Drug and Biologic Pipeline Update

Q4 2021

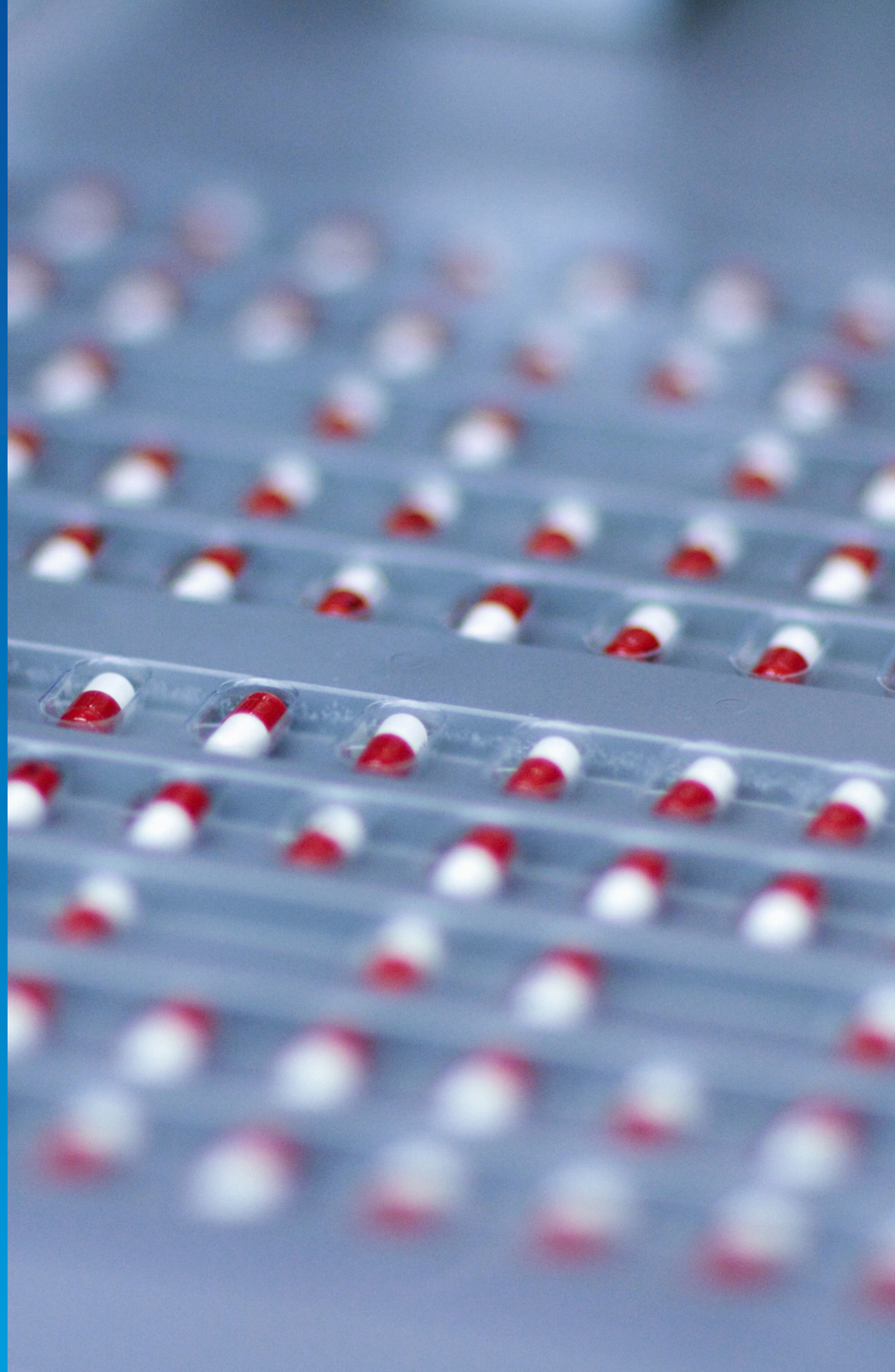
IngenioRx™

IngenioRx's quarterly *Drug and Biologic Pipeline Update*

Our Q4 2021 edition provides highlights of emerging therapies for the treatment of vasomotor symptoms associated with menopause, severe asthma, and hypertrophic cardiomyopathy. In addition, we evaluate select significant product approvals, including biosimilars expected in 2021 and 2022. This quarter will also offer insights on the current gene therapy pipeline and an overview of the psoriasis treatment and pipeline landscape. Our market trend section provides the latest on migraine and artificial intelligence used in drug discovery.

We continue to closely monitor the drug and biologic pipeline and provide this publication as part of our goals to improve health, reduce waste, lower total cost of care for pharmacy and medical, and estimate future cost impact.

Unless otherwise noted, the information contained in this document was obtained from the Centers for Disease Control and Prevention (cdc.gov), the Food and Drug Administration (fda.gov), clinicaltrials.gov, releases from pharmaceutical manufacturers, and uptodate.com (registration required). Information in this document is accurate as of August 3, 2021.



Top emerging new therapies

TEZEPELUMAB

Product:
Tezepelumab

Indication:
Treatment of people 12 or older with severe asthma

Estimated FDA approval:
January 2022

Therapeutic class:
Monoclonal antibody that inhibits thymic stromal lymphopoietin (TSLP)

Route of administration:
Subcutaneous (SC) injection

FDA designations:
Breakthrough, Priority Review

Manufacturer:
Amgen

Condition:

Asthma is a chronic condition that causes shortness of breath and chest tightness due to airway inflammation. The course of disease varies, with some people having few symptoms, while others experience exacerbations that result in hospitalization. Asthma affects 8% of the U.S. population.[1] For people with severe disease, measuring eosinophil levels, a white blood cell contributing to inflammation in eosinophilic asthma, can further direct therapy decisions. While estimates vary, one study approximates 4% of adults have severe, uncontrolled asthma.[2]

Role in treatment:

With a novel mechanism, tezepelumab would be the first asthma biologic to inhibit thymic stromal lymphopoietin (TSLP). Uniquely positioned, tezepelumab has potential to be approved as maintenance treatment in people 12 years of age or older with severe asthma, without an eosinophilic subtype. This differs from current asthma biologics, which are limited to use in people with eosinophilic subtype or oral steroid-dependent asthma.

Efficacy:

The NAVIGATOR trial evaluated tezepelumab given every four weeks versus placebo in people 12 or older with severe, uncontrolled asthma, along with the standard of care controller medications. Tezepelumab significantly reduced the risk of asthma exacerbations compared to placebo after one year of treatment across eosinophil subgroups, although numerically greater benefits were seen in people with higher eosinophils (> 300 cells per microliter).[3] In the SOURCE trial, tezepelumab added to the standard of care, but failed to meet its primary efficacy endpoint of maintaining asthma control while reducing the daily oral steroid dose compared to placebo in adults with severe, oral steroid-dependent asthma, regardless of eosinophil count.

Safety:

The most common side effects found in both trials with tezepelumab were nasopharyngitis, upper respiratory tract infection, and headache. Serious adverse events occurred in less than 3% of people in both groups, with the rate of severe infections and cancer similar between groups.

Financial impact:

While the price is unknown, as the first-to-market TSLP inhibitor, tezepelumab will likely set a price similar to other branded asthma biologics. Analysts predict peak annual U.S. sales of approximately $658 million by 2029 for tezepelumab.[4]

IngenioRx view:

If approved, tezepelumab could be the first biologic to treat a broader population of people with severe asthma, without a specific subtype. It will largely compete based on its novel mechanism of action for individuals with severe asthma who do not respond to or who do not qualify for existing biologics. Tezepelumab failed to show a reduction in the oral daily steroid dose required in individuals with severe, steroid-dependent asthma. Several questions remain unanswered for tezepelumab. Will it provide similar efficacy compared to marketed therapies? Can it differentiate itself through an improved safety profile? Will it be self-administered?

1 Centers for Disease Control and Prevention: *Asthma* (accessed July 2021): cdc.gov.
2 Global Initiative for Asthma: *Difficult-to-Treat & Severe Asthmas in adolescent and adult patients: Diagnosis and Management, GINA Pocket Guide* (accessed July 2021): ginasthma.org/.
3 Menzies-Gow A, Corren J, Bourdin A, Chupp G, Israel E, Wechsler ME, et al: *Tezepelumab in Adults and Adolescents with Severe, Uncontrolled Asthma. New England Journal of Medicine* (May 2021): nejm.org/doi/full/10.1056/NEJMoa2034975.
4 Decision Resources Group (accessed July 2021; registration required): insights.decisionresourcesgroup.com.

MAVACAMTEN

Product:
Mavacamten

Indication:
Symptomatic obstructive hypertrophic cardiomyopathy (oHCM)

Estimated FDA approval:
April 2022

Therapeutic class:
Myosin inhibitor

Route of administration:
Oral

FDA designations:
Breakthrough, Orphan

Manufacturer:
Bristol Myers Squibb

Condition:

Hypertrophic cardiomyopathy (HCM) is typically caused by abnormal genes in the heart muscle. The walls of the left chamber of the heart contract harder and become thick and stiff. There is a reduction in the amount of blood taken in and pumped out with every heartbeat. The majority of individuals with HCM have obstructive HCM (oHCM), classified when blood flow from the left chamber of the heart to the main artery is reduced. Some people develop symptoms such as chest pain, shortness of breath, fatigue, abnormal heart rhythms, dizziness, fainting, and swelling that may affect their daily living activities and can worsen over time. People with HCM are at a higher risk for serious cardiovascular complications, including blood clots, stroke, heart failure, and sudden cardiac death.[5] There are approximately 160,000 to 200,000 people diagnosed with symptomatic oHCM in the United States and the European Union.[6]

Role in treatment:

Mavacamten would be the first FDA-approved therapy for this condition. Current treatment options include symptom management or a surgical procedure to reduce heart-muscle thickening.[7]

Efficacy:

In the EXPLORER-HCM trial, the primary outcome was designed to demonstrate the treatment effect of mavacamten compared with placebo on symptoms and heart function. Statistically significant improvements were seen across all endpoints with mavacamten after 30 weeks.[7]

Safety:

Mavacamten was well tolerated, with overall rates of adverse events similar to placebo. There were more individuals receiving mavacamten who temporarily discontinued therapy due to ejection fractions reduced below 50%, a measure of blood volume pumped out with each heartbeat.[7]

Financial impact:

Although the product is expected to have a high cost, it is unlikely to have a major impact on overall drug spend due to the rarity of the condition.

IngenioRx view:

Mavacamten would be the first FDA-approved treatment for symptomatic oHCM. Long-term safety and efficacy need to be assessed. The question remains whether use of mavacamten will reduce the need for surgical interventions. In addition, prescribers should be aware of potential issues with dose titration. Future development of mavacamten will include use in nonobstructive HCM.[7,8]

5 American Heart Association: *Hypertrophic Cardiomyopathy (HCM)* (accessed July 2021): heart.org.
6 Business Wire: *U.S. Food and Drug Administration (FDA) Accepts Bristol Myers Squibb's Application for Mavacamten in Symptomatic Obstructive Hypertrophic Cardiomyopathy (oHCM)* (accessed July 2021): businesswire.com.
7 MDedge: *EXPLORER trial hints at potential new drug option in obstructive hypertrophic cardiomyopathy* (accessed July 2021): mdedge.com.
8 BioPharma Dive: *MyoKardia pops as heart drug passes most important test* (accessed July 2021): biopharmadive.com.

FEZOLINETANT

Product:
Fezolinetant

Indication:
Treatment of vasomotor symptoms (VMS) associated with menopause

Estimated FDA approval:
2022

Therapeutic class:
Neurokinin-3 (NK3) receptor antagonist

Route of administration:
Oral

FDA designations:
None

Manufacturer:
Astellas

Condition:

Menopause occurs when menstruation stops, on average at age 52. Changes in hormone levels associated with menopause can cause bothersome vasomotor symptoms (VMS), such as hot flashes and genitourinary syndrome of menopause (GSM), a term collectively involving vaginal atrophy, dryness, and painful intercourse. Symptoms can start years before menopause and fluctuate over time, with approximately 50% of individuals experiencing GSM and 75% experiencing hot flashes.[9]

Role in treatment:

Not everyone will require treatment for their symptoms. With a unique mechanism of action, fezolinetant would be the first FDA-approved Neurokinin-3 (NK3) receptor antagonist for VMS due to menopause. It would compete with one other oral nonhormonal therapy, generically available low-dose paroxetine, as well as several hormone-replacement therapies, such as estrogen, approved for VMS. These approved therapies carry black-box warnings, which the FDA uses to warn of potential harm with their use. Fezolinetant has the potential to provide a nonhormonal option for people who cannot use existing therapies due to their side effects or associated risks. It is unclear if fezolinetant will carry a black box warning.

Efficacy:

Two trials evaluating individuals with VMS associated with menopause, specifically hot flashes, showed both doses of once-daily fezolinetant significantly decreased the frequency and severity of VMS compared to placebo at weeks 4 and 12.

Safety:

The most common adverse event in both trials with fezolinetant was headache. Serious treatment-related adverse events occurred in less than 2% of participants, with additional data from a yearlong safety study expected in late 2021.

Financial impact:

While the price is unknown, as the first-to-market NK3 receptor antagonist, fezolinetant will likely set a price similar to other branded agents for VMS due to menopause. Fezolinetant will largely compete, based on its novel mechanism of action, as a nonhormonal option for those concerned about the risks associated with existing therapies.

IngenioRx view:

While hormone therapy works to reduce VMS, its use should be limited to the shortest amount of time needed due to an increased risk of blood clots, stroke, and cancer. Fezolinetant would be the first NK3 receptor antagonist approved for VMS due to menopause. It would join low-dose paroxetine as the second approved oral nonhormonal therapy, providing an additional alternative to using hormone-replacement therapies to manage VMS. It remains to be seen if fezolinetant will provide similar efficacy compared to marketed therapies or if it can differentiate itself through an improved safety profile.

9 U.S. Department of Health and Human Services Office on Women's Health: *Menopause* (accessed May 2021): womenshealth.gov.

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**

ESA: erythropoietin stimulating agent

HCM: hypertrophic cardiomyopathy

IV: intravenous

PD1: programmed cell death protein 1

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; expected to be high cost but with minimal impact to overall drug/medical spend due to low utilization


Potential to significantly increase overall drug/medical spend


New entrant into high-spend/ trending category


No significant impact to incremental spend due to replacement of existing competitors, based on initial analysis

Other significant product approvals

We expect these products to reach the market in late 2021 or 2022.*

Drug or biologic manufacturer	Indication/route**	Place in therapy**	Estimated approval date	Impact on overall drug or medical spend
Efgartigimod argenx	Myasthenia gravis/IV	**First in class:** would compete with Soliris®	12/17/2021	
Tezepelumab Amgen	Asthma/SC	**First in class:** in a clinical trial, reduced exacerbations, irrespective of baseline blood eosinophil count	01/10/2022	
Penpulimab Akeso	Third-line treatment of metastatic nasopharyngeal carcinoma/IV	**Addition to class:** would be first PD1 inhibitor approved for this type of cancer; current off-label use of Keytruda® and Opdivo®	01/24/2022	
Faricimab Roche	Wet age-related macular degeneration; diabetic macular; diabetic retinopathy edema/intraocular	**Addition to class:** will compete with other vascular endothelial growth factor (VEGF) inhibitors	01/31/2022	
Mitapivat Agios Pharmaceuticals	Pyruvate kinase deficiency/oral	**Addition to class:** would be first FDA-approved treatment for this indication	02/17/2022	
Tebentafusp Immunocore	Uveal melanoma/IV	**Addition to class:** would be first FDA-approved treatment for this indication	02/23/2022	

* As of October 18, 2021.

Other significant product approvals (continued)

Drug or biologic manufacturer	Indication/route**	Place in therapy**	Estimated approval date	Impact on overall drug or medical spend
Bardoxolone Reata	Alport syndrome/oral	**Addition to class:** would be first FDA-approved treatment for this indication	02/25/2022	
Gefapixant Merck	Chronic cough/oral	**First in class:** non-narcotic option for chronic cough	03/21/2022	
Udenafil AbbVie	Congenital heart disorders in adolescents/oral	**Addition to class:** would be first FDA-approved treatment for this indication	03/26/2022	
Vadadustat Akebia Therapeutics	Anemia in chronic renal disease; dialysis dependent and independent/oral	**Addition to class:** competing to be first oral-dosing option to compete with ESAs	03/29/2022	
Ganaxolone Marinus Pharmaceuticals	Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) in children and young adults, adjunctive therapy/oral	**First in class:** would be first FDA-approved treatment for this indication	04/03/2022	
Vutrisiran Alnylam	Hereditary transthyretin amyloidosis with polyneuropathy/SC	**Addition to class:** would compete with Onpattro® and Tegsedi®	04/14/2022	
Mavacamten Bristol Myers Squibb	Symptomatic obstructive hypertrophic cardiomyopathy/oral	**First in class:** would be first drug developed to target the specific molecular defect of HCM	04/28/2022	

* As of October 18, 2021.

Other significant product approvals (continued)

Drug or biologic manufacturer	Indication/route**	Place in therapy**	Estimated approval date	Impact on overall drug or medical spend
Zynteglo®/ LentiGlobin™ (betibeglogene autotemcel) bluebird bio	Beta thalassemia/IV	**First in class:** would be first gene therapy approved for treatment of beta thalassemia; potential safety issues seen in sickle cell disease studies	05/21/2022	
Tapinarof Roivant Sciences	Psoriasis/topical	**First in class:** will compete with topical and oral treatment options	05/26/2022	
Lenacapavir Gilead Sciences	Human immunodeficiency virus (HIV) treatment/SC	**First in class:** salvage therapy; administration every 6 months	06/28/2022	

* As of October 18, 2021.

Biosimilar pipeline update

Thirty biosimilars are currently FDA approved, with 21 launching, since 2015, in the United States.

Biosimilars are highly similar to their reference product in terms of structure and function, and lack clinically meaningful differences in safety and efficacy. Biosimilars may be approved for all or some of the reference products' indications due to patent exclusivity. Prescriptions for biosimilars need to be written by name.

The FDA announced in March 2020 that insulins would be redefined as biologics, meaning they will serve as reference products for biosimilars in development. On June 28, 2021, Semglee®, a biosimilar to Lantus® (insulin glargine), was granted interchangeability status, which would allow the biosimilar to be substituted for the reference product without a prescriber's authorization.

Cyltezo® recently received interchangeability status for Humira®.

Pipeline and unlaunched biosimilar landscape

Type of benefit	Brand name	Brand manufacturer	Biosimilar name*	Biosimilar manufacturer	FDA approval
Pharmacy	Enbrel®	Amgen	Erelzi®	Sandoz	8/30/16
Pharmacy	Enbrel	Amgen	Eticovo™	Samsung	4/25/19
Pharmacy	Humira	Abbvie	Amjevita™	Amgen	9/23/16
Pharmacy	Humira	AbbVie	Hadlima™	Samsung, Merck	7/23/19
Pharmacy	Humira	AbbVie	Cyltezo	Boehringer Ingelheim	8/25/17
Pharmacy	Humira	AbbVie	Hulio®	Fujifilm, Mylan	7/6/20
Pharmacy	Humira	AbbVie	Hyrimoz™	Sandoz	10/30/18
Pharmacy	Humira	AbbVie	Abrilada™	Pfizer	11/15/19
Pharmacy	Humira	AbbVie	AVT02	Alvotech; Teva	Pending
Pharmacy	Humira	AbbVie	CHS-1420	Coherus	Pending

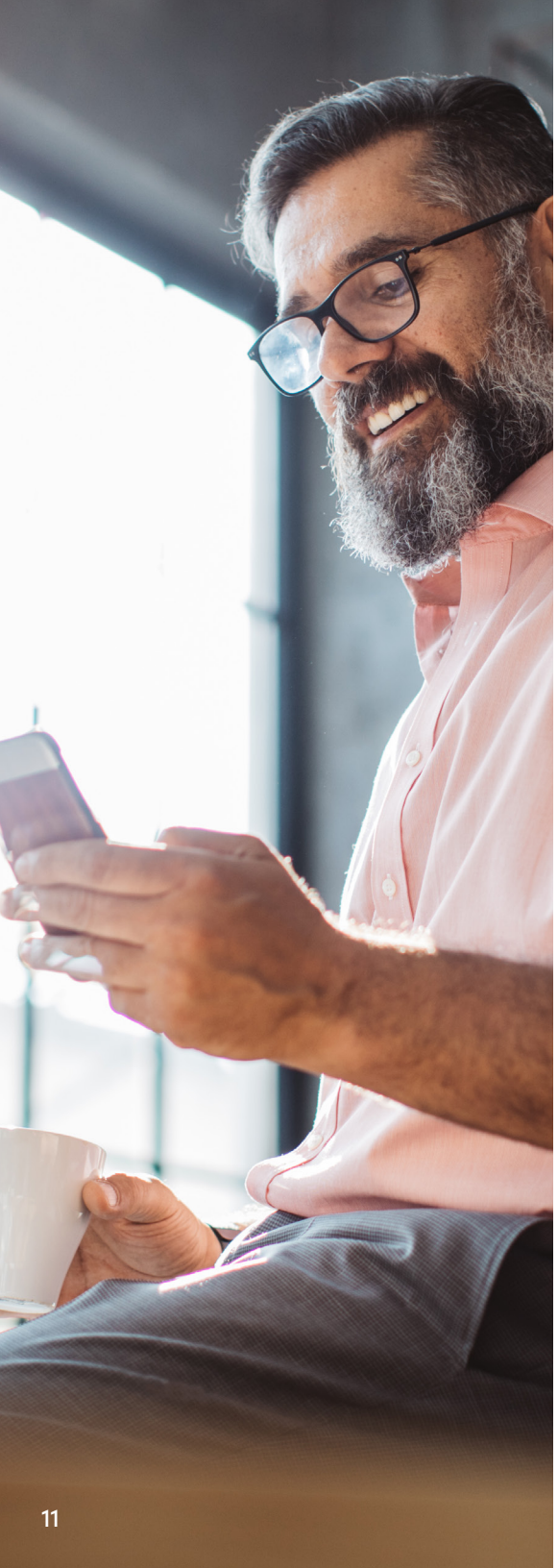
* Biosimilars seeking interchangeability include Abrilada and AVT02.[10]

10 Generics Bulletin: *Biosimilar Interchangeability: A Blessing Or A Curse?* (accessed September 2021): generics.pharmaintelligence.informa.com.

Biosimilar pipeline update (continued)

Type of benefit	Brand name	Brand manufacturer	Biosimilar name*	Biosimilar manufacturer	FDA approval
Medical	Avastin®	Genentech, Roche	Bmab-100	Biocon, Mylan	Pending
Medical	Avastin	Genentech, Roche	SB8	Samsung, Merck	Pending
Medical	Avastin	Genentech, Roche	FKB238	Centus; AstraZeneca	Pending
Medical	Avastin	Genentech, Roche	BAT1706	Bio-Thera	Pending
Medical	Avastin	Genentech, Roche	BEVZ92	mAbxience	Pending
Medical	Lucentis®	Genentech, Roche	SB11	Samsung Bioepis; Biogen	Pending
Medical	Neupogen®	Amgen	Grastofil®	Apotex, Accord	Pending
Medical	Neupogen	Amgen	Filgrastim Kashiv	Adello, Amneal	Pending
Medical	Neulasta®	Amgen	MSB11455	Fresenius, Dr. Reddy	Pending
Medical	Neulasta	Amgen	Lapelga Neupeg®	Apotex, Accord	Pending
Medical	Neulasta	Amgen	TPI-120	Adello Biologics; Kashiv	Pending
Medical	Neulasta	Amgen	Lupifil-P™	Lupin	Pending
Medical	Remicade®	Janssen	Ixifi PF™	Pfizer	12/13/17

* Biosimilars seeking interchangeability include Abrilada and AVT02.[10]



Update on psoriasis

The expanding psoriasis pipeline

Plaque psoriasis affects approximately 80% to 90% of the more than 7.5 million people with psoriasis in the United States.[11, 12] Symptoms may fluctuate over time, but plaque psoriasis is a chronic, inflammatory-driven disease that most frequently results in red, itchy, painful patches of skin, or plaques, in one or more areas of the body.

Biologics have transformed the treatment space for psoriasis. A few biosimilars are in late-stage development for psoriasis, with potential to join the already approved, but not launched, handful of biosimilars for Enbrel and Humira, as well as the first biosimilar approval for Stelara®. While biologics dominate spend in psoriasis, attention could expand to include four novel nonbiologic oral and topical therapies, with anticipated approval in 2022 and 2023.

The future of nonbiologic psoriasis treatments

National guidelines provide recommendations for the use of the following topical FDA-approved categories for mild-to-moderate psoriasis and as adjunctive therapy in more severe disease: steroids, vitamin D analogs, combination steroid/vitamin D analogs, and combination steroid/tazarotene products.[13] Two novel nonsteroidal therapies, roflumilast and tapinarof, have potential to shift utilization and generate additional competition in the topical treatment space.

For people with moderate-to-severe disease, prescribers often use oral or injectable therapies.[14] Deucravacitinib, a novel once-daily tyrosine kinase 2 (TYK2) inhibitor, could closely compete with Otezla® as another nonbiologic oral therapy approved for moderate-to-severe psoriasis. Trial data indicate deucravacitinib demonstrated better efficacy compared to Otezla. However, its lack of long-term safety data could limit uptake.

11 National Psoriasis Foundation: *About Psoriasis* (accessed September 2021): psoriasis.org.
12 National Psoriasis Foundation: *Plaque Psoriasis* (accessed September 2021): psoriasis.org.
13 Elmets CA, Korman NJ, Prater EF, Wu JJ, Hariharan V, Menter A, et al.: *Joint AAD-NPF Guidelines of care for the management and treatment of psoriasis with topical therapy and alternative medicine modalities for psoriasis severity measures. Journal of the American Academy of Dermatology (February 2021)*: jaad.org/article/S0190-9622(20)32288-X/fulltext.
14 MedlinePlus, U.S. National Library of Medicine: *Psoriasis* (accessed September 2021): medlineplus.gov.

Psoriasis pipeline

Four nonbiologic therapies, expected in 2022 and 2023, could garner attention with their novel mechanisms of action, potentially increasing competition in the oral and topical psoriasis space. Products in phase 3 development or higher are summarized in this table:

Drug or biologic/ manufacturer	Route/target*	Place in therapy	Estimated approval (phase of development)*
Oral competitors for psoriasis			
Deucravacitinib (BMS-986165) Bristol Myers Squibb	Oral/selective TYK2 inhibitor	Once-daily formulation for adults with moderate-to-severe plaque psoriasis	September 2022 (submitted)
Topical competitors for psoriasis			
Roflumilast (ARQ-151) Arcutis Biotherapeutics	Topical cream/PDE4 inhibitor	Once-daily formulation for people 2 years of age or older with plaque psoriasis	October 2022 (submitted)
Roflumilast (ARQ-154) Arcutis Biotherapeutics	Topical foam/PDE4 inhibitor	Once-daily formulation for people 12 years of age or older with scalp and/or body psoriasis	2023 (phase 3)
Tapinarof Roivant Sciences	Topical cream/TAMA	Once-daily formulation for the treatment of plaque psoriasis in adults	May 2022 (submitted)

*** Key**

TYK2: tyrosine kinase 2

PDE4: phosphodiesterase type 4

TAMA: therapeutic aryl hydrocarbon receptor modulating agent

Update on gene therapies

Gene therapy is a novel approach to treatment that introduces genetic material into an individual's body to help fight various diseases. Genome editing, also called gene editing, is a group of gene therapy technologies that allows genetic material to be added, removed, or altered. While major advances were made in the field of gene therapy, the FDA has not approved any new therapies since Zolgensma® in 2019. The topic of gene editing made national headlines after two scientists, Emmanuelle Charpentier and Jennifer Doudna, won the Nobel Prize in Chemistry in 2020 based on their research and discovery of CRISPR/Cas9 genetic scissors.[15] CRISPR/Cas9 is one of a handful of gene-editing technologies being evaluated in clinical trials. All FDA-approved gene therapies currently use viral-based therapy, where the infectious parts of viruses are replaced with a gene that can be used to help either treat or modify a disease.

What to expect in 2022

The FDA denied approval of Instiladrin® and Roctavian in 2020, and both are still working with the agency to refile their applications, with potential FDA approval in 2022. Other gene therapies with potential approval in 2022 or early 2023 are listed in this table:

*** Key**

EB: epidermolysis bullosa

IV: intravenous

FVIII: factor 8

FIX: factor 9

BCG: Bacillus Calmette-Guerin

NMIBC: non-muscle invasive bladder cancer

HCT: hematopoietic cell transplantation

RBC: red blood cell

Gene therapies with potential 2022/early 2023 approval

Gene therapy	Indication/route*	Expected use	Place in therapy*	Estimated approval*
B-VEC (beremagene geperpavec; KB103) Krystal Biotech	Epidermolysis bullosa/topical gel	Once-weekly application to wound(s)	Competing to be first localized, gene-based wound therapeutic for individuals 1 year of age or older with EB	2022 (expects to file in 2021)
D-Fi (FCX-007; dabocemagene autoficel) Castle Creek Biosciences	Epidermolysis bullosa/ autologous, gene-modified cells	Multiple intradermal injections to wound(s)	Competing to be first localized, gene-based wound therapeutic for individuals 2 years of age or older with EB	2022
EB-101 Abeona Therapeutics	Epidermolysis bullosa/ autologous, gene-modified skin grafts	One-time surgically placed skin graft to wound(s)	Competing to be first localized, gene-based wound therapeutic for individuals 6 years of age or older with EB	2023 (expects to file in 2022)
Etranacogene dezaparvovec (AMT-061) uniQure	Hemophilia B/IV	One-time dose; potentially curative	Competing to be first gene therapy for this indication; will compete with FIX products	2023 (expects to file in 2022)

15 The Nobel Prize in Chemistry 2020: *Nobel Prize Outreach AB 2021* (accessed August 2021): nobelprize.org.

Update on gene therapies (continued)

Gene therapies with potential 2022/early 2023 approval				
Gene therapy	**Indication/route***	**Expected use**	**Place in therapy***	**Estimated approval***
Fidanacogene elaparvovec (PF-06838435) Pfizer	Hemophilia B/IV	One-time dose; potentially curative	Competing to be first gene therapy for this indication; will compete with FIX products	2022 (expects to file in 2021)
Instiladrin (nadofaragene firadenovec) FKD Therapies	Bacillus Calmette-Guerin (BCG) unresponsive, non-muscle invasive bladder cancer (NMIBC)/intravesical	Administered every 3 months for a maximum of 4 instillations	First gene-based therapeutic for NMIBC; will compete with Valstar® and surgery	2022 (FDA denied; intends to refile)
Lenti-D™ bluebird bio	Cerebral adrenoleukodystrophy/IV	One-time dose; potentially curative	First gene therapy for this indication; will compete with HCT	2022 (expects to file by end of 2021, pending FDA hold is resolved)
PTC-AADC (AGIL-AADC) PTC Therapeutics	Aromatic L-amino acid decarboxylase deficiency/intracerebral	One-time dose; potentially curative	First gene therapy for this indication	2022 (expects to file in 2021)
Roctavian (valoctogene roxaparvovec) BioMarin	Hemophilia A/IV	One-time dose; potentially curative	Competing to be first gene therapy for hemophilia A; will compete with FVIII products and Hemlibra®	4Q 2022 to 2023 (expects to file in 2022)
Giroctocogene fitelparvovec (PF-07055480; SB-525) Pfizer and Sangamo Therapeutics	Hemophilia A/IV	One-time dose; potentially curative	Competing to be first gene therapy for hemophilia A; will compete with FVIII products and Hemlibra	2023 (pivotal results in 2022)
Zynteglo®; LentiGlobin™ bluebird bio	Beta-thalassemia/IV	One-time dose; potentially curative	First gene therapy for beta thalassemia; will compete with HCT and chronic red blood cell (RBC) transfusions	05/21/2022
	Sickle-cell anemia/IV	One-time dose; potentially curative	First gene therapy for this indication; will compete with HCT and chronic RBC transfusions	2022+ (expects to file in 2022)

Update on gene therapies (continued)

Gene therapies with potential 2022/early 2023 approval				
Gene therapy	**Indication/route***	**Expected use**	**Place in therapy***	**Estimated approval***
ABO-102 Abeona Therapeutics	Mucopolysaccharidosis IIIA (Sanfilippo Type A)/IV	One-time dose; potentially curative	First gene therapy for this indication; will compete with HCT	2022+ (potential to file in 2022)
OTL-103 Orchard Therapeutics	Wiskott-Aldrich syndrome/IV	One-time dose; potentially curative	First gene-based therapy for this indication; will compete with HCT	2022+ (expects to file in 2022)
TAVO (tavokinogene telseplasmid) OncoSec Medical	Advanced melanoma/intratumoral	Administered on days 1, 5, and 8, every 6 weeks	First gene-based therapeutic for this indication; used in combination with Keytruda®	2022+ (potential to file with accelerated pathway)

Six or more new gene therapies have the potential to receive FDA approval in 2022.

By 2025, the FDA expects to approve up to 20 cell and gene therapies yearly.[16]

Zero gene therapies were approved by the FDA in 2020 or to date in 2022.

At the end of 2020, there were approximately 420 clinical trials evaluating gene therapies with:

- **~70** clinical trials in phase 3 (late-stage) development
- **~350** clinical trials in phase 1 and 2 (early stage) development[16]

Two gene therapies are currently FDA approved: Luxturna® in 2017 and Zolgensma in 2019.

Analysts predict the global gene therapy market to expand from approximately $3.4B in 2021 to $10B by 2028.[17]

The global cell and gene therapy market is anticipated to exceed $15B in 2025 and $34B in 2030.[18]

16 Alliance for Regenerative Medicine: *2020: Growth & Resilience in Regenerative Medicine* (accessed August 2021): alliancerm.org.
17 Grand View Research: *Report Overview: Gene Therapy Market Size, Share & Trends Analysis Report By Indication (Large B-cell Lymphoma, Beta-Thalassemia Major/SCD), By Vector Type (Lentivirus, AAV), By Region, And Segment Forecasts, 2021 – 2028* (accessed August 2021): grandviewresearch.com.
18 Globe Newswire: *Gene Therapy Accounts For A Major Portion Of The Cell And Gene Therapy Market And It Is Expected To Have The Most Growth* (accessed August 2021): globenewswire.com.

Market trends

Pharmaceutical companies are investing in various methods of artificial intelligence (AI) to enhance the drug-discovery process at all stages, as well as repurposing old drugs for new uses. It has been estimated that AI in drug discovery is a market that will reach a global value of $1.4B by 2024, compared to $259M in 2019.[19]

- For example, machine learning-based techniques are being explored. Natural language processing (NLP) algorithms can analyze data and identify relevant disease patterns. Once these trends are identified, they could lead to drug-development programs that may better target a disease.[19]
- Machine learning can also obtain valuable information from looking at image data. Companies are using AI to analyze magnetic resonance imaging (MRI) data in people with various diseases. For example, MRIs are being analyzed to learn about disease onset and progression in the liver disease nonalcoholic steatohepatitis (NASH). The approach is also being used in neurological diseases and oncology.[19]

The drug-development process from preclinical to marketing can take 12 to 18 years and cost between $2B and $3B, and only approximately 10% of candidates receive FDA approval.[20] Experts believe that AI can improve drug development by providing more candidates, increasing the number of agents that ultimately gain approval, and speeding up the entire process.[21]

Although many pharmaceutical companies are exploring AI, only a few AI-discovered agents are in human testing, and none have begun phase 3 clinical trials. It remains to be seen if the use of AI will lead to more discovery and development of better agents.[21]

19 Genetic Engineering & Biotechnology News: *AI in Drug Discovery Starts to Live Up to the Hype* (accessed August 2021): genengnews.com.
20 Clinical Trials Arena: *Big Pharma is forging an increased number of partnerships with artificial intelligence vendors for drug discovery services* (accessed August 2021): clinicaltrialsarena.com.
21 Nature: *Hunting for New Drugs with AI* (accessed August 2021): nature.com.

Update on migraine

Migraine is a disabling neurological disease characterized by intense throbbing head pain. Pain can occur on one or both sides of the head, and these attacks can last hours to several days. Other symptoms include sensitivity to light, sound, smell, or touch; difficulty concentrating; dizziness; nausea; or vomiting. Severe migraines can cause absence or hinder performance at school, work, or other activities. Migraine is ranked sixth for most disabling disorders globally.[22,23]

It is unclear what causes migraine, but genetics, environment, and hormones are thought to play a role. Migraine attacks can occur spontaneously or after an identifiable trigger. Common triggers include certain foods or alcohol, sleeping too little or too much, stress, hormone fluctuations, weather changes, or brain injury, such as a concussion.[22,23]

Types of migraine[22,24]

- **Migraine with aura:** About 20% of people with migraine, called migraineurs, experience aura. Aura most commonly presents as visual disturbances, such as flashes of light, blind spots, and blurred vision; however, others may notice numbness, tingling, or have trouble speaking. Aura usually occurs before the headache and can prompt individuals to administer acute medication.
- **Episodic migraine:** Headache occurring 14 or fewer days a month. If not treated properly, episodic migraine can progress to chronic.
- **Chronic migraine:** Headache occurring 15 or more days a month for at least three months, with at least eight of these days having migraine symptoms.

Prevalence of migraine[22,23,24]

- Migraine is a common disorder estimated to affect 12% of the population — 39 million people in the United States. The majority of migraineurs have episodic migraine.
- Chronic migraine occurs in about 1% of the population; however, approximately 3% of episodic migraineurs will transition to chronic each year.
- Women are three times more likely to have migraines compared to men.

22 American Migraine Foundation: *What Is Migraine?* (accessed August 27, 2021): americanmigrainefoundation.org.
23 American Migraine Foundation: *Chronic Migraine* (accessed August 27, 2021): americanmigrainefoundation.org.
24 American Migraine Foundation: *Demystifying Migraine with Aura* (November 11, 2021): americanmigrainefoundation.org.

Migraine treatments: There are two main types of migraine treatment, acute and preventive medication. Migraine treatment plans are individualized and often require a process of trial and error before treatment is optimized.[22,25]

- **Acute treatment with over-the-counter and prescription medications:** Taken at the first sign of an attack to relieve pain and stop the migraine from getting worse. All migraineurs should have access to acute treatment.
    - Mild-to-moderate attacks are typically treated with oral nonsteroidal anti-inflammatory drugs (NSAIDs), like ibuprofen or naproxen, acetaminophen, or caffeinated pain-relieving combination products.
    - Moderate-to-severe attacks should be treated with migraine-specific drugs like triptans such as sumatriptan, or ergot derivatives such as dihydroergotamine. These drugs are available in different formulations, including oral tablets, nasal sprays, and injections.
    - Newer oral drugs for acute treatment include the calcitonin gene-related peptide (CGRP) antagonists Ubrelvy™ (ubrogepant) and Nurtec® ODT (rimegepant), and the selective serotonin (5-HT1F) antagonist Reyvow® (lasmiditan). Guidelines recommend reserving these newer drugs for individuals who have contraindications to triptans or have failed to respond to or tolerate at least two oral triptans.

25 American Headache Society: *AHS Consensus Statement: The American Headache Society Position Statement On Integrating New Migraine Treatments Into Clinical Practice* (accessed August 30, 2021): headacheajournal.onlinelibrary.wiley.com.

- **Preventive treatment with prescription medications:** When indicated, such as when an individual has four or more attacks in a month or there is overuse of acute treatment, preventive medication may be added onto acute treatment with the goal of reducing migraine frequency, severity, and/or duration.
    - First-line oral treatments for migraine prevention include certain antiepileptics such as topiramate, beta-blockers such as propranolol, and antidepressants such as venlafaxine, which are all administered daily. Botox® (onabotulinumtoxinA) is another option, injected by a healthcare provider every few months into multiple areas of the head or neck, for individuals with chronic migraine only.
    - Newer drugs for episodic and chronic migraine prevention include the injectable CGRPs Aimovig® (erenumab), Ajovy® (fremanezumab), Emgality® (galcanezumab), and Vyepti® (eptinezumab). The injectable CGRPs are self-administered subcutaneously at home every 1 to 3 months, except for Vyepti, which requires administration in a healthcare setting every three months in 30-minute intravenous infusions.
    - Nurtec ODT received a second FDA-approved indication in May 2021 for episodic migraine prevention. Nurtec ODT is administered every other day for migraine prevention and is the first oral CGRP approved to treat and prevent migraine.
    - A second oral CGRP, Qulipta™ (atogepant), was FDA approved for episodic migraine prevention in September 2021. Qulipta is administered daily for migraine prevention and will compete with Nurtec ODT and the injectable CGRPs.
    - National guidelines recommend CGRPs for migraine prevention after individuals have had an inadequate response or intolerance to two or more first-line oral treatments or Botox for chronic migraine only.

Migraine pipeline

The pipeline contains investigational drugs being studied for various migraine indications, as well as new combination products, formulations, delivery technologies, and indications for drugs already on the market. Pipeline drugs in phase 3 or higher are listed in this table.

Drug or biologic manufacturer	Route/drug class*	Place in therapy*	Estimated approval (phase of development)
Seeking FDA approval for acute migraine treatment			
Dihydroergotamine Amneal Pharmaceuticals	Injection/ergot derivative	• Auto-injector for self-administration • Would compete with other DHE formulations (injection, nasal spray)	Mid-2022
Meloxicam/rizatriptan Axsome Therapeutics	Oral/NSAID and triptan	• Fixed-dose combination product • Would compete with Treximet®	April 2022
Zavegepant (formerly vazegepant) Biohaven	Nasal/CGRP	• Would be the first nasal CGRP • Would compete with oral CGRPs (Ubrelvy and Nurtec ODT) • Also being studied for migraine prevention	Phase 3
STS101 (dihydroergotamine) Satsuma	Nasal/ergot derivative	• Drug-device combination product that uses a proprietary dry-powder nasal formulation and delivery technology • Would compete with other DHE nasal formulations	Phase 3
Vyepti (eptinezumab) Lundbeck	IV/CGRP	• Would be the first injectable CGRP for acute treatment; already FDA approved for prevention • Also being studied subcutaneously for self-administration	Phase 3

*** Key**

NSAID: nonsteroidal anti-inflammatory drug

CGRP: calcitonin gene-related peptide

IV: intravenous

DHE: dihydroergotamine

TRPV-1: transient receptor potential vanilloid 1 agonist

CRL: complete response letter from FDA denying approval at this time

ODT: orally disintegrating tablet

The future of migraine treatments

There is growing interest in expanding use of CGRPs by exploring new routes of administration. Two additional CGRPs are in phase 3 development for acute migraine treatment. If approved, zavegepant would be the first nasal CGRP, and Vyepti would be the first intravenous CGRP for acute migraine treatment. Zavegepant and Vyepti would compete with the oral CGRPs Ubrelvy and Nurtec ODT, and other nasal or injectable products for acute use, such as triptans. Vyepti is currently approved for migraine prevention.

Drug or biologic manufacturer	Route/drug class*	Place in therapy*	Estimated approval (phase of development)*
Rizaport® (rizatriptan) Gensco Pharma	Oral film/triptan	• Would be the first oral film product for migraine • Would compete with other triptan formulations that are orally disintegrating tablets	CRL issued
Qtrypta™ (zolmitriptan) Zosano Pharma	Patch/triptan	• Delivers drug through a proprietary transdermal microneedle system • Would compete with other triptan formulations, such as nasal sprays and injectables	CRL issued
Semprana (dihydroergotamine) AbbVie[26]	Oral inhalation/ergot derivative	• Rapid onset • Would compete with other DHE formulations (nasal spray, injection)	CRL issued
Seeking FDA approval for episodic cluster headache			
Civanex (zucapsaicin) Winston Laboratories	Nasal/TRPV-1 agonist	• Cis isomer of capsaicin • Would compete with Emgality	Phase 3

26 Fierce Pharma: Manufacturing questions lead to another CRL for Allergan migraine drug (accessed September 8, 2021): fiercepharma.com.

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