Today, we are CarelonRx, but when we created this document, we were IngenioRx.

Our name may be new, but our commitment to you remains the same.

Drug and Biologic Pipeline Update

Q2 2022

IngenioRx's quarterly *Drug and Biologic Pipeline Update*

Our Q2 2022 edition highlights emerging therapies in the pharmaceutical pipeline. We share insights on a gene therapy for cerebral adrenoleukodystrophy (CALD), a new agent for amyotrophic lateral sclerosis (ALS), and a novel oral agent for psoriasis. We provide highlights on other select significant product approvals expected in 2022. We review the latest Humira® biosimilars and a gene therapy for hemophilia A, previously delayed by the Food and Drug Administration (FDA). An overview of 2021 FDA approval statistics and trends is also included. Finally, our market trends section gives an update on beta amyloid products for Alzheimer's disease and a focus on agents for dry age-related macular degeneration (AMD).

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

Unless otherwise noted, information contained in this document was obtained from the Centers for Disease Control and Prevention (CDC) (cdc.gov), the FDA (fda.gov), clinicaltrials.gov, releases from pharmaceutical manufacturers, and UpToDate.com (registration required). Information in this document is accurate as of April 6, 2022.

Top emerging new therapies

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

ELIVALDOGENE AUTOTEMCEL (ELI-CEL)

Product:
Elivaldogene autotemcel (eli-cel, Lenti-D®)

Indication:
Cerebral adrenoleukodystrophy (CALD) in people less than 18 years of age

Estimated FDA approval:
September 2022

Therapeutic class:
Gene therapy

Route of administration:
Intravenous (IV) infusion

FDA designations:
Breakthrough; Orphan; Priority; Rare pediatric disease

Manufacturer:
bluebird bio

Condition:
Adrenoleukodystrophy (ALD) is a rare disorder that occurs when a person has a mutation in the *ABCD1* gene. There are four main types of ALD. The most severe subtype, cerebral adrenoleukodystrophy (CALD), affects the brain, resulting in neurodegeneration, rapid functional decline, and ultimately death.[1]

Role in treatment:
Currently the only treatment known to slow or stop progression of CALD is a hematopoietic stem cell (HSC) transplant. This is for people identified in early stages of CALD with a matched HSC transplant donor.[2] Elivaldogene autotemcel (eli-cel) is a one-time personalized therapy that requires removal and modification of each person's own HSCs. Eli-cel uses a lentiviral vector to insert two functional copies of the *ABCD1* gene. After a chemotherapy-conditioning regimen, the modified HSCs are reinfused, with the goal to stop CALD progression. Eli-cel, approved and then later withdrawn from the European Union (EU) in 2021 under the brand name Skysona™, would be an option for children less than 18 years of age who do not have a matched HSC donor.

Efficacy:
The phase 2/3 Starbeam study found 91% (29/32) of the children 17 years of age and younger with CALD were alive and did not develop any major functional disabilities (MFDs) two years after receiving eli-cel. Another ongoing phase 3 trial has enrolled and administered eli-cel to an additional 23 children using a different chemotherapy-conditioning regimen.

Safety:
Trials were placed on a clinical hold, meaning they cannot enroll new participants, while the FDA reviews a serious adverse event, a case of myelodysplastic syndrome (MDS), reported as likely related to eli-cel. Since then, two more cases of MDS were identified. Additional safety concerns related to eli-cel include bladder inflammation, low numbers of blood cells, and vomiting.

Financial impact:
The price for eli-cel is unknown; however, it may be costly. bluebird bio withdrew Skysona from the market in the EU partly due to the inability to reach a consensus on pricing for gene therapies.

IngenioRx view:
Eli-cel would be the first gene therapy approved for CALD, introducing an option for children less than 17 years of age who do not have a matched HSC donor. It is unclear if eli-cel will gain FDA approval, based on the current clinical hold due to MDS safety events after eli-cel administration. The question remains whether efficacy effects established two years after dosing would continue to modify the course of disease long term.

DEUCRAVACITINIB

Product:
Deucravacitinib

Indication:
Moderate-to-severe plaque psoriasis

Estimated FDA approval:
September 2022

Therapeutic class:
Tyrosine kinase 2 (TYK2) inhibitor

Route of administration:
Oral

FDA designations:
None

Manufacturer:
Bristol Myers Squibb

Condition:
Plaque psoriasis affects about 80% to 90% of the more than 7 million people with psoriasis in the United States.[3,4] It is a chronic inflammatory-driven disease that often results in red, itchy, painful patches of skin, or plaques, in one or more areas of the body.

Role in treatment:
Prescribers often use oral or injectable therapies for people with moderate-to-severe psoriasis.[5] There are several injectable biologics approved by the FDA. Deucravacitinib, a novel once-daily tyrosine kinase 2 (TYK2) inhibitor, could closely compete with Otezla®, a twice-daily phosphodiesterase 4 (PDE4) inhibitor, as potentially the second nonbiologic oral therapy approved for moderate-to-severe psoriasis. Otezla has an indication for adults who are candidates for phototherapy or systemic therapy, including those with mild psoriasis. Numerous tyrosine kinase inhibitors are FDA approved for the treatment of cancer. Deucravacitinib selectively blocks TYK2-inhibiting interleukin (IL) 23, IL-12, and Type 1 interferon.

Efficacy:
In two trials, adults given deucravacitinib once daily had significantly greater improvements in skin clearance compared to both placebo and to Otezla taken twice daily from baseline to week 16. Guidelines include Otezla as a treatment option for people who prefer to avoid frequent injections as well as laboratory monitoring and will accept a slower onset of skin clearance and lower likelihood of clearing.[6]

Safety:
The most common side effects with deucravacitinib are nasopharyngitis, upper respiratory tract infection, headache, diarrhea, and nausea. Yearlong safety data report similar rates of cancer, major adverse cardiovascular events (MACE), serious infections, and blood clots between people taking deucravacitinib and Otezla.

Financial impact:
Analysts predict deucravacitinib peak-year major-market sales could exceed $1B in psoriasis.[7] Deucravacitinib is being studied in other immune conditions including, psoriatic arthritis, lupus nephritis, systemic lupus erythematosus, Crohn's disease, and ulcerative colitis.

IngenioRx view:
Deucravacitinib would be the first FDA-approved TYK2 inhibitor and the first once-daily oral therapy for treatment of moderate-to-severe plaque psoriasis. Trial data show deucravacitinib demonstrated better efficacy compared to twice-daily, oral Otezla. However, its lack of long-term safety data could limit uptake. If approved, deucravacitinib offers another option for people who want a noninjectable treatment or who cannot tolerate currently available biologics for moderate-to-severe psoriasis.

AMX0035 (sodium phenylbutyrate/taurursodiol)

Product:
AMX0035 (sodium phenylbutyrate/taurursodiol)

Indication:
Amyotrophic lateral sclerosis (ALS)

Estimated FDA approval:
June 2022

Therapeutic class:
Mitochondrial and endoplasmic reticulum (ER) blocker

Route of administration:
Oral

FDA designations:
Orphan; Priority

Manufacturer:
Amylyx Pharmaceuticals

Condition:
Amyotrophic lateral sclerosis (ALS) is a neurological disease that affects nerve cells responsible for voluntary muscle movement. Early symptoms include muscle weakness or stiffness. The disease is progressive, and eventually people with ALS lose the ability to speak, move, eat, and breathe, with most dying from respiratory failure within 3 to 5 years.[8] ALS affects approximately 30,000 people in the United States, with 5,000 new cases diagnosed every year.[9]

Role in treatment:
There is no cure for ALS and no treatment that will stop or reverse its progression. Current FDA-approved treatments can help slow progression and modestly extend survival. These include generic riluzole tablets (also available in branded liquid and oral film formulations) and Radicava® (edaravone intravenous infusion). An oral formulation of edaravone has been approved by the FDA.[8,10] AMX0035 would be a new FDA-approved treatment option with a different mechanism of action for ALS. It has potential for both functional and survival benefits, but further studies are needed.[11] Phase 2 trials had significant limitations. AMX0035 was not studied against the individual components, and the trials had significant discontinuation rates. Individual components are currently available and may be used off label.[12] Sodium phenylbutyrate is an oral prescription product. Taurursodiol may be purchased as an over-the-counter (OTC) supplement.

Efficacy:
The phase 2 CENTAUR trial evaluated the impact of AMX0035 on ALS progression as measured by the amyotrophic lateral sclerosis functional rating scale-revised (ALSFRS-R) compared with placebo over a 6-month period. People taking AMX0035 demonstrated a statistically significant slowing of ALS disease progression. Subjects in CENTAUR were allowed to enroll in a long-term, open-label extension (OLE) trial for up to 30 months. Most participants were receiving an approved ALS therapy (riluzole, edaravone, or both) during and/or before the trial and were allowed to continue these medications during the OLE.[13] In an overall survival analysis of all randomized participants from CENTAUR and the OLE, initiation of AMX0035 at baseline resulted in a 6.5-month longer median survival compared with placebo.[14]

Safety:
In CENTAUR, more subjects in the AMX0035 group stopped treatment due to adverse events than the placebo group (19% vs. 8%). Gastrointestinal (GI) adverse events were the most common. No new concerns were seen in the OLE.

Financial impact:
With its potential to prolong survival and slow disease progression, AMX0035 is predicted to gain approximately 16% of ALS cases treated with drugs in the U.S. The price is unknown; however, analysts predict U.S. sales of more than $418M in 2030.[15]

IngenioRx view:
AMX0035 is gaining interest due to modestly positive data in phase 2 trials. A phase 3 trial has been started to further evaluate survival, disease progression, and safety. AMX0035 would expand treatment options for AMX0035, and it could be used in combination with current FDA-approved ALS therapies. Potential off-label use of individual components could also be considered when assessing possible uptake of this new product. An FDA panel of experts held a meeting to assess AMX0035, and they did not recommend approval due to concerns about the available evidence. The FDA is not required to follow these recommendations.

In addition to treatments listed previously, important drugs and biologics are scheduled to receive FDA approval within the next 12 to 18 months.

**** Key**

ABT: add-back therapy

ALS: amyotrophic lateral sclerosis

CART: chimeric antigen receptor T-cell therapy

HER2: human epidermal growth factor receptor 2

IV: intravenous

KRAS: Kirsten rat sarcoma

OTC: over the counter

PD-1: programmed cell death protein 1

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

SC: subcutaneous

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 2022 to 2023.*

Drug or biologic manufacturer	Indication/route**	Place in therapy**	Estimated approval date**	Impact on overall drug or medical spend**
AT-GAA (cipaglucosidase alfa + miglustat) Amicus Therapeutics	Pompe disease/ IV + oral	**Addition to class:** IV and oral components coadministered; will compete with Lumizyme® and Nexviazyme®	5/29/22 (oral); 7/29/22 (IV)	
Tirzepatide Eli Lilly	Type 2 diabetes/SC	**First in class:** unique dual mechanism of action; will not see cardiovascular outcomes data for several years	5/30/22	
Narsoplimab Omeros Corporation	Transplant-associated thrombotic microangiopathy/IV	**Addition to class:** will be first FDA-approved treatment for this indication	June 2022	
Spesolimab Boehringer Ingelheim	Generalized pustular psoriasis (GPP) flares/IV	**First in class:** will be first FDA-approved treatment for this indication	6/16/22	
AMX0035 (sodium phenylbutyrate/ taurursodiol) Amylyx Pharmaceuticals	Amyotrophic lateral sclerosis/oral	**Addition to class:** may be used in combination with current standard therapy for ALS; individual components (sodium phenylbutyrate) are available by prescription and OTC (tauroursodeoxycholic acid), with potential off-label use	6/29/22	
Olipudase alfa Sanofi	Niemann-Pick disease type B/IV	**Addition to class:** will be first FDA-approved treatment for this indication	7/03/22	

* As of April 6, 2022.

Other significant product approvals (continued)

Drug or biologic manufacturer	Indication/route**	Place in therapy**	Estimated approval date	Impact on overall drug or medical spend**
Tislelizumab BeiGene	Esophageal cancer/IV	**Addition to class:** will compete with other PD-1 inhibitors	7/12/22	
Roflumilast Arcutis Biotherapeutics	Psoriasis/topical	**Addition to class:** topical cream formulation of Roflumilast; will compete with topical treatment options	7/29/22	
Zynteglo® (betibeglogene autotemcel) bluebird bio	Beta thalassemia/IV	**First in class:** will be first gene therapy FDA approved for treatment of beta thalassemia; potential safety issues seen in sickle cell disease studies	8/21/22	
Teclistamab Johnson & Johnson	Multiple myeloma/IV	**First in class:** for relapsed or refractory disease; will compete with Darzalex® and CART	8/29/22	
Deucravacitinib Bristol Myers Squibb	Plaque psoriasis/oral	**First in class:** once-daily oral formulation for adults with moderate-to-severe plaque psoriasis	9/10/22	
Yselty® (linzagolix) ObsEva	Uterine fibroids/oral	**Addition to class:** will compete with Oriahnn® and Myfembree®; low-dose non-ABT option	9/15/22	
Lenti-D (elivaldogene autotemcel) bluebird bio	Cerebral adrenoleukodystrophy/ IV	**First in class:** will be first gene therapy FDA approved for this indication	9/17/22	
Ublituximab TG Therapeutics	Multiple sclerosis/IV	**Addition to class:** anti-CD20 monoclonal antibody; one-hour administration time	9/30/22	

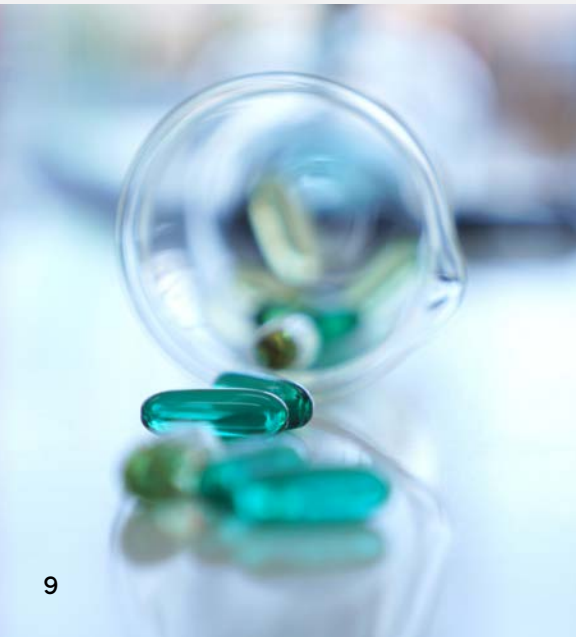
Other significant product approvals (continued)

Drug or biologic manufacturer	Indication/route**	Place in therapy**	Estimated approval date	Impact on overall drug or medical spend**
Hepcludex® (bulevirtide) Gilead Sciences	Hepatitis D treatment/SC	**First in class:** will be first FDA-approved treatment for this indication	11/19/22	
Poziotinib Spectrum Pharmaceuticals	Non-small cell lung cancer, HER2 exon 20 insertion mutations/oral	**First in class:** will be first FDA-approved treatment for this mutation	11/24/22	
Omecamtiv mecarbil Cytokinetics	Chronic heart failure/oral	**First in class:** for heart failure with reduced ejection fraction	11/30/22	
Adagrasib Mirati Therapeutics	Non-small cell lung cancer, KRAS mutations/oral	**Addition to class:** will compete with Lumakras™	12/14/22	
Dovitinib Novartis	Renal cell cancer/oral	**Addition to class:** tyrosine kinase inhibitor	12/22/22	
Lecanemab Eisai	Alzheimer's disease/IV	**Addition to class:** rolling submission initiated; will compete with Aduhelm	2023	
Donanemab Eli Lilly	Alzheimer's disease/IV	**Addition to class:** rolling submission initiated; will compete with Aduhelm	2023	

Humira® (adalimumab) was approved in 2002 by the FDA and has become a top-selling biologic in the U.S. AbbVie reported more than $17B in net revenues in the U.S. for 2021, an increase of 7.6% from the previous year.[16]

There are currently seven FDA-approved biosimilars to Humira, but none have launched. While several of these are seeking interchangeability status, Cyltezo® is the only Humira biosimilar to reach this goal. Cyltezo was granted interchangeability status in October 2021, making it the first noninsulin biosimilar to be interchangeable with its reference product.

FDA-approved indications differ between Humira and the FDA-approved biosimilars. Only Humira is approved for hidradenitis suppurativa (HS), uveitis, and pediatric ulcerative colitis. Humira and Cyltezo are approved for pediatric Crohn's disease. Differences in indications between reference products and biosimilars are typically attributed to patent exclusivities.



Humira biosimilar pipeline update – Q2 2022

Humira biosimilar products in the near-term pipeline or pending launch

Type of benefit	Biosimilar name	Biosimilar manufacturer	FDA approval	Launched
Pharmacy	Abrilada™* 50 mg/mL	Pfizer	11/15/19 Interchangeability pending	No
Pharmacy	Amjevita™* 50 mg/mL	Amgen	9/23/16	No
Pharmacy	Cyltezo* 50 mg/mL	Boehringer Ingelheim	8/25/17 Interchangeability granted 10/15/21	No
Pharmacy	Hadlima™ 50 mg/mL	Samsung, Merck	7/23/19	No
Pharmacy	Hulio®* 50 mg/mL	Fujifilm, Mylan	7/6/20	No
Pharmacy	Hyrimoz™ 50 mg/mL	Sandoz	10/30/18	No
Pharmacy	Yusimry™ 50 mg/mL	Coherus	12/17/21	No
Pharmacy	AVT02* 100 mg/mL	Alvotech	Pending (12/22) Interchangeability pending	No
Pharmacy	Yuflyma™ (CT-P17)* 100 mg/mL	Celltrion	Pending Interchangeability pending	No
Pharmacy	SB5 HC*† 100 mg/mL	Samsung Bioepis, Organon	Pending[17]	No

* Manufacturer states this is a citrate-free formulation.
† SB5 HC (100 mg/mL) is the higher-concentration formulation of Hadlima (SB5 50 mg/mL).

Update on valoctocogene roxaparvovec (formerly Roctavian)

Hemophilia A is a rare hereditary bleeding disorder that causes a deficiency of factor VIII (FVIII). This leads to impaired blood clotting and increased susceptibility to bleeds. The worldwide incidence rate is about 1 in 5,000 male births, with an estimated 60% having severe hemophilia A, when FVIII levels are less than 1%.[18]

Currently FVIII replacement therapies are the backbone of treatment for severe hemophilia. Selection of a specific FVIII therapy considers many factors but, in general, therapy requires injections 3 to 4 times a week. Valoctocogene roxaparvovec is a single-dose, intravenous infusion gene therapy being evaluated for treatment of adults with severe hemophilia A. It aims to increase FVIII levels, decrease use of FVIII replacement therapies, and decrease bleeding events.

The past

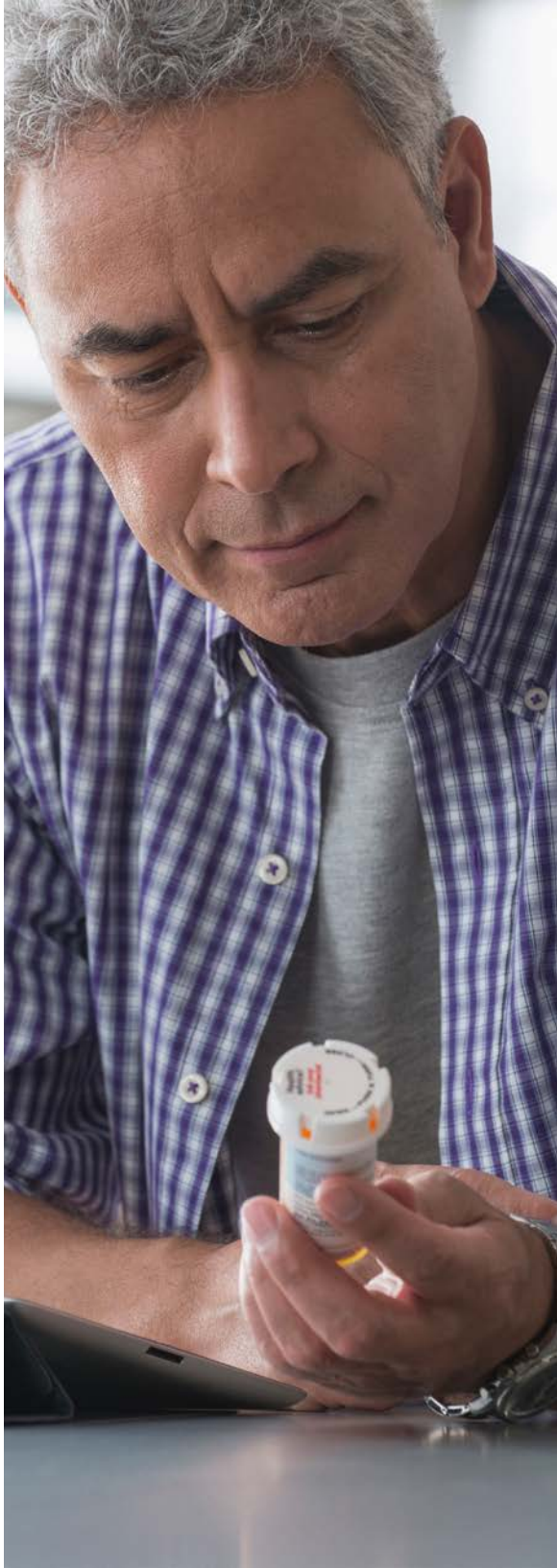
In 2020, the FDA denied BioMarin's first application for valoctocogene based on their submitted interim data from a phase 3 confirmatory trial coupled with four-year data from an early phase 1/2 trial. Four-year data from the early phase trial found 6 of the 7 people treated remained free of bleeding events. Interestingly, after initially increasing to near-normal range at the end of year one, FVIII activity levels continually decreased from the end of year one to the end of year four, introducing doubt in how long effects will last. In their denial, the FDA requested BioMarin submit two-year data from its ongoing phase 3 trial to address durability of effect.

The present

In February 2022, two-year data from the phase 3 confirmatory trial shows a significant reduction in bleeding events after a single dose of valoctocogene compared to preventive treatment with standard of care FVIII replacement therapies. The bleeding rate was reduced by 4.1 treated bleeds per year. In addition, FVIII replacement utilization significantly decreased, with 95% of participants stopping FVIII preventive therapy by the end of year two. The outstanding question on durability remains, as the FVIII activity levels decreased from the end of year one to the end of year two. The most common safety concern is an elevation in liver enzymes, which appears to be transient.

The future

Valoctocogene has potential to be the first FDA-approved gene therapy for adults with hemophilia A. The durability of effect for valoctocogene remains unknown. Redosing is not being studied as an option for late-stage hemophilia A gene therapies. With other gene therapies in development for this condition, approval of valoctocogene would force people to make a choice to use the first approved option or wait for other gene therapies with potentially better efficacy or durability data. BioMarin plans to meet with the FDA in the second quarter of 2022 to discuss resubmitting their application for potential valoctocogene approval using the two-year phase 3 trial data. With valoctocogene's breakthrough status, it seems possible the FDA could decide its fate by the end of 2022 or early 2023.



Analysis: novel drug approvals in 2021

The FDA Center for Drug Evaluation and Research (CDER) releases an annual report entitled "Advancing Health Through Innovation: New Drug Therapy Approvals". The report summarizes notable approvals for the prior year.

Below are approval highlights from the 2021 report:[19]

50 therapies
approved in total

18 therapies
approved with Fast Track status

14 therapies
approved as Breakthrough Therapies

34 therapies
approved with Priority Review status (6-month review versus 10-month standard review)

27 first-in-class therapies
(unique mechanisms of action)

26 therapies
approved for Orphan diseases (affect less than 200,000 people in the U.S.)

14 therapies
approved under Accelerated Approval (confirmatory trials must be conducted)

37 of the 50 approvals
used one or more expedited programs (Fast Track designation, Breakthrough Therapy designation, Priority Review, and/or Accelerated Approval)

49 of the 50 approvals
came on or before the Prescription Drug User Fee Act (PDUFA) goal date

Market trends

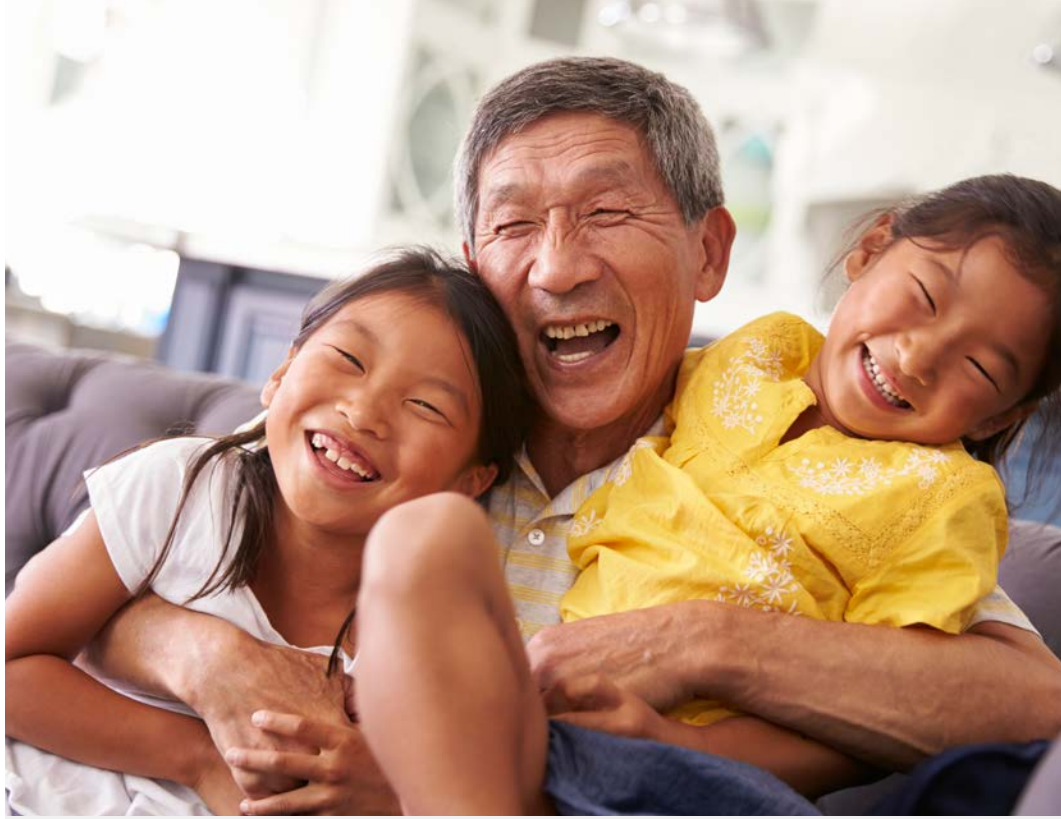
Anti-beta-amyloid antibodies for early Alzheimer's disease

Aduhelm™ (aducanumab intravenous infusion) was approved in June 2021 for the treatment of early Alzheimer's disease with the presence of beta-amyloid plaques. It was approved under FDA Accelerated Approval pathway using results of surrogate endpoints measuring beta-amyloid plaque reduction in the brain. Surrogate endpoints are markers such as laboratory measurements or radiographic images that may predict clinical benefit. Clinical significance of these endpoints is questionable, and we continue to await confirmatory trials evaluating cognitive decline. In addition, reports of amyloid-related imaging abnormalities (ARIA), including cerebral edema and microhemorrhages that may lead to death, are concerning.[20]

Two products like Aduhelm are now under FDA review in the hopes of gaining accelerated approvals based on plaque measurements. We expect to see the same limitations with efficacy and safety. Lecanemab intravenous infusion from Eisai and donanemab intravenous infusion from Eli Lilly have initiated rolling submissions to the FDA. However, we will likely not see final approvals for these products before 2023. A third anti-amyloid antibody from Roche, gantenerumab, has not submitted to the FDA yet, but is also on the horizon.[20]

Finding treatments for Alzheimer's disease that are successful in slowing clinical decline is important, as an **estimated 5.8 million people in the U.S. have dementia due to Alzheimer's disease**. This number is expected to grow to 13.8 million by 2050.[21]

Analysts predict that peak sales for lecanemab, donanemab, and gantenerumab in major markets may exceed $10B, $15B, and $4B, respectively.[22] It remains to be seen whether these anti-beta-amyloid products will ultimately be successful.



Adoption of these agents and which one may gain the most market share depends on many factors, including:[22]

- Future confirmatory trials focused on clinically significant endpoints (for example, clinical differences in cognitive decline).
- Future trials that contain individuals with racial diversity to evaluate therapy in those most likely to develop dementia.[23]
- Additional information on severity and frequency of safety events.
- Future trial comparing Aduhelm to donanemab.
- Twice-monthly dosing potentially leading to lower adoption of lecanemab.
- Earlier detection of Alzheimer's disease.
- Medicare coverage determinations.

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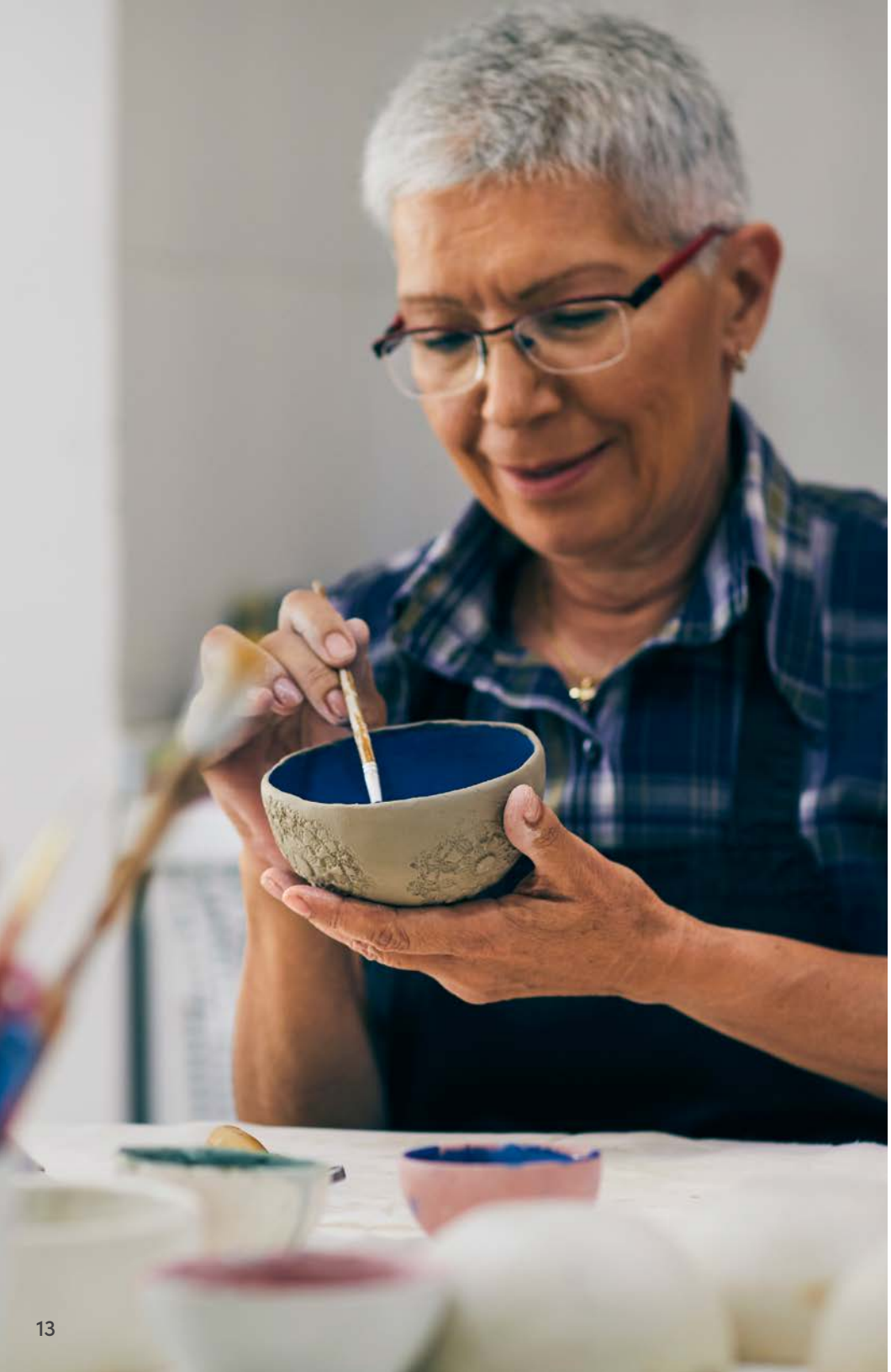

Dry age-related macular degeneration

Age-related macular degeneration (AMD) is a common disease resulting in central vision loss in approximately 11 million adults in the U.S.[24] The dry subtype of AMD accounts for more than 70% of cases, yet there are no FDA-approved treatments currently available for people who progress to late-stage disease.

Two pipeline intravitreal injections are in late-stage development for treatment of geographic atrophy secondary to dry AMD, the most advanced stage of dry AMD.[25] Iveric Bio is evaluating Zimura® (avacincaptad pegol), with pivotal trial results expected in the second half of 2022. If results are positive, FDA approval could happen in 2023. Apellis is finalizing their FDA new drug submission package for intravitreal pegcetacoplan, with a goal of attaining priority review as well as an FDA decision in the fourth quarter of 2022. A subcutaneous pegcetacoplan formulation is currently FDA approved under the brand name Empaveli™ for the treatment of paroxysmal nocturnal hemoglobinuria. There is a large unmet need in the market for therapies to treat dry AMD, with analysts predicting peak-year sales for each of these drugs to exceed $1B in the U.S. and Europe.[26]

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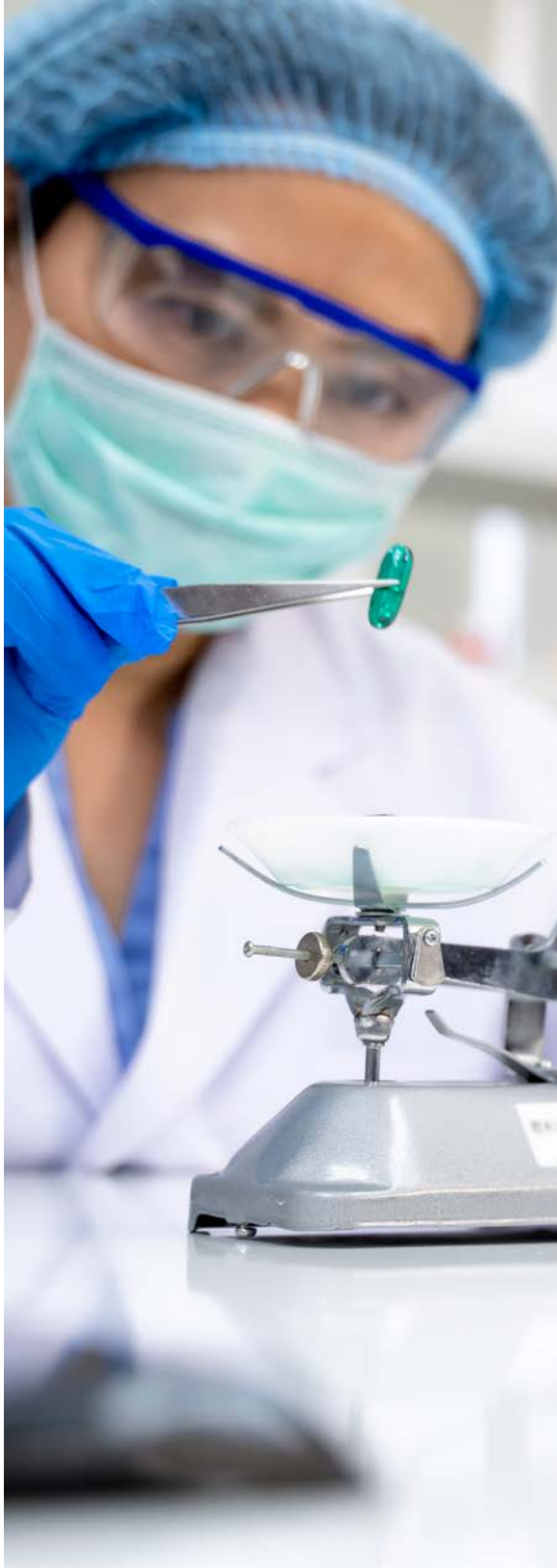

For more insights, see **ingenio-rx.com**.

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