-H); dostarlimab has activity against MSI-H and microsatellite stable disease; currently no FDA-approved treatments for microsatellite stable disease	1/14/2021	
<b>Voclosporin</b> Aurinia Pharmaceuticals	Lupus nephritis/oral	<b>Addition to class:</b> would be first FDA-approved treatment for this indication	1/22/2021	
<b>Alpha-galactosidase</b> Protalix Biotherapeutics	Fabry disease/IV	<b>Addition to class:</b> enzyme replacement therapy (ERT); will compete with Fabrazyme™; potential advantage of decreased dosing frequency	1/27/2021	
<b>Aducanumab</b> Biogen	Alzheimer's disease/IV	<b>First in class:</b> anti-amyloid antibody for early disease; potential to slow disease progression	3/07/2021	
<b>Ponesimod</b> Actelion	Multiple sclerosis/oral	<b>Addition to class:</b> sphingosine-1-phosphate (S1P) receptor; no clear advantage over others in class	3/18/2021	



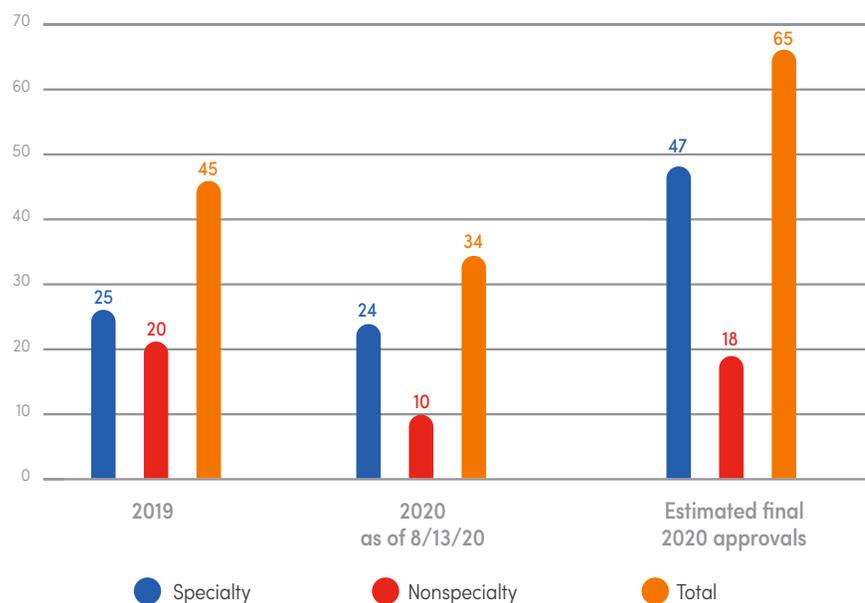
## Other significant product approvals (continued)

Drug or biologic manufacturer	Indication/route**	Place in therapy**	Estimated approval date	Impact on overall drug spend**
<b>Arimoclomol</b> CytRx	Niemann-Pick Disease/oral	<b>First in class:</b> first FDA-approved agent for this indication; may compete or be used in combination with off-label Zavesca™	3/20/2021	
<b>Casimersen</b> Sarepta	Duchenne muscular dystrophy (DMD)/IV	<b>Addition to class:</b> first agent for people with DMD with deletions amenable to exon 45 skipping	6/26/2021	
<b>Avacopan</b> ChemoCentryx	Antineutrophil cytoplasmic antibody-associated vasculitis/oral	<b>Addition to class:</b> first antibody complement C5a receptor inhibitor for this indication; will compete with prednisone	7/09/2021	
<b>Zynteglo® (lentiglobin)</b> bluebird bio	Beta-thalassemia/IV	<b>First in class:</b> would be first gene therapy-approved for treatment of beta-thalassemia	2021 (rolling submission)	

## Analysis: the minimal effect of COVID-19 on drug approvals

Despite early concerns, it appears COVID-19 will not have a significant impact on FDA approvals in 2020.<sup>1</sup> We could see a potential record number of decisions and approvals in the latter half of 2020 due to the number of applications submitted in December 2019. Travel restrictions affecting manufacturing site inspections have led to FDA delays with complete response letters (CRLs) issued for certain drugs. The FDA issues a CRL to ask for information from the manufacturer, pausing the approval process. Even with these delays, the FDA approved more than 25 novel agents in the first half of 2020.<sup>1</sup>

Drug approvals by the FDA



Total number of final approvals is dependent on FDA reviews and potential denials, delays, or both. As a result, the final 2020 number will likely be lower than shown above. Counts may differ slightly from the FDA, depending on how new molecular entity is defined.

Sources: U.S. Food and Drug Administration website: *Novel Drug Approvals for 2019* (January 14, 2020): [fda.gov](https://www.fda.gov).

U.S. Food and Drug Administration website: *Novel Drug Approvals for 2020* (August 12, 2020): [fda.gov](https://www.fda.gov).

<sup>1</sup> Silverman B: *User Fee Calendar Puts Another Record-Setting Year For US FDA Novel Approvals Within Reach*. Pink Sheet (July 5, 2020): [pink.pharmintelligence.informa.com](https://www.pink.pharmintelligence.informa.com).

<sup>2</sup> U.S. Food and Drug Administration: *New Drug Therapy Approvals 2019* (January 2020): [fda.gov](https://www.fda.gov).

### Large number of FDA approvals expected in 2020

Despite COVID-19, we don't expect approvals to slow down in 2020, following a record 58 in 2018 and 45 last year.<sup>1</sup> Fast-tracked, breakthrough therapies are leading the way, including oncology treatments.



**Therapies with fast-track** status have expedited approval. Certain fast-track drugs and biologics are designated as breakthrough treatments for serious or life-threatening diseases that have an unmet medical need.<sup>2</sup>



**Seventeen approved** therapies (35% of approvals) last year were on fast-track status, with 13 designated as breakthrough therapies.<sup>2</sup> In the first half of 2020, 10 of 25 FDA approvals were breakthrough therapies.<sup>1</sup>



**Oncology agents** accounted for 11 of the 25 first-half approvals. Of the remaining agents under review for 2020, 23% are oncology.<sup>1</sup>

## Therapy market trends

**1. There are approximately 900 gene therapies in development — but fewer than 10 are expected to receive approval in the next several years.** The first potential gene therapy for hemophilia A was recently denied by the FDA. It may be several years before we see FDA approval. By 2024, the cost of gene therapies is expected to reach over \$16 billion in the United States, with single treatments priced at over \$1 million.<sup>1</sup>

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**2. The oncology market continues to grow, especially with immunotherapies.** We expect to see another chimeric antigen receptor T-cell (CAR-T) therapy this year for certain blood cancers. Treatment of solid tumors with these therapies is highly anticipated, but remains further away. Programmed cell death 1 (PD-1) inhibitors continue to gain expanded indications and increased use in combination regimens.

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**3. A treatment that may reduce cognitive decline in Alzheimer's disease, a condition with limited treatment options and high unmet need, awaits approval.** Biogen submitted aducanumab to the FDA for approval; a decision is expected in early 2021. However, approval is uncertain due to questionable efficacy and safety issues surrounding this product. There have been therapies for Alzheimer's disease that have previously made it to late-stage trials only to fail prior to FDA submission.<sup>2</sup>

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**4. FDA approval of costly novel drugs and biologics — especially specialty products — continues to increase.** In 2019, 44% of new drugs approved by the FDA were for rare or orphan diseases, representing an extremely small patient population.<sup>3</sup> The outlook for 2020 appears to be similar. One study suggests the average annual cost for orphan drugs is 25 times more expensive than traditional drugs.<sup>4</sup>

<sup>1</sup> Healthgram website: *Gene Therapies By The Numbers: 3 strategies employers need to know about managing multi-million dollar treatments* (accessed September 2020); healthgram.com.

<sup>2</sup> Terry M: *A Long Line of Alzheimer's Failures: Roche Drops Two Drug Trials*. BioSpace (January 30, 2019); biospace.com.

<sup>3</sup> U.S. Food and Drug Administration website: *New Drug Therapy Approvals 2019* (January 2020); fda.gov.

<sup>4</sup> Jozsi L: *Orphan Drugs Are Driving Skyrocketing Drug Costs, AHIP Finds*. American Journal of Managed Care (September 12, 2019); ajmc.com.





## Update on NASH

### The nonalcoholic steatohepatitis pipeline

The biopharma industry has been active in developing possible treatments for nonalcoholic steatohepatitis (NASH), an aggressive form of a broader disease called nonalcoholic fatty liver disease (NAFLD). Trial results have been disappointing, leading to delays in development.

Unlike other diseases that fall under NAFLD, a NASH diagnosis entails excess fat accumulation and inflammation of liver cells. It's a chronic condition that can occur with or without fibrosis, and can progress to advanced fibrosis, cirrhosis, liver failure, cancer, or death.

#### **Prevalence of NASH:**

Currently, diagnosis of NASH requires a liver biopsy. The actual prevalence of NASH is imprecise due to the invasive nature of a liver biopsy combined with the lack of available treatments for NASH. The estimated prevalence of NASH is 3% to 12% of the U.S. population.\* Less-invasive diagnosis methods could someday lead to increased reported prevalence.

#### **NASH treatments:**

In its early stages, NASH may resolve on its own with weight loss and lifestyle changes. Liver transplants may be the only treatment option for those with advanced fibrosis. In fact, NASH is expected to eventually become the leading cause of liver transplantation in the United States.

#### **NASH pipeline:**

An FDA-approved treatment for NASH could possibly be a blockbuster drug if it has the potential to reduce liver transplants. Development and FDA approval of such a drug has been slow.

The FDA recently denied approval of obeticholic acid (OCA) for the treatment of fibrosis due to NASH. An interim analysis showed the higher dose of OCA versus placebo only met one of the two co-primary surrogate endpoints. Significantly more patients taking 25 mg OCA achieved fibrosis improvement by  $\geq 1$  stage with no worsening of NASH compared to the placebo, 23% versus 12%, respectively. There was no difference between OCA and the placebo in the percentage of patients achieving NASH resolution. Safety signals include elevated levels of bad cholesterol, gallbladder events, and higher trial discontinuation rates with OCA due to itching.

#### **The future for NASH treatments:**

The FDA has requested additional clinical data with the resubmission for OCA, which could result in a delay of several years before approval. Although the NASH pipeline is robust, it is unlikely that we will see the first FDA-approved therapy for NASH until 2022.

\* National Institute of Diabetes and Digestive and Kidney Diseases: *Definition & Facts of NAFLD & NASH*: [niddk.nih.gov](http://niddk.nih.gov).

For more insights: [ingenio-rx.com](https://ingenio-rx.com)



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