Drug Monograph Digest

2024(January)–2025 (April) US FDA Drug Approvals

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Fast Facts **Snapshot Summaries** **Exclusivities and Patents**

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Drug Monograph Digest – First Edition

NOTICE

DISCLAIMER

This book is intended for informational purposes only. Information contained herein has been sourced from publicly available materials.

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How to Use This Book

Drug Monograph Digest is a practical, easy-to-navigate resource for professionals in drug development, regulatory affairs, intellectual property, investment, and education—anyone seeking a clear, consolidated view of recent FDA drug approvals. It compiles essential information—product characteristics, pharmacokinetics, clinical study outcomes, patents, and exclusivity—from multiple public sources into a single reference, saving time and effort.

Getting Started

Begin with the introductory summary tables to explore drug approvals, organized by proprietary names, active ingredients, dosage forms, routes of administration, regulatory pathways, and therapeutic areas.

Proprietary (brand) drug names are listed in Tables A and B, as well as in the Table of Contents. Generic names (active ingredients) are included in the Index at the back of the book, with appropriate hyperlinks to the corresponding tables and entries.

Using the Monographs

Each drug monograph is organized alphabetically by proprietary name and follows a consistent, standardized format for easy browsing and comparison.

Each entry includes:

- Fast facts – Sponsor, approval type, route of administration, and exclusivity status
- Indication, dosage, and administration
- Mechanism and pharmacokinetics
- Clinical study design and efficacy outcomes
- Exclusivity and patents – Orange Book listings with plain-language summaries of claims

The patent sections provide an overview of the intellectual property landscape, potentially saving hours of manual research. While not a substitute for legal due diligence, they help identify areas where deeper analysis may be needed.

Putting It to Work

Drug Monograph Digest serves as a launchpad—a quick-reference tool to help you get oriented and navigate information more efficiently. While not a substitute for full prescribing information or complete patent filings, it delivers focused insight when time is limited.

Simply browse recent FDA approvals for industry awareness, strategic planning, or academic use. Use the digest as a focused reference to avoid navigating multiple databases—cut through complexity and focus on what matters most.

Resources

The following public databases and official resources were consulted in compiling the content of *Drug Monograph Digest*. While not exhaustive, these sources form the core foundation of the data presented:

- **Drugs@FDA (Approval information and Labels)**
  https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
- **Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations**
  https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book
- **Purple Book: Database of Licensed Biological Products**
  https://purplebooksearch.fda.gov/
- **Orphan Drug Designations and Approvals Database**
  https://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm
- **United States Patent and Trademark Office (USPTO)**
  https://www.uspto.gov/patents/search
- **National Library of Medicine – PubChem (for chemical structures)**
  https://pubchem.ncbi.nlm.nih.gov/

ABBREVIATIONS

Abbreviation	Expansion
2-HG	2-Hydroxyglutarate
6MWD	6 Minute Walk Distance
AA	Alopecia Areata
ABR	Annualized Bleeding Rate
ABSSSI	Acute Bacterial Skin And Skin Structure Infections
ACM	All-Cause Mortality
ACTH	Adrenocorticotrophic Hormone
ADA	Anti-Drug Antibodies
ADAS	Alzheimer Disease Assessment Scale
ADC	Antibody Drug Conjugate
ADCC	Antibody-Dependent Cellular Cytotoxicity
ADCP	Antibody-Dependent Cellular Phagocytosis
ADCS	Alzheimer'S Disease Cooperative Study
AGRN	AGRN Gene
ALC	Absolute Lymphocyte Count
ALK	Anaplastic Lymphoma Kinase
ALL	Acute Lymphocytic Leukemia
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ALT	Alanine Transaminase
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
ANC	Absolute Neutrophil Count
APP	Amyloid Precursor Protein Gene
ARIA	Amyloid-Related Imaging Abnormalities
ARIA-E	Aria With Edema
ARIA-H	Aria With Hemosiderin Deposition
ASO	Antisense Oligonucleotide
AST	Aspartate Aminotransferase
AST	Aspartate Aminotransferase
AT	Antithrombin
AT-DR	Antithrombin-Based Dosing Regimen
ATTR-CM	Transthyretin Amyloid Cardiomyopathy
ATTR-CM	Transthyretin Amyloid Cardiomyopathy
AUC	Area Under The Curve
BBB	Blood Brain Barrier
BCG	Bacillus Calmette-Guerin
BCRP	Breast Cancer Resistance Protein
BICR	Blinded Independent Central Review
BID	Twice A Day

Abbreviation	Expansion
BLA	Biologics License Application
BMI	Body Mass Index
BPA	Bypassing Agents
BPI	Brief Pain Index
BRAF	BRAF Gene
BSA	Body Surface Area
BSEP	Bile Salt Export Pump
BTC	Bile Tract Cancer
CABP	Community Acquired Bacterial Pneumonia
CAD	Coronary Artery Disease
CAH	Congenital Adrenal Hyperplasia
CDC	Complement Dependent Cytotoxicity
CDH1	E-Cadherin Gene
CDR-SB	Clinical Dementia Rating Scale-Sum Of Boxes
CES	Carboxylesterases
CF	Cystic Fibrosis
CFC	Clotting Factor Concentrates
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFTR	Cystic Fibrosis Transmembrane-Conductance Regulators
CGI-S	Clinical Global Impression-Severity
cGVHD	Chronic Graft-Versus-Host Disease
CHO	Chinese Hamster Ovary Cell Line
cIAI	Complicated Intra-Abdominal Infections
CIS	Carcinoma-In Situ
CKD	Chronic Kidney Disease
CL	Clearance
CLCr	Creatinine Clearance
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CR	Complete Response
CRF	Corticotropin-Releasing Factor
CRS	Cytokine Release Syndrome
CSF-1R	Colony-Stimulating Factor-1
CT	Computer Tomography
CV	Coefficient Of Variance
CVH	Cardiovascular-Related Hospitalization
CXC	Chemokine Receptor
CYP	Cytochrome P450
DCIS	Ductal Carcinoma In Situ
DD CKD	Dialysis Dependent Chronic Kidney Disease
D-IVA	Deutivacaftor
DMD	Duchenne Muscular Dystrophy
DNA	Deoxyribonucleic Acid

Abbreviation	Expansion
DOR	Duration Of Response
DSA	Digital Subtraction Angiography
DSM5	The Diagnostic And Statistical Manual Of Mental Disorders 5
DVS	Direct Visualization System
DVT	Deep Vein Thrombosis
EASI	Eczema Area And Severity Index
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
eGFR	Estimated Glomerular Filtration Rate
ELF	Endothelial Lining Fluid
ELISA	Enzyme-Linked Immunoassay
ELX	Elexacaftor
ERA	Endothelin Receptor Antagonist
ERK	Erk Gene
ESA	Erythropoiesis-Stimulating Agents
ESBL	Extended-Spectrum B-Lactamase
ESRD	End-Stage Renal Disease
ES-SCLC	Extensive-Stage Small Cell Lung Cancer
ET	Endocrine Therapy
ET	Endothelin Receptors
ETA	Endothelin Receptor Antagonist
EVH	Extravascular Hemolysis
FCS	Familial Chylomicronemia Syndrome
FDA	Federal Drug Administration
FGF21	Fibroblast Growth Factor 21
fSARA	Functional Scale For Assessment And Rating Of Ataxia
GAIN	Generating Antibiotic Incentives Now
GEJ	Gastroesophageal Junction
GLP-1	Glucagon-Like Peptide 1
GLS	Glabellar Line Scale
GSP	Gravimetric Sweat Production
HABP	Hospital Acquired Bacterial Pneumonia
HAwI	Hemophilia A With Inhibitors
HB/APAP	Hydrocodone Bitartrate/Acetaminophen
HBwI	Hemophilia B With Inhibitors
HDPE	High Density Polyethylene
HDSM-Ax	Hyperhidrosis Disease Severity Measure Axillary Score
HER-2	Human Epidermal Growth Factor Receptor-2
HIF-PH	Hypoxia-Inducible Factor Prolyl Hydroxylase
HIF-PH	Hypoxia-Inducible Factor Prolylhydroxylase
HIV	Human Immune Deficiency Virus
HR	Hazard Ratio
HR	Hormone Receptor

Abbreviation	Expansion
HSCT	Hematopoietic Stem Cell Transplant
iADRS	Integrated Alzheimer'S Disease Rating Scale
IA-DSA	Intra-Arterial Digital Subtraction Angiography
ICA	Invasive Coronary Imaging
ICANS	Immune-Effector Cell-Associated Neurotoxicity Syndrome
ICC	Investigators Choice Of Chemotherapy
ICS	Inhaled Corticosteroid
IDH	Isocitrate Dehydrogenase
IGA	Investigators Global Assessment
IHC	Immunohistochemistry
IL	Interleukin
IM	Intramuscular
INR	International Normalization Ratio
IP	Intellectual Property
IPSS	International Prognostic Scoring System
IRC	Independent Review Committee
ISH	In Situ Hybridization
ITT	Intent-To-Treat
IV	Intravenous
IVH	Intravascular Hemolysis
IVSS	Iv Solution Stabilizer
JAK	Janus Kinase Gene
LABA	Long-Acting Beta-Agonist
laCSCC	Locally Advanced Cutaneous Squamous Cell Carcinoma
LAMA	Long-Acting Muscarinic Antagonist
LGG	Low-Grade Glioma
LHRH	Luteinizing Hormone Releasing Hormone
LS	Least Squares
LVEF	Left Ventricular Ejection Fraction
MAC	Membrane Attack Complex
MACE	Major Adverse Cardiovascular Events
MATE-2K	Multidrug And Toxin Extrusion Protein Gene
MC	Molluscum Contagiosum
MC-1	Mitochondrial-Complex-1
MCC	Microcrystalline Cellulose
mCSCC	Metastatic Cutaneous Squamous Cell Carcinoma
MDS	Myelodysplastic Syndromes
MET	Met Gene
MI	Myocardial Infarction
micro-ITTS	Microbiological Intent-To-Treat Nitrofurantoin Susceptible
micro-MITT	Microbiological Modified Intent-To-Treat
MMP	Matrix Metalloproteases
MPAL	Mixed Phenotype Acute Leukemia

Abbreviation	Expansion
MPI	Myocardial Perfusion Imaging
MR	Minor Response
MRSA	Methicillin Resistant Staphylococcus Aureus Infection
MSSA	Methicillin Susceptible Staphylococcus Aureus Infection
NA	Not Available
NAFLD	Non-Alcoholic Fatty Liver Disease
NASH	Non-Alcoholic Steatohepatitis
NASH	Nonalcoholic Steatohepatitis
NCE	New Chemical Entity
NCT	National Clinical Trial
NDA	New Drug Application
NE	Not Estimable
NGS	Next Generation Sequencing
NK	Natural Killer
NMIBC	Non-Muscle Invasive Bladder Cancer
NPC	Niemann-Pick Disease Type C
NPRS	Numeric Pain Rating Scale
NR	Not Reached
NRG	Neuregulin
NRS	Numerical Rating Scale
NSAA	North Star Ambulatory Assessment
NSCLC	Non-Small Cell Lung Cancer
NTCP	Sodium Taurocholate Co-Transporting Polypeptide
OAT	Organic Anion Transporter
OCT	Organic Cationic Transporter
ODE	Orphan Drug Exclusivity
ORR	Overall Response Rate
OS	Overall Survival
PAH	Pulmonary Arterial Hypertension
PANSS	Positive And Negative Syndrome Scale
PBC	Primary Biliary Cholangitis
PCR	Polymerase Chain Reaction
PD-1	Programmed Death Receptor-1
PDE	Phosphodiesterase
PD-L1	Programmed Death Ligand-1
PEG	Polyethylene Glycol
PEG	Peg
PET	Positron Emission Tomography
PET	Polyethylene Terephthalate (Bottles)
PFS	Progression-Free Survival
P-gp	P-Glycoprotein
PK	Pharmacokinetics
PN	Plexiform Neurofibromas

Abbreviation	Expansion
PN	Prurigo Nodularis
PNH	Paroxysmal Nocturnal Hemoglobinuria
PPAR	Peroxisome Proliferator–Activated Receptors
ppFEV	Percent Predicted Forced Expiratory Volume
PP-NRS	Peak Pruritis Numeric Rating Scale
PPT	Proton Pump Inhibitor
PR	Partial Response
PTGR	Prostaglandin Receptor
PTH	Parathyroid Hormone
PVALB	Parvalbumin Gene
RA	Rheumatoid Arthritis
RAF	Raf Gene
RAPNO	Response Assessment In Pediatric Neuro-Oncology
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria In Solid Tumors
REMS	Risk Evaluation And Mitigation Strategy
rFVIIa	Recombinant Factor Vii A
RI	Renal Impairment
SAB	Staphylococcus Bloodstream Infection
SALT	Severity Of Alopecia Tool
SBP	Systolic Blood Pressure
SC	Subcutaneous
SDC4	Syndecan-4 Gene
SDF-1alfa	Stromal Derived Factor 1 Alfa
SGRQ	St George'S Respiratory Questionnaire
SiDBP	Sitting Diastolic Blood Pressure
SiSBP	Sitting Systolic Blood Pressure
SOC	Standard Of Care
SPECT MPI	Single Photon Emission Computed Tomography Myocardial Perfusion Imaging
SPID	Sum Of The Pain Intensity Difference From 0 To 48 Hours
SPRO	Satisfaction Of Hair Patient Reported Outcome
STAT	Signal Transducer And Activation Of Transcription
SVT	Supraventricular Tachycardia
TATALC	Time Above The Absolute Lymphocyte Count
TATANC	Time Above The Absolute Neutrophil Count
TB	Total Bilirubin
TB	Tuberculosis
TBD	To Be Determined
TCS	Topical Corticosteroids
TEZ	Tezacaftor
TFPI	Tissue Factor Pathway Inhibitor
TG	Triglycerides

Abbreviation	Expansion
TGCT	Tenosynovial Giant Cell Tumor
THBS1	Thrombospondin 1
THR-β	Thyroid Hormone Receptor-Beta
TI	Transfusion Independence
Tmax	Time To Maximal Concentration
TMDD	Target-Mediated Drug Disposition
TNF	Tumor-Necrosis Factor
TOC	Test Of Cure
TTNI	Time To Next Intervention
TTR	Transthyretin
TURBT	Transurethral Resection Of Bladder Cancer
TVS	Tumor Volume Score
UACR	Urine Albumin Creatinine Ratio
UAOBP	Unattended Automated Office Blood Pressure
UDCA	Ursodeoxycholic Acid
UGT	Udp-Glucuronosyltransferase
ULN	Upper Limit Of Normal
USP	United States Pharmacopeia
USPTO	United States Patent And Trademark Office
UTI	Urinary Tract Infection
Vc	Central Volume Of Distribution
VLDL	Very Low-Density Lipoproteins
VNZ	Vanzacaftor
VTCN1	V-Set Domain Containing T Cell Activation Inhibitor 1
WHIM	Warts, H (Low Antibody Levels), Recurrent Infections, And Myelokathexis
WHO	World Health Organization

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INTRODUCTION

Drug Monograph Digest: 2024–2025 FDA Novel Drug Approvals

In 2024, the FDA approved fifty novel drugs, comprising sixteen biologics and thirty-four small molecules. These approvals spanned a wide range of therapeutic areas and utilized a diverse array of dosage forms. Among the injectable products, there were eight subcutaneous and sixteen intravenous formulations. Oral dosage forms included thirteen tablets, five capsules, and four oral suspensions. Additionally, the approvals included two gels, two nasal sprays, and one inhalation suspension.

These new therapies targeted a wide spectrum of conditions. Notably, about 52% were indicated for rare or orphan diseases, and approximately 48% were classified as first-in-class. Furthermore, roughly 66% of the approvals utilized expedited regulatory pathways—including Fast Track, Breakthrough Therapy, Priority Review, and Accelerated Approval.

As of April 2025, seven novel drugs have been approved, consisting of one biologic and six small molecules. Of these, three received Orphan Drug Designation/Exclusivity (ODE). A summary of these approvals is presented in Tables A and B. The approved drugs are categorized by therapeutic indication and regulatory designation (biologic or small molecule and ODE status) and are presented in Table A. Additionally, the approved drugs are classified by dosage form in Table B, which also summarizes the effect of food on absorption, when applicable.

The drug monographs are presented as individual chapters in alphabetical order. Brief summaries of the Orange Book patents for applicable monographs are provided in the tables in Appendix A.

Table A: Overview of FDA Approved Drugs (2024–2025): By Therapeutic Area and Regulatory Designations

The table below lists FDA-approved drugs for 2024–2025 (covering all of 2024 and through April 2025), categorized by therapeutic area and regulatory designation. An 'x' indicates the applicable classification. For complete indication details, please refer to the individual monographs.

Proprietary Name	Active Ingredient(s)	BLA	NDA	ODE	Indication
2024 Drug Approvals					
Alhemo	Concizumab-mtci	x		x	Hemophilia A/B
Alyftrek	Vanzacaftor, tezacaftor, deutivacaftor		x	x	Cystic Fibrosis
Anktiva	Nogapendekin alfa inbakicept-pmln	x			Non-muscle invasive bladder cancer
Aqneursa	Levacetylleucine		x	x	Niemann-Pick Disease Type C
Attruby	Acoramidis		x	x	Transthyretin Amyloid Cardiomyopathy
Bizengri	Zenocutuzumab-zbco	x		x	Non-Small Cell Lung Cancer, NSCLC)
Cobenfy	Xanomeline, trospium chloride		x		Schizophrenia

Proprietary Name	Active Ingredient(s)	BLA	NDA	ODE	Indication
Crenessity	Crinecerfont		x	x	Congenital Adrenal Hyperplasia
Duvyzat	Givinostat		x	x	Duchenne Muscular Dystrophy
Ebglyss	Lebrikizumab-lbkz	x			Atopic Dermatitis
Ensacove	Ensartinib		x		ALK+ Non-Small Cell Lung Cancer
Exblifep	Cefepime, enmetazobactam		x		Complicated Urinary Tract Infection (UTI)
Flyrcado	Furpiridaz F 18		x		Myocardial Perfusion for CAD
Hympavzi	Marstacimab-hncq	x		x	Hemophilia A/B
Imdelltra	Tarlatamab-dlle	x		x	Extensive-stage small cell lung cancer (ES-SCLC)
Iomervu*	Iomeprol		x		Cerebral arteriography,
Iqirvo	Elafibranor		x	x	Primary Biliary Cholangitis
Itovebi	Inavolisib		x		PIK3CA-mutated, HR-positive, HER2-negative breast cancer.

Proprietary Name	Active Ingredient(s)	BLA	NDA	ODE	Indication
Kisunla	Donanemab-azbt	x			Alzheimer's Disease
Lazcluze	Lazertinib		x		EGFR mutated NSCLC
Leqselvi	Deuruxolitinib		x		Alopecia Areata
Letybo	LetibotulinumtoxinA-wlbg	x			Glabellar lines
Livdelzi	Seladelpar		x	x	Primary Biliary Cholangitis
Lumisight	Pegulicianine		x		Imaging agent for breast cancer surgery
Miplyffa	Arimoclomol		x	x	Niemann-Pick Disease Type C
Nemluvio	Nemolizumab-ilto	x			Prurigo Nodularis
Niktimvo	Axatilimab-csfr	x		x	Chronic Graft-Versus-Host Disease
Ohtuvayre	Ensifentrine		x		COPD
Ojemda	Tovorafenib		x	x	Low-Grade Glioma
Orlynvah	Sulopenem etzadroxil, probenecid		x	x	Uncomplicated UTI

Proprietary Name	Active Ingredient(s)	BLA	NDA	ODE	Indication
Piasky	Crovalimab-akkz	x		x	Paroxysmal Nocturnal Hemoglobinuria - PNH
Rapiblyk	Landiolol		x		Supraventricular Tachycardia - SVT
Revuforj	Revumenib		x	x	Acute Leukemia with KMT2A
Rezdiffra	Resmetirom		x		NASH with Fibrosis
Rytelo	Imetelstat		x	x	Myelodysplastic Syndromes - MDS
Sofdra	Sofpironium		x		Primary Axillary Hyperhidrosis
Tevimbra	Tislelizumab-jsgr	x		x	Esophageal Squamous Cell Carcinoma
Tryngolza	Olezarsen		x	x	Familial Chylomicronemia Syndrome
Tryvio	Aprocitentan		x		Hypertension
Unloxcyt	Cosibelimab-ipdl	x			Locally advanced Cutaneous Squamous Cell Carcinoma

Proprietary Name	Active Ingredient(s)	BLA	NDA	ODE	Indication
Vafseo	Vadadustat		x		Anemia of chronic kidney disease in dialysis patients
Voranigo	Vorasidenib		x	x	Low-Grade astrocytoma or oligodendroglioma with IDH Mutation
Voydeya	Danicopan		x	x	PNH with Extravascular Hemolysis
Vyloy	Zolbetuximab-clzb	x		x	HER2- gastric and gastroesophageal junction adenocarcinoma
Winrevair	Sotatercept-csrk	x		x	Pulmonary Arterial Hypertension
Xolremdi	Mavorixafor		x	x	WHIM Syndrome
Yorvipath	Palopegteriparatide		x	x	Hypoparathyroidism (parathyroid hormone analog)
Zelsuvmi	Berdazimer		x		Molluscum contagiosum

Proprietary Name	Active Ingredient(s)	BLA	NDA	ODE	Indication
Zevtera	Ceftobiprole medocaril sodium		x		Staphylococcus aureus bloodstream infection
Ziihera	Zanidatamab-hrii	x		x	HER2+ (IHC 3+) Biliary Tract Cancer
2025 Drug Approvals					
Blujepa	Gepotidacin		x		Uncomplicated Urinary Tract Infection (UTI)
Datroway	Datopotamab deruxtecan-dlnk	x			unresectable or metastatic breast cancer that is HR positive and HER2-negative (IHC 0, 1+, or 2+/ISH-)
Gomekli	Mirdametinib		x	x	Neurofibromatosis type 1 (NF1) with symptomatic plexiform neurofibromas (PN)
Grafapex	Treosulfan		x	x	Conditioning regimen prior to allogeneic hematopoietic stem cell transplantation

Proprietary Name	Active Ingredient(s)	BLA	NDA	ODE	Indication
Journavx	Suzetrigine		x		Short-term moderate to severe pain
Qfitlia	Fitusiran		x	x	Hemophilia A or B
Romvimza	Vimseltinib		x		Tenosynovial Giant Cell Tumor - TGCT

Abbreviation key: BLA = Biologics License Application, NDA = New Drug Application, ODE = Orphan Drug Exclusivity, NASH = Non-Alcoholic Steatohepatitis, COPD = Chronic Obstructive Pulmonary Disease, WHIM = Warts, H (low antibody levels), recurrent Infections, and Myelokathexis,

*Iomervu is now listed as “discontinued” in the Orange Book.

Table B: Overview of FDA Approved Drugs (2024–2025): *By Product Characteristics*

The table below summarizes FDA-approved drugs from January, 2024 – April 2025, categorized by key product characteristics, with each attribute indicated by an "x" in the appropriate column. It also highlights whether food affects drug absorption and specifies if the drug should be taken with food, without food, or without regard to food. The effect of food on absorption is described as unchanged (no meaningful change in AUC/Cmax), increased (higher AUC/Cmax), or decreased (lower AUC/Cmax) when the drug is administered with food.

Proprietary Name	Active Ingredient(s)	IV	SC	Oral Capsule	Oral Tablet	Other Dosage Forms	Food effect	Taken with or without food?
2024 Drug Approvals								
Alhemo	Concizumab-mtci		x (prefilled pen)				NA	NA
Alyftrek	Vanzacaftor Tezacaftor				x		Increased Unchanged	Taken with fat containing food

Proprietary Name	Active Ingredient(s)	IV	SC	Oral Capsule	Oral Tablet	Other Dosage Forms	Food effect	Taken with or without food?
	Deutivacaftor						Increased	
Anktiva	Nogapendekin alfa inbakicept-pmln					Intravesical solution	NA	NA
Aqneursa	Levacetylleucine					Granules for suspension	Unchanged	With or without food
Attruby	Acoramidis				x		Unchanged	With or without food
Bizengri	Zenocutuzumab-zbco	x						NA
Cobenfy	Xanomeline Trospium chloride			x			Unchanged Decreased	1h before or 2h after meal
Crenessity	Crinecerfont			x		Oral solution	Increased	With food

Proprietary Name	Active Ingredient(s)	IV	SC	Oral Capsule	Oral Tablet	Other Dosage Forms	Food effect	Taken with or without food?
Duvyzat	Givinostat					Oral suspension	Increased	With food
Ebglyss	Lebrikizumab-lbkz		x (prefilled syringe & prefilled pen)				NA	NA
Ensacove	Ensartinib			x			Unchanged	With or without food
Exblifep	Cefepime, enmetazobactam	x					NA	NA
Flyrcado	Furpiridaz F 18	x					NA	NA
Hympavzi	Marstacimab-hncq		x (Prefilled syringe,				NA	NA

Proprietary Name	Active Ingredient(s)	IV	SC	Oral Capsule	Oral Tablet	Other Dosage Forms	Food effect	Taken with or without food?
			prefilled pen)					
Imdelltra	Tarlatamab-dlle	x					NA	NA
Iomervu*	Iomeprol	x				Intra-arterial	NA	NA
Iqirvo	Elafibranor				x		Unchanged	With or without food
Itovebi	Inavolisib				x		Unchanged	With or without food
Kisunla	Donanemab-azbt	x						NA
Lazcluze	Lazertinib				x		Unchanged	With or without food
Leqselvi	Deuruxolitinib				x		Unchanged	With or without food
Letybo	LetibotulinumtoxinA-wlbg					IM		NA

Proprietary Name	Active Ingredient(s)	IV	SC	Oral Capsule	Oral Tablet	Other Dosage Forms	Food effect	Taken with or without food?
Livdelzi	Seladelpar			x			Unchanged	With or without food
Lumisight	Pegulicianine	x						NA
Miplyffa	Arimoclomol			x			Unchanged	With or without food
Nemluvio	Nemolizumab-ilto		x			Dual chamber pen	NA	NA
Niktimvo	Axatilimab-csfr	x					NA	NA
Ohtuvayre	Ensifentrine					Inhalation suspension	NA	NA
Ojemda	Tovorafenib				x	Powder for oral suspension	Unchanged (delayed Tmax)	With or without food
Orlynvah	Sulopenem etzadroxil				x		Increased	With food

Proprietary Name	Active Ingredient(s)	IV	SC	Oral Capsule	Oral Tablet	Other Dosage Forms	Food effect	Taken with or without food?
	Probenecid						Decreased	
Piasky	Crovalimab-akkz	x	x				NA	NA
Rapiblyk	Landiolol	x					NA	NA
Revuforj	Revumenib				x		Slightly reduced AUC and Cmax	Fasted or with low fat food
Rezdiffra	Resmetirom						Slightly reduced AUC and Cmax	With or without food
Rytelo	Imetelstat	x					NA	NA
Sofdra	Sofpironium					Topical gel	NA	NA

Proprietary Name	Active Ingredient(s)	IV	SC	Oral Capsule	Oral Tablet	Other Dosage Forms	Food effect	Taken with or without food?
Tevimbra	Tislelizumab-jsgr	x					NA	NA
Tryngolza	Olezarsen		x (auto-injector pen)				NA	NA
Tryvio	Aprocitentan				x		Unchanged	With or without food
Unloxcyt	Cosibelimab-ipdl	x						NA
Vafseo	Vadadustat				x		Unchanged	With or without food
Voranigo	Vorasidenib				x		Increased	With or without food
Voydeya	Danicopan				x		Increased	With or without food

Proprietary Name	Active Ingredient(s)	IV	SC	Oral Capsule	Oral Tablet	Other Dosage Forms	Food effect	Taken with or without food?
Vyloy	Zolbetuximab-clzb	x					NA	NA
Winrevair	Sotatercept-csrk		x				NA	NA
Xolremdi	Mavorixafor						Decreased	Fasted
Yorvipath	Palopegteriparatide		x				NA	NA
Zelsuvmi	Berdazimer					Topical gel	NA	NA
Zevtera	Ceftobiprole medocaril sodium	x					NA	NA
Ziihera	Zanidatamab-hrii	x					NA	NA
2025 Drug Approvals								
Blujepa	Gepotidacin				x		Unchanged	After meal
Datroway	Datopotamab deruxtecan-dlnk	x					NA	NA
Gomekli	Mirdametinib			x		Tablet for oral suspension	Cmax decreased AUC nearly unchaged	With or without food

Proprietary Name	Active Ingredient(s)	IV	SC	Oral Capsule	Oral Tablet	Other Dosage Forms	Food effect	Taken with or without food?
Grafapex	Treosulfan	x						NA
Journavx	Suzetrigine				x		Delayed	On empty stomach or 1 h before 2 h after meal
Qfitlia	Fitusiran		x (Prefilled pen)				NA	NA
Romvimza	Vimseltinib			x			Unchanged	With or without food

Abbreviations key: IV = intravenous administration, SC = subcutaneous administration, IA = intraarterial administration, IM = intramuscular injection, NA = not applicable

*Iomervu is now listed as “discontinued” in the Orange Book.

2024 Drug Monographs

Alhemo®

Concizumab-mtci injection, for subcutaneous use

Fast Facts	
BLA Holder	Novo Nordisk Inc.
Product Presentation	Prefilled pen
Route of Administration	Subcutaneous
BLA Approval	December 20, 2024*
ODE	Yes. End date TBD**
Mechanism of action	Monoclonal antibody antagonist of endogenous Tissue Factor Pathway Inhibitor (TFPI)

*BLA exclusivity is typically granted for 12 years from date of approval. **To be determined (TBD). Not yet listed in Orphan Drug Database. Typically, 7 years from date of approval

Indication

Alhemo (concizumab-mtci) is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients aged 12 years and older with hemophilia A (congenital factor VIII deficiency) with FVIII inhibitors, or hemophilia B (congenital factor IX deficiency) with FIX inhibitors.

Description

Concizumab-mtci is a humanized immunoglobulin G4 (IgG4) monoclonal antibody produced using recombinant DNA technology in CHO cells. It has an approximate molecular weight of 149 kDa.

Dosage Form and Handling

Alhemo injection is supplied in the following strengths: 60 mg/1.5 mL, 150 mg/1.5 mL, and 300 mg/3 mL, each in a single-patient-use prefilled pen.

Before first use, Alhemo should be stored in a refrigerator at 2°C to 8°C in its original carton to protect it from light. Freezing is not permitted. After first use, the device may be stored either in the refrigerator or at room temperature below 30°C for up to 28 days. Each 1 mL of Alhemo in the single-patient-use prefilled pen contains the following excipients : arginine hydrochloride (5.27 mg), histidine (5.12 mg), phenol (3.5 mg), polysorbate 80 (0.25 mg), sodium chloride (1.46 mg), sucrose (51.3 mg), and water for injection. Hydrochloric acid and sodium hydroxide may be used to adjust the pH to 6.0.

Dosing Regimen

The Alhemo dosing regimen begins with a loading dose of 1 mg/kg on Day 1, followed by a daily dose of 0.2 mg/kg from Day 2 until the maintenance dose is adjusted. Four weeks after treatment initiation, concizumab-mtci plasma concentration should be measured using an ELISA method before the next scheduled dose. The maintenance dose is individualized within 8 weeks based on plasma concentration levels, ranging from 0.15 to 0.25 mg/kg.

Mechanism of Action

Concizumab-mtci is a monoclonal antibody antagonist of endogenous TFPI. By inhibiting TFPI, concizumab-mtci enhances the production of activated factor X (FXa) during the initiation phase of coagulation. This enhancement leads to increased thrombin generation

and clot formation, thereby promoting hemostasis in patients with hemophilia A or B who have developed inhibitors.

Pharmacokinetics

Concizumab-mtci reaches steady-state plasma concentrations by Day 4 following a 1 mg/kg loading dose, with stable exposure maintained through daily maintenance dosing. After a subcutaneous dose ranging from 0.05 to 3 mg/kg, the time to maximum plasma concentration (Tmax) varies from 8 to 99 hours, averaging 4.1 days. The volume of distribution for a 70 kg patient is approximately 3 L.

Elimination occurs through both non-linear saturable target-mediated drug disposition (TMDD) and linear pathways. Population pharmacokinetic analysis indicates that 90% of the drug is cleared within 4 days, with a half-life of approximately 1 day. The drug undergoes catabolic metabolism, breaking down into small peptides.

No clinically significant differences in pharmacokinetics were observed based on age, race, or hemophilia type (A vs. B). No dedicated studies have been conducted to assess its pharmacokinetics in patients with renal or hepatic impairment. The apparent volume of distribution increases with body weight.

In four clinical trials lasting 11 to 76 weeks, 47 out of 185 patients (25.4%) developed anti-concizumab-mtci antibodies (Anti-drug Antibodies, ADA). Among them, 12 patients (25.5%) had neutralizing antibodies (NAbs). In one patient, NAbs restored free TFPI levels to baseline, suggesting a potential reduction in treatment effectiveness. For the remaining 46 patients, no clinically significant impact on pharmacokinetics, pharmacodynamics, safety, or effectiveness was observed.

Clinical Studies

The EXPLORER7 trial evaluated the efficacy and safety of Alhemo for routine prophylaxis in patients with hemophilia A or B with inhibitors. This multinational, open-label, phase 3 study included 91 adults (≥18 years) and 42 adolescents (12–17 years) who required or were eligible for bypassing agent treatments due to a high risk of bleeding. Eptacog alfa (rFVIIa) was used as the bypassing agent.

The study was divided into two randomized arms and two non-randomized arms. Arm 1 included 52 patients randomized to either no prophylaxis (n = 26; on-demand treatment with a bypassing agent) or Alhemo prophylaxis (n = 26), with stratification based on hemophilia type and baseline bleeding frequency. Arm 2 consisted of 39 patients previously treated with bypassing agents, who underwent a 24-week assessment of bleeding episodes**.**

Arms 3 and 4 were non-randomized and included 81 patients—53 with hemophilia A with inhibitors (HAwI) and 28 with hemophilia B with inhibitors (HBwI)—who received Alhemo prophylaxis.

Patients in the Alhemo treatment arms began with a 1 mg/kg loading dose on the first day, followed by a daily maintenance dose of 0.20 mg/kg. Dose adjustments were allowed based on plasma concentrations measured four weeks after initiation, with possible increases to 0.25 mg/kg or decreases to 0.15 mg/kg.

The study assessed the effectiveness of Alhemo by comparing bleeding episodes in patients with hemophilia A or B with inhibitors who received either Alhemo prophylaxis (Arm 2) or no prophylaxis (Arm 1). Patients in Arm 1 were observed for at least 24 weeks, while those in Arm 2 were observed for at least 32 weeks.

Results showed that patients receiving Alhemo prophylaxis experienced an 86% reduction in annualized bleeding episodes compared to those without prophylaxis, with an annualized bleeding rate (ABR) ratio of 0.14 ($p < 0.001$). Using a negative binomial model, the ABR ratio was confirmed to be 0.14 ($p < 0.001$), indicating a consistent 86% reduction in ABR for patients on Alhemo prophylaxis.

The mean ABR was estimated at 1.7 (95% CI: 1.01–2.87) for patients on Alhemo prophylaxis (Arm 2) and 11.8 (95% CI: 7.03–19.86) for patients without prophylaxis (Arm 1).

Exclusivity and Patents

No exclusivities or patents are currently listed.

Alyftrek

Vanzacaftor, tezacaftor, and deutivacaftor tablets, for oral use

Fast Facts	
NDA Holder	Vertex Pharmaceuticals Inc.
Product Presentation	Oral Tablet
Route of Administration	Oral
NDA Approval	December 20, 2024 (New Molecular Entity)
NCE Exclusivity	Not listed*
ODE	Yes. End date TBD*
Mechanism of action	Vanzacaftor and tezacaftor are cystic fibrosis transmembrane conductance regulators (CFTR) Deutivacaftor is a CFTR potentiator

*NCE typically lasts 5 years from date of approval

**To be determined (TBD). Not yet listed in Orphan Drug Database. ODE typically lasts 7 years from date granted

Indication

Alyftrek is approved for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who carry at least one F508del mutation or another responsive mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

Boxed Warning

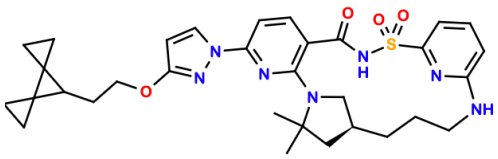
Alyftrek is associated with a risk of elevated liver enzymes and drug-induced liver injury, including liver failure, which may be fatal. These adverse events have been observed primarily within the first month of therapy and up to 15 months after treatment initiation.

Liver function tests (ALT, AST, alkaline phosphatase, and bilirubin) must be performed prior to initiating treatment and monitored regularly during therapy. Treatment should be interrupted if clinically indicated.

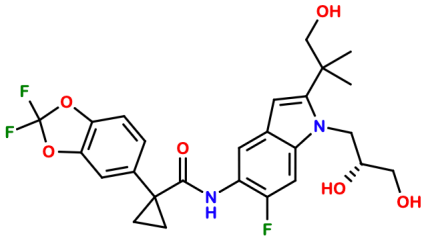
Alyftrek is contraindicated in patients with severe hepatic impairment and should be used in those with moderate hepatic impairment only when clearly necessary.

Description

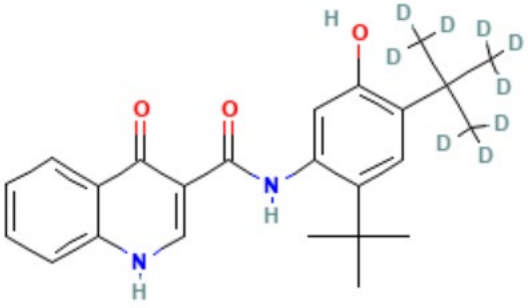
Vanzacaftor is presented as a calcium salt dihydrate and has a molecular weight of 654.82. The chemical structure of the free form is shown below.



Tezacaftor has a molecular weight of 520.50. Its chemical structure is shown below:



Deutivacaftor has a molecular weight of 401.55. Its chemical structure is shown below



Dosage Form and Handling

Alyftrek is supplied as fixed-dose combination tablets in two strengths: one containing 4 mg of vanzacaftor, 20 mg of tezacaftor, and 50 mg of deutivacaftor; and the other containing 10 mg of vanzacaftor, 50 mg of tezacaftor, and 125 mg of deutivacaftor. The drug product should be stored at 20°C to 25°C, with permitted excursions between 15°C and 30°C.

Dosing Regimen

The recommended dosage of Alyftrek depends on the patient's age and weight. For children aged 6 to less than 12 years:

Those weighing less than 40 kg should take three tablets daily, each containing 4 mg vanzacaftor, 20 mg tezacaftor, and 50 mg deutivacaftor.

Those weighing 40 kg or more should take two tablets daily, each containing 10 mg vanzacaftor, 50 mg tezacaftor, and 125 mg deutivacaftor.

For patients aged 12 years and older, regardless of weight, the recommended dose is two tablets daily, each containing 10 mg vanzacaftor, 50 mg tezacaftor, and 125 mg deutivacaftor.

Alyftrek should be taken orally once daily with fat-containing food, at the same time each day.

Mechanism of Action

Vanzacaftor and tezacaftor work by binding to different sites on the CFTR protein, improving its processing and delivery to the cell surface, particularly in mutant forms such as F508del-CFTR. Deutivacaftor enhances the gating of the CFTR protein, increasing the channel's open probability at the cell surface. Together, these three compounds increase

both the quantity and functionality of the CFTR protein, leading to improved chloride transport. This effect has been demonstrated in vitro and is supported by reduced sweat chloride levels in patients with cystic fibrosis.

Pharmacokinetics

The pharmacokinetics of vanzacaftor, tezacaftor, and deutivacaftor were studied in patients with cystic fibrosis (CF) aged 12 years and older. No clinically significant differences in pharmacokinetics were observed between healthy adult subjects and patients with CF. Vanzacaftor reaches steady state within 20 days, while tezacaftor and deutivacaftor reach steady state within eight days. The time to maximum plasma concentration (Tmax) ranges from 1.6 hours for tezacaftor to 7.8 hours for vanzacaftor. Food increases exposure to vanzacaftor (4- to 6-fold) and deutivacaftor (3- to 4-fold) but does not significantly affect tezacaftor.

Vanzacaftor has an apparent mean (SD) volume of distribution of 121 L (28.6), deutivacaftor 159 L (26.1), and tezacaftor 73.1 L (13.3), with all three exhibiting high protein binding (>99%). The mean elimination half-lives are 92.8 hours for vanzacaftor, 19.2 hours for deutivacaftor, and 22.5 hours for tezacaftor. The compounds are primarily metabolized via CYP3A4/5. Vanzacaftor produces no active metabolites, whereas tezacaftor and deutivacaftor generate metabolites with similar or reduced potency. Excretion is predominantly fecal, with minimal urinary elimination (91.6% fecal excretion for vanzacaftor and 72% for tezacaftor).

No significant pharmacokinetic differences were observed across age, sex, race, CFTR genotype, or in individuals with mild to moderate renal impairment. The impact of severe renal impairment remains unknown. Body weight has a clinically meaningful effect on the

pharmacokinetics of vanzacaftor, tezacaftor, and deutivacaftor. Pediatric patients aged 6 to less than 18 years showed exposures comparable to those of adults when administered the recommended dosages.

Pharmacokinetics vary based on body weight and hepatic function. In moderate hepatic impairment, the AUCs of vanzacaftor and deutivacaftor were reduced by approximately 30% and 20%, respectively, while tezacaftor exposure remained unaffected. The effects of mild or severe hepatic impairment are unknown.

Drug Interactions

Itraconazole (a strong CYP3A inhibitor) significantly increases exposure (AUC and Cmax) of tezacaftor (TEZ), deutivacaftor (D-IVA), and vanzacaftor (VNZ) when co-administered. Fluconazole significantly raises VNZ and D-IVA exposure when combined with VNZ + TEZ + D-IVA. Co-administration of erythromycin substantially increases VNZ and D-IVA exposure. Verapamil causes a significant increase in VNZ and D-IVA exposure.

Rifampin (a strong CYP3A inducer) drastically reduces VNZ and D-IVA exposure. Efavirenz significantly lowers VNZ and D-IVA exposure. Carbamazepine significantly reduces VNZ and D-IVA exposure due to strong CYP3A induction.

Ciprofloxacin has a slight effect on TEZ when co-administered with TEZ + D-IVA. Digoxin shows a moderate increase in its exposure when taken with TEZ + IVA.

Clinical Studies

The efficacy of Alyftrek was assessed in two large, randomized, double-blind, active-controlled clinical trials involving patients aged 12 years and older with cystic fibrosis (CF) who carried at least one F508del mutation or a mutation responsive to CFTR modulators.

Both trials compared the efficacy of Alyftrek with ELX/TEZ/IVA (elexacaftor, tezacaftor, and ivacaftor).

In Trial 1, 398 patients with CF who were heterozygous for F508del and had a CFTR "minimal function mutation" were enrolled. Following a 4-week run-in period with ELX/TEZ/IVA, participants were randomized to receive either Alyftrek or continue with ELX/TEZ/IVA for 52 weeks. Trial 2 enrolled 573 patients who were either homozygous for F508del or heterozygous for F508del with a gating or residual function mutation.

For the primary efficacy endpoint, the absolute change in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) from baseline to Week 24 demonstrated the non-inferiority of Alyftrek compared to ELX/TEZ/IVA. In both trials, the least-squares (LS) mean difference in $ppFEV_1$ change was 0.2 percentage points, with the lower bounds of the 95% confidence intervals above the pre-specified non-inferiority margin of -3.0 percentage points. This indicated similar efficacy in lung function improvement between the two treatments.

Secondary endpoints, including changes in sweat chloride levels, showed statistically significant reductions favoring Alyftrek in both trials. In Trial 1, the LS mean difference in sweat chloride change through Week 24 was -8.4 mmol/L (95% CI: -10.5, -6.3), while in Trial 2, it was -2.8 mmol/L (95% CI: -4.7, -0.9).

Additional evaluations, such as changes in the Cystic Fibrosis Questionnaire-Revised (CFQ-R RD) respiratory domain and pulmonary exacerbation rates, showed no significant differences between the two groups, reflecting comparable quality-of-life outcomes. Overall, these findings establish that Alyftrek provides an effective and non-inferior alternative to ELX/TEZ/IVA.

Exclusivity and Patents

No exclusivities or patents are currently listed.

Anktiva®

Nogapendekin alfa inbakicept-pmln solution, for intravesical use

Fast Facts	
BLA Holder	Altor Bioscience, LLC
Product Presentation	Solution for intravesical injection
Route of Administration	Intravesical (intra bladder)
BLA Approval	April 22, 2024*
ODE	No
Mechanism of action	Interleukin-15 (IL-15) receptor agonist

*BLA exclusivity is typically granted for 12 years from date of approval

Indication

Anktiva, in combination with Bacillus Calmette-Guérin (BCG), is approved for the treatment of adult patients with BCG-unresponsive non-muscle invasive bladder cancer (NMIBC) who have carcinoma in situ (CIS), with or without accompanying papillary tumors.

Description

Nogapendekin alfa inbakicept-pmln is an interleukin-15 (IL-15) receptor agonist. It is a soluble protein complex composed of two components: (a) nogapendekin alfa, a human IL-15N72D variant containing 114 amino acids, and (b) inbakicept, a fusion protein consisting of a dimeric human IL-15Rα sushi domain (65 amino acids) linked to a human IgG1 Fc region (232 amino acids). Each nogapendekin alfa inbakicept-pmln complex

comprises one inbakicept molecule and two nogapendekin alfa molecules, with each IL-15N72D variant binding to one of the IL-15Rα sushi domains.

The recombinant protein complex is produced in a CHO-K1 cell line that has been transfected with plasmids encoding the genes for IL-15N72D and the IL-15RαSu/IgG1 Fc fusion protein. The molecular weight of the deglycosylated nogapendekin alfa inbakicept-pmln complex is 92,106.5 Da. The deglycosylated molecular weights of the individual subunits are 66,565.6 Da for the IL-15RαSu/IgG1 Fc dimer and 12,770.45 Da for the IL-15N72D domain.

Dosage Form and Handling

Anktiva (nogapendekin alfa inbakicept-pmln) is supplied as a solution in a single-dose vial containing 400 mcg in 0.4 mL, intended for intravesical administration after dilution with normal saline (containing the BCG suspension for administration).

Each vial is formulated with dibasic sodium phosphate (0.57 mg), monobasic potassium phosphate (0.54 mg), sodium chloride (3.27 mg), and Water for Injection, USP. Hydrochloric acid and sodium hydroxide are added to adjust the pH to 7.4.

Vials should be stored refrigerated at 2°C to 8°C in the original carton to protect them from light.

Dosing Regimen

Anktiva is administered intravesically at a dose of 400 mcg in combination with BCG for both induction and maintenance therapy. For induction, it is given once weekly for six weeks, with an option for a second induction course if a complete response is not achieved by month 3.

For maintenance therapy, Anktiva is administered once weekly for three weeks at months 4, 7, 10, 13, and 19 (totaling 15 doses) following the induction phase. Patients with a sustained complete response may receive additional BCG maintenance instillations once weekly for three weeks at months 25, 31, and 37, with a maximum of nine additional doses. Treatment continues until disease persistence after the second induction, recurrence or progression, unacceptable toxicity, or a maximum duration of 37 months.

Mechanism of Action

Nogapendekin alfa inbakicept-pmln binds to the IL-15 receptor complex, leading to the proliferation and activation of NK cells, CD8+ T cells, and memory T cells while avoiding the proliferation of immunosuppressive T regulatory (Treg) cells. In vivo studies using a carcinogen-induced bladder cancer model in immunocompetent rats demonstrated that intravesical administration of nogapendekin alfa inbakicept-pmln, either alone or in combination with BCG, resulted in enhanced anti-tumor activity compared to BCG alone.

Pharmacokinetics

Systemic exposure to nogapendekin alfa inbakicept-pmln was less than 100 pg/mL (the quantitation limit) in all patients receiving the approved recommended dosage.

There is insufficient data to fully characterize the anti-drug antibody response to Anktiva or to assess the impact of anti-drug antibodies on pharmacokinetics, pharmacodynamics, safety, or efficacy.

Clinical Studies

The efficacy of Anktiva was assessed in the QUILT-3.032 trial, a single-arm, multicenter study involving 77 adult patients with BCG-unresponsive, high-risk non-muscle invasive

bladder cancer (NMIBC) with carcinoma in situ (CIS), with or without Ta or T1 papillary disease following transurethral resection of bladder tumor (TURBT).

Patients received Anktiva combined with BCG weekly for six consecutive weeks during induction, followed by maintenance therapy administered weekly for three weeks at months 4, 7, 10, 13, and 19, totaling 15 doses.

Patients with an ongoing complete response (CR) at month 25 could continue receiving maintenance therapy at months 25, 31, and 37. Routine monitoring included cytology, cystoscopy, and random biopsies as needed.

Key efficacy outcomes focused on CR at defined time points. A second induction course was administered to 31% of patients. In the QUILT-3.032 trial, Anktiva combined with BCG demonstrated a CR rate of 62% (95% CI: 51%, 73%). The duration of response varied from 0 to over 47 months (ongoing). Of the 48 patients who achieved a CR at any time, 58% (28 patients) maintained their response for at least 12 months, and 40% (19 patients) maintained their response for at least 24 months.

Exclusivity and Patents

No exclusivities or patents currently listed.

Aqneursa™

Levacetylleucine for oral suspension

Fast Facts	
NDA Holder	IntraBio Inc.
Product Presentation	Granules for suspension
Route of Administration	Oral
NDA Original Approval	September 24, 2024
NCE Exclusivity	September 24, 2029
ODE	Yes, exclusivity ending September 24, 2031
Mechanism of action	Unknown

Indication

Aqnuersa™ is approved for the treatment of neurological symptoms associated with Niemann-Pick disease type C (NPC) in adults and pediatric patients weighing 15 kg or more.

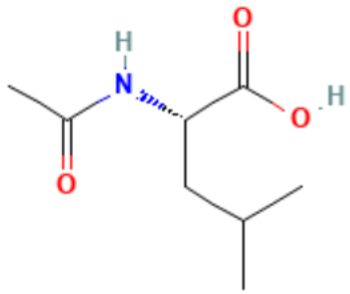
Dosage Form and Handling

Aqneursa™ (levacetylleucine) for oral suspension is supplied as white to off-white granules in a unit-dose, multi-layer aluminum/polyethylene packet. Each packet contains 1.7 grams of granules, equivalent to 1 gram of levacetylleucine. The formulation includes the inactive ingredients hypromellose, isomalt, and strawberry flavor. The drug product should be stored at room temperature (20°C to 25°C), with permissible excursions between 15°C and 30°C.

For oral administration, Aqnuersa™ packets should be opened and mixed with 40 mL of water, orange juice, or almond milk (avoiding hot liquids), then stirred to form a suspension. The mixture must be consumed within 30 minutes, and any unused portion should be discarded. If needed, Aqnuersa™ can also be administered via a feeding tube by preparing the suspension as directed and delivering the dose with an appropriate syringe.

Description

Levacetylleucine has a molecular weight of 173.21. Its chemical structure is shown below:



Dosing Regimen

Aqnuersa™ (levacetylleucine) dosage is based on the patient's body weight and is administered orally up to three times daily. Patients weighing between 15 kg and less than 25 kg should take 1 gram in the morning and 1 gram in the evening, with no afternoon dose. Those weighing 25 kg to less than 35 kg should take 1 gram in the morning, 1 gram in the afternoon, and 1 gram in the evening. Patients weighing 35 kg or more require 2 grams in the morning, 1 gram in the afternoon, and 1 gram in the evening. The medication may be taken with or without food.

Mechanism of Action

The specific molecular target of levacetylleucine in treating NPC remains unknown.

Pharmacokinetics

Levacetylleucine reaches peak concentration (Cmax) in approximately 1 hour, with no accumulation observed after repeated dosing. It has an apparent volume of distribution of 253 L, a half-life of about 1 hour, and a clearance rate of 139 L/h. Metabolism occurs via non-CYP450 enzymes, producing acetate and L-leucine. Pharmacokinetics are consistent across age, gender, and race; however, data on effects in renal or hepatic impairment and pregnancy are lacking. Clearance and distribution increase with body weight, but weight-based dosing compensates for these variations. Levacetylleucine does not inhibit major CYP450 enzymes and interacts with certain transporters, including OAT1 and OAT3, while inhibiting P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP).

Clinical Studies

The clinical efficacy and safety of Aqnuersa™ for treating Niemann-Pick disease type C (NPC) were evaluated in a randomized, double-blind, placebo-controlled, two-period crossover study. The trial enrolled 60 patients aged four years and older with confirmed NPC diagnosis and mild neurological symptoms. Participants were randomized into two sequences: one group received Aqnuersa™ first, then placebo; the other received placebo first, then Aqnuersa™, with each treatment period lasting 12 weeks.

Patients aged 13 years and older received a total daily dose of 4 grams, while dosing for pediatric patients under 13 years was weight-based. Of the 60 participants, 59 (98%) completed the study. The majority (85%) had been treated with miglustat prior to and during the study.

The primary outcome was assessed using the Functional Scale for Assessment and Rating of Ataxia (fSARA), which evaluates gait, sitting, stance, and speech disturbance domains of the original SARA. The estimated mean fSARA score was 5.1 with Aqnuersa™ and 5.6 with placebo, yielding a treatment difference of -0.4 (95% CI: -0.7, -0.2; $p < 0.001$).

Patients in Treatment Sequence 1, who received Aqnuersa™ in Period I followed by placebo in Period II, showed a mean change in fSARA score from baseline of -0.5 (SD 1.2) during Period I. After switching to placebo in Period II, the mean change was 0 (SD 1.5).

Patients in Treatment Sequence 2, who received placebo in Period I followed by Aqnuersa™ in Period II, had a mean change from baseline of -0.3 (SD 0.9) in Period I and -0.7 (SD 0.9) during Period II.

The fSARA total score plot over time demonstrated a decreasing trend in fSARA scores for Aqnuersa™, while scores in the placebo group remained stable or slightly increased.

Exclusivity and Patents

One New Chemical Entity (NCE) exclusivity is listed in the Orange Book, expiring on September 24, 2029. Additionally, Orphan Drug Exclusivity (ODE) is also listed, expiring on September 24, 2031, for the treatment of neurological manifestations of Niemann-Pick disease type C (NPC) in adults and pediatric patients weighing greater than or equal to 15 kg. No patents are currently listed in the Orange Book.

Atturby™

Acoramidis tablets, for oral administration

Fast Facts	
NDA Holder	BridgeBio Pharma Inc.
Product Presentation	Tablet
Route of Administration	Oral
NDA Original Approval	November 22, 2024
NCE Exclusivity	November 22, 2029
ODE	Yes, exclusivity ending November 22, 2031
Mechanism of action	A selective transthyretin (TTR) stabilizer

Indication

Attruby™ is prescribed for adults with cardiomyopathy caused by wild-type or variant transthyretin-mediated amyloidosis (ATTR-CM) to reduce the risk of cardiovascular death and hospitalization related to cardiovascular conditions.

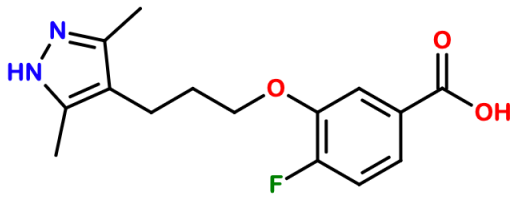
Dosage Form and Handling

Attruby™ (acoramidis) is available as a 356 mg white, film-coated, oval tablet. Each tablet contains acoramidis and is packaged in blister cards, with 28 tablets per card and four cards per carton. Attruby™ should be stored at a controlled room temperature of 20°C to 25°C, with permissible excursions between 15°C and 30°C. To protect against moisture, tablets should remain in their original blister packaging until use.

The inactive ingredients include croscarmellose sodium, magnesium stearate, microcrystalline cellulose, and silicon dioxide. The film coating and printing ink consist of black iron oxide, glyceryl monocaprylocaprate, hypromellose, polyvinyl alcohol, propylene glycol, talc, titanium dioxide, and vinyl alcohol graft copolymer.

Description

Acoramidis hydrochloride (HCl) has a molecular weight of 328.77 g/mol. The chemical structure of the free base form is shown below:



Dosing Regimen

The recommended dose of Attruby™ is 712 mg, administered orally twice daily, with or without food.

Mechanism of Action

Acoramidis is a selective transthyretin (TTR) stabilizer that binds to TTR at the thyroxine-binding sites, reducing the dissociation of the TTR tetramer into monomers— the rate-limiting step in amyloid formation.

Pharmacokinetics

Systemic exposure (Cmax and AUC) to acoramidis increased in a less-than-dose-proportional manner following single and multiple doses across the 89–712 mg twice-daily range. Steady-state concentrations were achieved within four days, with approximately 1.3-fold accumulation observed at the recommended dose. Following oral administration, peak plasma concentrations (Tmax) occurred at approximately one hour. Food intake did not

significantly affect pharmacokinetics, except for minor variations when administered with a high-fat meal.

Acoramidis exhibits an apparent steady-state volume of distribution of 654 liters. Plasma protein binding is approximately 96%, primarily to transthyretin (TTR). The drug is eliminated with an effective half-life of about six hours and a steady-state apparent clearance of 16 L/hr.

Metabolism occurs predominantly via glucuronidation by the UGT1A9, UGT1A1, and UGT2B7 enzymes. The primary metabolite, acoramidis-β-D-glucuronide (acoramidis-AG), accounts for approximately 8% of circulating drug-related moieties and is about one-third as pharmacologically active as the parent compound, contributing minimally to overall activity.

Population pharmacokinetic analyses show no significant differences in acoramidis exposure based on age, race/ethnicity, or renal impairment. However, the effects of hepatic impairment on pharmacokinetics remain unknown.

Drug interaction studies indicate that acoramidis does not significantly alter the exposure of the organic anion transporter-1 (OAT1) substrate cefuroxime. Co-administration with diuretics does not impact steady-state plasma concentrations. In vitro, acoramidis is a substrate of CYP2C9 but neither inhibits nor induces major cytochrome P450 enzymes, including CYP1A2, CYP2B6, CYP2C8, CYP2C19, CYP2D6, or CYP3A4/5. It is also a substrate of OAT1 and the breast cancer resistance protein (BCRP), but it does not inhibit key transporters such as MATE1, OCT2, OATP1B1, OATP1B3, MATE2-K, BCRP, P-gp, or BSEP. These data suggest a low potential for clinically meaningful drug-drug interactions.

Clinical Studies

The efficacy of Attruby™ was evaluated in a multicenter, international, randomized, double-blind, placebo-controlled study involving 611 adult patients with wild-type or variant (hereditary or de novo) ATTR-CM. Participants were randomly assigned in a 2:1 ratio to receive Attruby™ 712 mg (n = 409) or placebo (n = 202) twice daily for 30 months. After 12 months, 61 patients (14.9%) in the Attruby™ group and 46 patients (22.8%) in the placebo group received open-label tafamidis. The median duration of tafamidis use among these patients was 17 months.

The primary composite efficacy endpoint included all-cause mortality (ACM) and the cumulative frequency of cardiovascular-related hospitalizations (CVH) over 30 months. The stratified Finkelstein-Schoenfeld (F-S) test demonstrated a statistically significant reduction in ACM and CVH in the Attruby™ group compared to placebo ($p = 0.018$ and $p = 0.002$, respectively). All-cause mortality (ACM) occurred in 19% of patients receiving Attruby™ compared to 26% of those on placebo, with cardiovascular causes accounting for 79% of deaths. Cardiovascular-related hospitalizations (CVH) were reported in 27% of Attruby™-treated patients and 43% of placebo patients, with event rates of 0.6 and 0.8 per year, respectively. The majority (59%) of CVH events were due to heart failure, resulting in hospitalization in 13% of patients treated with Attruby™ versus 26% in the placebo group.

Functional capacity and health status were assessed using the 6-minute walk distance (6MWD) test and the Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS) score. At month 30, the least squares mean difference (95% CI) in change from baseline in 6MWD was 40 meters (21 to 58; $p < 0.0001$), while the change from baseline in KCCQ-OS was 16 points (9 to 14; $p < 0.0001$).

A Cox regression analysis showed a 35.5% reduction in the risk of ACM or first CVH hospitalization with Attruby™ treatment, with a hazard ratio of 0.645 (95% CI: 0.500 - 0.832).

A Kaplan-Meier plot demonstrated a higher event-free probability in the Attruby™ group compared to the placebo group over 30 months. Additionally, a Win-Ratio analysis for ACM and CVH showed an overall win ratio of 1.5 (95% CI: 1.1 - 2.0), favoring Attruby™.

Exclusivity and Patents

One New Chemical Entity (NCE) exclusivity is listed in the Orange Book, expiring on November 22, 2029. Additionally, one Orphan Drug Exclusivity (ODE) is listed for indication ODE-506*, expiring on November 22, 2031. The patents listed in the Orange Book are summarized in Table 1 (Appendix A).

*ODE-506: Treatment of the cardiomyopathy of wild-type or variant transthyretin-mediated amyloidosis (ATTR-CM) in adults to reduce cardiovascular death and cardiovascular-related hospitalization.

Bizengri®

Zenocutuzumab-zbco injection, for intravenous use

Fast Facts	
BLA Holder	Merus N.V.
Product Presentation	Injection solution
Route of Administration	Intravenous
BLA Approval	December 4, 2024 (New Biological Entity)* Accelerated Approval
ODE	December 4, 2031
Mechanism of action	A bispecific antibody that inhibits HER2:HER3 dimerization and prevents NRG1 binding to HER3, inhibiting tumor cell signaling. First-in-class

**BLA exclusivity is typically granted for 12 years from date of approval

Indication

Bizengri is approved for the treatment of adults with advanced, unresectable, or metastatic non-small cell lung cancer (NSCLC) harboring a neuregulin 1 (NRG1) gene fusion, who have experienced disease progression following prior systemic therapy.

Boxed Warning

Exposure to Bizengri during pregnancy can cause embryo-fetal harm. Patients should be advised of this risk and the need to use effective contraception.

Dosage Form and Handling

Bizengri is supplied as a sterile, preservative-free injection for intravenous infusion in single-dose vials. Each vial contains 375 mg of *zenocutuzumab-zbco* in 18.75 mL (20 mg/mL) of bizengri, and a full dose consists of two vials packaged together in a single carton. Dilution is required prior to intravenous administration.

Each vial also contains the following inactive ingredients: histidine (34.9 mg), L-histidine hydrochloride monohydrate (51.1 mg), polysorbate 20 (3.7 mg), trehalose (1412 mg), and water for injection.

Store refrigerated at 2°C to 8°C in the original carton to protect from light. Do not freeze or shake.

Description

Zenocutuzumab-zbco is a low-fucose, humanized, full-length immunoglobulin G1 (IgG1) bispecific antibody targeting HER2 and HER3. It has a molecular weight of approximately 146 kDa and is produced in the CHO cell line.

Dosing Regimen

The recommended dosage of Bizengri is 750 mg administered as an intravenous (IV) infusion every two weeks until disease progression or unacceptable toxicity occurs. Premedications should be administered prior to each Bizengri infusion as recommended to reduce the risk of infusion-related reactions.

Mechanism of Action

Zenocutuzumab-zbco is a bispecific antibody that binds to the extracellular domains of HER2 and HER3, which are expressed on the surface of cells, including tumor cells. It inhibits HER2:HER3 dimerization and prevents neuregulin 1 (NRG1) from binding to

HER3. Consequently, zenocutuzumab-zbco reduces cell proliferation and suppresses signaling through the phosphoinositide 3-kinase (PI3K)-AKT-mammalian target of rapamycin (mTOR) pathway.

Additionally, it mediates antibody-dependent cellular cytotoxicity (ADCC). In mouse models of NRG1 fusion-positive lung and pancreatic cancers, Zenocutuzumab-zbco demonstrated antitumor activity.

Pharmacokinetics

Zenocutuzumab-zbco exposure increases proportionally over a dose range of 480 mg (0.6 times the approved recommended dose) to 900 mg (1.2 times the approved recommended dose). The median time to reach steady-state concentrations is eight weeks, with a median accumulation ratio of 1.6-fold at the approved recommended dose.

Zenocutuzumab-zbco has a volume of distribution of 6 L (CV 18%). The steady-state half-life is 8 days (±1.3 days), and clearance is 22 mL/h (CV 37%). It is expected to be metabolized into small peptides via catabolic pathways.

No clinically significant differences in the pharmacokinetics of zenocutuzumab-zbco were observed based on age, sex, race, body weight, albumin level, mild or moderate renal impairment, or mild hepatic impairment. The pharmacokinetics in patients with moderate to severe hepatic impairment or severe renal impairment remain unknown.

Among patients who received Bizengri at the approved recommended dose for up to 30 months, 7 of 153 (4.6%) developed anti-zenocutuzumab antibodies. Due to the low incidence of anti-drug antibodies, their effect on the pharmacokinetics, pharmacodynamics, safety, and efficacy of zenocutuzumab is unknown.

Clinical Studies

The efficacy of Bizengri was evaluated in the eNRGy study, a multicenter, open-label, multi-cohort clinical trial. The study enrolled adult patients with advanced or metastatic NRG1 fusion-positive NSCLC who had experienced disease progression following standard-of-care treatment. Patients received Bizengri as an intravenous infusion of 750 mg every two weeks until disease progression or unacceptable toxicity. Tumor assessments were conducted every eight weeks. Key efficacy endpoints included overall response rate (ORR) and duration of response (DOR), confirmed by blinded independent central review (BICR) based on RECIST v1.1 criteria.

NSCLC:

The ORR for Bizengri in previously treated NRG1 fusion-positive NSCLC (n = 64), the ORR was 33% (95% CI: 22%, 46%), comprising a complete response rate of 1.6% and a partial response rate of 31%. The median DOR was 7.4 months (95% CI: 4.0, 16.6), with 43% of responders maintaining a DOR of at least six months.

The efficacy of Bizengri was also evaluated by NRG1 fusion partners. Among patients with the CD74 fusion partner (n = 37), the ORR was 32% (95% CI: 18%, 50%), with a duration of response (DOR) ranging from 1.8+ to 20.3+ months. For those with the SLC3A2 fusion partner (n = 14), the ORR was 36% (95% CI: 13%, 65%), with a DOR range of 3.6+ to 20.8+ months. Patients harboring the SDC4 fusion partner (n = 7) achieved an ORR of 29% (95% CI: 3.7%, 71%), with DORs ranging from 7.4+ to 16.6 months. Other fusion partners, including FUT10, PVALB, and ST14, were associated with progressive disease or had insufficient response data.

Pancreatic Adenocarcinoma:

The eNRGy study also evaluated the efficacy of Bizengri in 30 adult patients with advanced or metastatic NRG1 fusion-positive pancreatic adenocarcinoma. Patients received Bizengri 750 mg intravenously every two weeks, with tumor assessments conducted every eight weeks. Efficacy was evaluated using overall response rate (ORR) and duration of response (DOR), confirmed by blinded independent central review (BICR) based on RECIST v1.1 criteria.

In this cohort, the ORR was 40% (95% CI: 23%, 59%), including a complete response rate of 3.3% and a partial response rate of 37%. The DOR ranged from 3.7 to 16.6 months, with 67% of responders maintaining a DOR of at least six months.

Efficacy also varied by NRG1 fusion partner. Among patients with the ATP1B1 fusion partner (n = 14), the ORR was 50% (95% CI: 23%, 77%), with a DOR ranging from 3.7 to 16.6 months. For those with the SLC4A4 partner (n = 3), the ORR was 67% (95% CI: 9%, 99%), with ongoing DORs of 7.5+ and 15.2+ months. Patients harboring the NOTCH2 partner (n = 3) had an ORR of 33% (95% CI: 0.8%, 91%), with a DOR of 7.4+ months. Partial responses were also observed in patients with AGRN and APP fusion partners, with DORs of 9.1+ and 3.7 months, respectively. Fusion partners such as CD44, CDH1, SDC4, THBS1, and VTCN1 were associated with stable or progressive disease outcomes. The "+" symbol indicates ongoing responses at the time of analysis.

Exclusivity and Patents

No exclusivities or patents are currently listed**.**

Cobenfy™

Xanomeline and trospium chloride capsules, for oral use

Fast Facts	
NDA Holder	Bristol Myers-Squibb
Product Presentation	Capsules
Route of Administration	Oral
NDA Original Approval	September 26, 2024
NCE Exclusivity	September 26, 2029
ODE	No
Mechanism of action	A combination of central muscarinic acetylcholine agonist and peripheral muscarinic antagonist activity

Indication

Cobenfy™ is indicated for the treatment of schizophrenia in adults.

Dosage Form and Handling

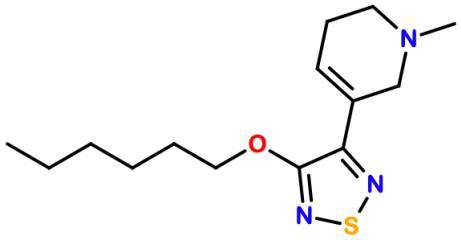
Cobenfy™ is available in capsule form in three dosage strengths: 50 mg/20 mg, 100 mg/20 mg, and 125 mg/30 mg of xanomeline/trospium chloride. It should be stored at a temperature of 20°C to 25°C, with permitted excursions between 15°C and 30°C. Each Cobenfy™ capsule contains a combination of xanomeline pellets and trospium chloride pellets. The xanomeline tartrate pellets include ascorbic acid, microcrystalline cellulose, and talc, while the trospium chloride pellets contain lactose monohydrate, microcrystalline

cellulose, and talc. The capsules also contain hypromellose, red iron oxide, titanium dioxide, and yellow iron oxide (the latter two present only in the 50 mg/20 mg and 100 mg/20 mg strengths).

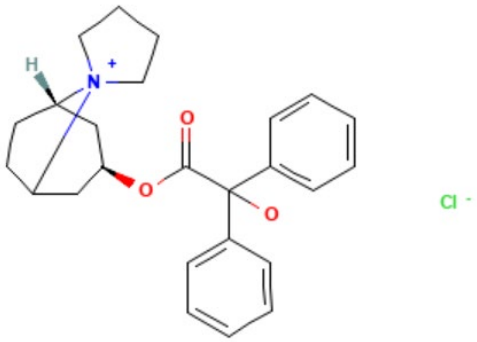
Description

Cobenfy™ is a combination therapy consisting of xanomeline, a muscarinic agonist, and trospium chloride, a muscarinic antagonist.

Xanomeline tartrate has a molecular weight of 431.51 g/mol. The chemical structure of the free base form is:



Trospium chloride has a molecular weight of 427.96 g/mol. Its chemical structure is:



Dosing Regimen

The recommended dosage of Cobenfy™ begins at 50 mg/20 mg (xanomeline/trospium chloride) orally twice daily for at least two days. The dose is then increased to 100 mg/20 mg twice daily for at least five days. Based on patient

tolerability, the dose may be further increased to 125 mg/30 mg twice daily, which is the maximum recommended dose. Cobenfy™ should be taken at least one hour before or two hours after a meal.

Mechanism of Action

The mechanism of action of xanomeline in the treatment of schizophrenia is not fully understood; however, its efficacy is believed to result from its agonist activity at M1 and M4 muscarinic acetylcholine receptors in the central nervous system.

Trospium chloride is a muscarinic antagonist that primarily antagonizes muscarinic receptors in peripheral tissues.

Pharmacokinetics

Xanomeline exposure increases more than proportionally when the dose escalates from 100 mg/20 mg to 125 mg/30 mg twice daily, while trospium exposure increases proportionally. Both drugs reach steady-state in 3 to 5 days. Peak plasma concentrations occur at ~2 hours for xanomeline and ~1 hour for trospium. Food does not significantly affect xanomeline absorption, but high-fat meals reduce trospium exposure by up to 90%. Xanomeline is metabolized by CYP2D6, other CYP450 enzymes, and flavin monooxygenases, while trospium is eliminated primarily via renal excretion.

Xanomeline has a central volume of distribution (oral) of 10,800 liters, with ~95% plasma protein binding, and a half-life of 5 hours. Trospium has a central volume of distribution of 531 liters, with ~80% plasma protein binding, and a half-life of 6 hours.

Pharmacokinetic changes occur with age, renal function, hepatic function, and body weight. Trospium exposure is ~60% higher in individuals aged 65 years and older. Renal impairment increases exposure, with moderate impairment leading to 2.4-fold higher

xanomeline and 2.9-fold higher trospium exposure, and greater increases observed in severe impairment. Mild hepatic impairment increases xanomeline exposure 2.8-fold, while severe impairment increases it by ≥7-fold. Trospium exposure in severe hepatic impairment has not been evaluated. Compared to individuals weighing 70 kg, those at 120 kg have 30–35% lower xanomeline and 20–31% lower trospium exposure.

Trospium undergoes active tubular secretion, and co-administered drugs using this pathway may compete, altering exposure. Metformin reduces trospium exposure by ~29–34%, with no change in metformin pharmacokinetics. CYP2D6 inhibitors increase xanomeline exposure. Xanomeline transiently inhibits P-gp and CYP3A4 in the intestine, increasing plasma concentrations of substrates, but does not systemically inhibit CYP3A4.

Clinical Studies

The efficacy of Cobenfy™ for the treatment of schizophrenia in adults was evaluated in two five-week, randomized, double-blind, placebo-controlled, multi-center studies (N = 470). Patients were diagnosed with schizophrenia based on DSM-5 criteria.

Patients initiated treatment with 50 mg/20 mg twice daily for the first two days, after which the dosage was increased to 100 mg/20 mg twice daily for the remainder of the first week. Beginning on Day 8, the dose was escalated to 125 mg/30 mg twice daily, provided it was tolerated. If a patient was unable to tolerate the higher dose, they were permitted to revert to 100 mg/20 mg twice daily for the rest of the study.

The primary efficacy measure was the change from baseline in Positive and Negative Syndrome Scale (PANSS) total score at Week 5. In Study 1, the mean change from baseline in PANSS total score was -21.2 (Standard Error, SE: 1.7) for the Cobenfy™ group and -11.6 (SE: 1.6) for the placebo group, with a placebo-subtracted difference of -9.6 (95% CI:

-13.9, -5.2). In Study 2, the mean change from baseline was -20.6 (SE: 1.6) for Cobenfy™ and -12.2 (SE: 1.6) for placebo, with a placebo-subtracted difference of -8.4 (95% CI: -12.4, -4.3).

The secondary endpoint, change in Clinical Global Impression–Severity (CGI-S) score at Week 5, showed a statistically significant difference in Study 1 for cobenfy™ compared to placebo. The examination of subgroups by age, sex, and race did not suggest differences in response, though there were no patients over 65 years of age in the studies.

Exclusivity and Patents

One New Chemical Entity (NCE) exclusivity is listed in the Orange Book, expiring on September 27, 2029. The patents listed in the Orange Book are summarized in Table 2 (Appendix A).

Crennesity™

Crinecerfont capsules, for oral use

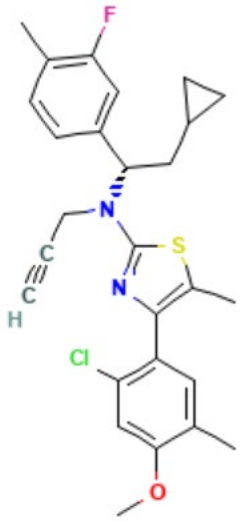
Fast Facts	
NDA Holder	Neurocrine Biosciences Inc.
Product Presentation	Capsules, Oral Solution
Route of Administration	Oral
NDA Approval	December 13, 2024 (New Molecular Entity)
NCE Exclusivity	December 13, 2029
ODE	December 13, 2031
Mechanism of action	A selective corticotropin-releasing factor type 1 receptor antagonist. First-in-class

Indication

Crenessity™ is approved as an adjunct therapy to glucocorticoid replacement for managing androgen levels in adults and children aged 4 and older with classic congenital adrenal hyperplasia (CAH).

Description

Crinecerfont has a molecular weight of 483.04 g/mol. Its chemical structure is as follows:



Dosage Form and Handling

Crenessity™ is available as oral capsules in strengths of 25 mg, 50 mg, and 100 mg, packaged in HDPE bottles. Each capsule contains 25 mg, 50 mg, or 100 mg of crinecerfont free base, along with inactive ingredients such as lauroyl polyoxyl-32 glycerides, medium-chain triglycerides, propylene glycol dicaprylate/dicaprate, and vitamin E polyethylene glycol succinate.

Crenessity™ is also available as an oral solution containing 50 mg/mL of crinecerfont free base, packaged in a PET bottle. The oral solution includes inactive ingredients such as butylated hydroxytoluene, medium-chain triglycerides, oleoyl polyoxyl glycerides, orange flavor, and saccharin.

Crenessity™ capsules should be stored at 15°C to 25°C. Unopened bottles of the oral solution must be stored upright under refrigeration at 2°C to 8°C. Once opened, the solution may be stored either refrigerated (2°C to 8°C) or at room temperature (15°C to 25°C) for up to 30 days, provided it remains upright. Do not freeze.

Dosing Regimen

The recommended dosage of Crenessity™ for adults is 100 mg taken orally twice daily, with a meal in the morning and evening. For pediatric patients aged 4 years and older, the dosage is based on body weight and is also administered orally twice daily with meals - once in the morning and once in the evening.

For children weighing 10 kg to less than 20 kg, the recommended dose is 25 mg twice daily. For those weighing 20 kg to less than 55 kg, the dose is 50 mg twice daily. For children weighing 55 kg or more, the recommended dose is 100 mg twice daily.

Mechanism of Action

Crinecerfont is a selective corticotropin-releasing factor (CRF) type 1 receptor antagonist that blocks CRF from binding to CRF type 1 receptors in the pituitary. This inhibition reduces the secretion of adrenocorticotropic hormone (ACTH), thereby decreasing ACTH-mediated adrenal androgen production.

Pharmacokinetics

The pharmacokinetics of crinecerfont are characterized by dose-proportional increases in maximum plasma concentration (Cmax) and area under the curve (AUC) across the approved dosing range. Steady-state concentrations are achieved approximately seven days after daily administration, with an accumulation ratio of 1.4. Following oral administration, the median time to reach Cmax is approximately four hours. No clinically relevant differences have been observed between Crenessity™ oral capsules and the oral solution.

When Crenessity™ capsules were administered with a high-fat meal (800 to 1000 calories, 50% fat), crinecerfont Cmax increased 4.9-fold and AUC increased 3.3-fold compared to fasted conditions. Similarly, administration of the oral solution with a high-fat meal

resulted in an 8.6-fold increase in Cmax and an 8.3-fold increase in AUC compared to the fasted state.

In adults with classic congenital adrenal hyperplasia (CAH), the mean apparent volume of distribution of crinecerfont is 852 L (CV 31%). Plasma protein binding is ≥99.9%. The effective half-life is approximately 14 hours, with a mean apparent clearance of 3.5 L/h (CV: 37%). Crinecerfont is primarily metabolized via the CYP3A4 enzyme, with minor contributions from CYP2B6. CYP2C8 and CYP2C19 may also play a role.

Pharmacokinetic analyses revealed no clinically significant differences based on age, sex, race, or in patients with mild to severe hepatic impairment or mild to moderate renal impairment. However, crinecerfont has not been studied in patients with severe renal impairment or end-stage renal disease.

Co-administration of crinecerfont with rifampin (a CYP3A4 inducer) reduced Cmax by 23% and AUC by 62%. Conversely, ketoconazole (a CYP3A4 inhibitor) increased Cmax by 25% and AUC by 45%. Crinecerfont had no significant effect on the pharmacokinetics of midazolam (a CYP3A4 substrate) or oral contraceptives containing ethinyl estradiol and levonorgestrel.

In vitro studies indicate that crinecerfont does not inhibit or induce cytochrome P450 enzymes or affect key transporter systems, suggesting a low potential for metabolic or transporter-mediated drug interactions.

Clinical studies

Adults and Pediatric Patients:

The efficacy of Crenessity™ in reducing androgen levels and enabling glucocorticoid dose reduction while maintaining androgen control was evaluated in two randomized, double-

blind, placebo-controlled trials: Study 1 (NCT#04490915) in adults and Study 2 (NCT#04806451) in pediatric patients with classic congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency. Both studies enrolled patients receiving supraphysiological doses of glucocorticoids who had either normal-range or inadequately controlled androgen levels.

In Study 1, 182 adults were randomized to receive Crenessity™ 100 mg twice daily (N=122) or placebo (N=60) for 24 weeks. In Study 2, 103 pediatric patients aged 4 to 17 years were assigned to a weight-based dosing regimen. Patients weighing less than 55 kg received 50 mg twice daily (oral solution), with 37 in the Crenessity™ group and 14 in the placebo group. Those weighing 55 kg or more received 100 mg twice daily (capsules), with 32 in the Crenessity™ group and 20 in the placebo group.

During the initial four-week period, patients in both studies continued their baseline glucocorticoid regimen, with adjustments permitted only for stress dosing. After Week 4, glucocorticoid doses were gradually tapered while maintaining androstenedione control, according to study-specific protocols. In Study 1 (adults), dose adjustments began at Week 4, targeting 8 to 10 mg/m²/day (hydrocortisone equivalents) by Week 12, with further modifications through Week 24 as needed. In Study 2 (pediatrics), reductions occurred every four weeks from Weeks 4 to 20, aiming to reach the target dose by Week 28.

Efficacy Outcomes:

At Week 24 in adults, the least squares (LS) mean percent reduction in glucocorticoid dose was −27% in the Crenessity™ group compared to −10% in the placebo group. A significantly greater proportion of Crenessity™-treated patients (63%) achieved a physiologic glucocorticoid dose (≤11 mg/m²/day) while maintaining androstenedione

control (≤120% of baseline or ≤ULN), compared to 18% in the placebo group ($p < 0.0001$). The placebo-subtracted LS mean difference in glucocorticoid dose reduction was −17% (95% CI: −24.1 to −10.1).

At Week 28 in pediatric patients, the LS mean percent change in daily glucocorticoid dose, while maintaining androstenedione control, was −18% in the Crenessity™ group versus a 6% increase in the placebo group. The placebo-subtracted LS mean difference was −24% (95% CI: −34.2 to −14.0, $p < 0.0001$).

At Week 4, following a stable glucocorticoid regimen, the LS mean change in serum androstenedione was −299 ng/dL in the Crenessity™ group compared to an increase of 46 ng/dL in the placebo group among adults. In pediatric patients, the LS mean reduction in serum androstenedione was −197 ng/dL in the Crenessity™ group versus an increase of 71 ng/dL in the placebo group. The placebo-subtracted LS mean difference was −345 ng/dL ($p < 0.0001$) in adults and −268 ng/dL ($p = 0.0003$) in pediatrics.

Additionally, at Week 4 in pediatric patients, the LS mean reduction in serum 17-hydroxyprogesterone was −5865 ng/dL in the Crenessity™ group compared to an increase of 556 ng/dL in the placebo group. The placebo-subtracted LS mean difference was −6421 ng/dL (95% CI: −8387 to −4454, $p < 0.0001$).

Exclusivity and Patents

An NCE exclusivity, expiring on December 13, 2029, and an Orphan Drug Exclusivity, expiring on December 13, 2031, are listed in the Orange Book. The patents listed in the Orange Book are summarized in Table 3 (Appendix A).

Duvyzat

Givinostat oral suspension

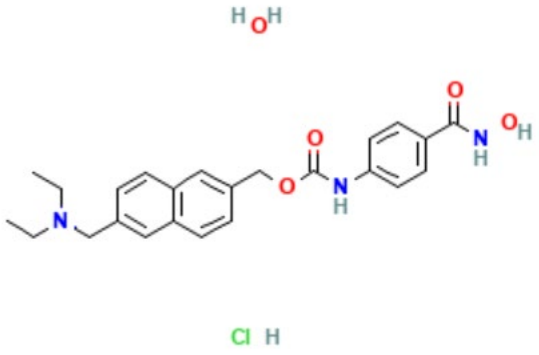
Fast Facts	
NDA Holder	Italfarmaco SPA.
Product Presentation	Oral suspension
Route of Administration	Oral
NDA Approval	March 21, 2024 (New Molecular Entity)
NCE Exclusivity	March 21, 2029
ODE	March 21, 2031
Mechanism of action	A histone deacetylase inhibitor First-in-class

Indication

Duvyzat is a histone deacetylase inhibitor indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients aged 6 years and older.

Description

Givinostat hydrochloride monohydrate has a molecular weight of 475.97 g/mol. Its chemical structure is:



Dosage Form and Handling

Duvyzat is an oral suspension containing 8.86 mg/mL of givinostat (equivalent to 10 mg/mL of givinostat hydrochloride monohydrate), packaged in an amber PET bottle. It includes inactive ingredients such as cream and peach flavors, glycerin, sorbitol solution, polysorbate 20, purified water, saccharin sodium, sodium benzoate, sodium hydroxide, tartaric acid, and tragacanth. The suspension should be stored at 20°C to 25°C, with permitted temperature excursions between 15°C and 30°C.

Dosing Regimen

Duvyzat is dosed twice daily with food based on body weight. The recommended dose for patients aged 6 years and older is 2.5 mL (for body weight 10–20 kg), 3.5 mL (20–40 kg), 5 mL (40–60 kg), and 6 mL (for body weight greater than 60 kg), taken twice daily with food.

Mechanism of Action

Duvyzat is a histone deacetylase inhibitor. The precise mechanism by which Duvyzat exerts its effect in patients with DMD is unknown.

Pharmacokinetics

Givinostat exhibits linear kinetics with dose-proportional exposure throughout the therapeutic dose range. Steady-state levels are achieved within 5 to 7 days, with less than a two-fold accumulation observed during twice-daily dosing. Following oral administration, peak plasma concentrations (Tmax) occur between 2 and 3 hours. A high-fat meal increases overall exposure by 40%, raises Cmax by 23%, and delays Tmax from 2 to 3 hours.

Givinostat is 96% bound to plasma proteins and demonstrates limited distribution into red blood cells (blood-to-plasma ratio = 1.3). It is extensively metabolized into inactive metabolites, with minimal unchanged drug excreted in urine. The plasma half-life is approximately 6 hours.

Body weight affects givinostat's pharmacokinetics, whereas age does not. Hepatic impairment may increase exposure, but renal impairment is unlikely to have a significant effect.

Givinostat is not metabolized by CYP450 or UGT enzymes and does not inhibit major CYP enzymes. However, it induces CYP1A2, 2B6, and 3A4. It interacts with P-gp and BCRP transporters and weakly inhibits OCT2. Clinical studies indicate a slight increase in midazolam exposure due to inhibition of intestinal CYP3A4. Strong P-gp inhibitors, such as clarithromycin, raise Cmax by approximately 40% without significantly affecting AUC. The impact of BCRP inhibitors is expected to be less pronounced than that of P-gp inhibitors.

Clinical Studies

The efficacy of Duvyzat was evaluated in a double-blind, placebo-controlled, 18-month study (Study 1; NCT02851797) involving 179 male patients aged six and older with

confirmed Duchenne muscular dystrophy (DMD). Patients were randomized 2:1 to receive either Duvyzat (n=118) or placebo (n=61), with weight-based dosing. All patients were ambulatory and maintained a stable corticosteroid regimen.

The primary efficacy measure was the change from baseline to 18 months in time to climb four stairs (4SC), a measure of muscle function. The primary analysis focused on a prespecified range of baseline fat fraction, measured by MR spectroscopy. Patients treated with Duvyzat showed a statistically significant smaller decline in 4SC time compared to placebo, with a treatment difference of –1.78 seconds (95% CI: –3.46, –0.11), p = 0.037.

A secondary efficacy endpoint was the change in physical function as assessed by the North Star Ambulatory Assessment (NSAA). Patients receiving Duvyzat experienced less decline in NSAA scores compared to placebo; however, this difference was nominally significant and did not reach statistical significance after prespecified multiplicity adjustment.

Exclusivity and Patents

An NCE exclusivity, expiring on March 21, 2029, and an Orphan Drug Exclusivity, expiring on March 21, 2031, are listed in the Orange Book. The patents listed in the Orange Book are summarized in Table 4 (Appendix A).

Ebglyss

Lebrikizumab-lbkz injection, for subcutaneous use

Fast Facts	
BLA Holder	Eli Lily and Company
Product Presentation	Prefilled syringe, Prefilled pen
Route of Administration	Subcutaneous
BLA Approval	September 13, 2024 (New Biological Entity)*
ODE	No
Mechanism of action	Inhibits IL-13-induced responses including proinflammatory cytokines

**BLA exclusivity is typically granted for 12 years from date of approval

Indication

Ebglyss is an interleukin-13 antagonist approved for the treatment of moderate-to-severe atopic dermatitis in adults and pediatric patients aged 12 years and older who weigh at least 40 kg. It is intended for patients whose condition is inadequately controlled with topical prescription therapies or for whom such therapies are unsuitable. Ebglyss may be used alone or in combination with topical corticosteroids.

Description

Lebrikizumab-lbkz, an interleukin-13 antagonist, is an immunoglobulin G4 (IgG4) monoclonal antibody that binds to interleukin-13 (IL-13) and inhibits its signaling.

Lebrikizumab-lbkz is produced in CHO) cells using recombinant DNA technology. It has an approximate molecular weight of 145 kDa.

Dosage Form and Handling

Ebglyss (lebrikizumab-lbkz) is a sterile solution for subcutaneous injection, available as a 250 mg/2 mL single-dose prefilled pen or syringe with a needle shield. The formulation contains glacial acetic acid, histidine, polysorbate 20, sucrose, and Water for Injection as inactive ingredients. It should be stored refrigerated at 2°C to 8°C but may be kept at room temperature up to 30°C for a maximum of 7 days in its original carton.

Dosing Regimen

The recommended dosage of Ebglyss is an initial dose of 500 mg at Week 0 and Week 2, followed by 250 mg every two weeks until Week 16 or later, once an adequate clinical response is achieved. The maintenance dose is 250 mg every four weeks thereafter.

Mechanism of Action

Lebrikizumab-lbkz is an IgG4 monoclonal antibody that binds interleukin-13 (IL-13) with high affinity and a slow dissociation rate. This binding allows IL-13 to interact with IL-13Rα1 while blocking its signaling through the IL-4Rα/IL-13Rα1 receptor complex. IL-13 is a cytokine associated with Type 2 inflammation, a key driver of atopic dermatitis pathogenesis. By inhibiting IL-13 activity, lebrikizumab-lbkz suppresses the release of proinflammatory cytokines, chemokines, and IgE. Additionally, IL-13 bound to lebrikizumab-lbkz retains the ability to bind IL-13Rα2, facilitating its internalization and clearance.

Pharmacokinetics

Lebrikizumab-lbkz exhibits dose-proportional pharmacokinetics across a subcutaneous dose range of 37.5 to 500 mg. Following a single 250 mg injection, peak serum concentrations are reached approximately 7 to 8 days post-dose, with a bioavailability of about 86%. The drug's volume of distribution is approximately 5.14 L.

Lebrikizumab-lbkz is metabolized via natural catabolic pathways similar to endogenous IgG, breaking down into small peptides and amino acids. It clears at a rate of 0.154 L/day and has a half-life of approximately 24.5 days.

Population pharmacokinetic analyses indicate that age, sex, and race do not significantly affect the pharmacokinetics of lebrikizumab-lbkz. However, individuals with higher body weight tend to have lower trough concentrations. Although no dedicated studies have been conducted in patients with renal or hepatic impairment, significant elimination through these pathways is not expected. Patients with mild to moderate renal impairment showed no clinically meaningful differences in drug pharmacokinetics.

Regarding immunogenicity, approximately 2.8% of patients on a regimen of 250 mg every two weeks—later switching to every four weeks for a year—developed anti-drug antibodies (ADA), most of which were neutralizing and detected at low levels. Pediatric patients treated under the same regimen exhibited similar results. The presence of ADA did not appear to affect drug levels, efficacy, or safety; however, the long-term clinical implications remain unclear due to the low incidence rate.

Clinical Studies

The efficacy of Ebglyss for moderate-to-severe atopic dermatitis was evaluated in three multicenter, randomized, double-blind, placebo-controlled trials (ADvocate 1, ADvocate 2, and ADhere), which enrolled 1,062 subjects aged 12 years and older. Disease severity

was assessed using the Investigator's Global Assessment (IGA) and the Eczema Area and Severity Index (EASI). Subjects received subcutaneous injections of 500 mg Ebglyss at Week 0 and Week 2, followed by 250 mg every two weeks (Q2W) or every four weeks (Q4W).

At Week 16, significantly more subjects treated with Ebglyss achieved clear or almost clear skin (IGA 0 or 1) with at least a 2-point improvement from baseline compared to placebo. In ADvocate 1, 43% of subjects (n = 283) receiving Ebglyss Q2W reached this endpoint versus 13% in the placebo group (n = 141), yielding a 30% difference (95% CI: 22%–38%). Similarly, in ADvocate 2, 33% of Ebglyss Q2W-treated subjects (n = 281) achieved IGA 0 or 1, compared to 11% in the placebo group (n = 146), representing a 22% difference (95% CI: 14%–30%).

For EASI-75 improvement, defined as at least a 75% reduction in disease severity, 59% of subjects in ADvocate 1 receiving Ebglyss achieved this endpoint compared to 16% in the placebo group (treatment difference: 42%; 95% CI: 33%–51%). In ADvocate 2, 52% of Ebglyss-treated subjects reached EASI-75, while only 18% of placebo-treated subjects met this criterion (treatment difference: 33%; 95% CI: 24%–42%).

EASI-90 improvement, indicating a 90% or greater reduction in disease severity, was also significantly higher in the Ebglyss groups. In ADvocate 1, 38% of subjects receiving Ebglyss achieved this level of clearance compared to 9% in the placebo group, a 29% difference (95% CI: 21%–36%). In ADvocate 2, 31% of Ebglyss-treated subjects reached EASI-90 versus 10% in the placebo group, with a 21% difference (95% CI: 13%–28%).

Pruritus improvement, measured by at least a 4-point reduction in the Numerical Rating Scale (NRS), was also significantly greater in the Ebglyss groups. In ADvocate 1, 46% of

Ebglyss-treated subjects experienced meaningful itch severity reduction compared to 13% in the placebo group, yielding a 33% difference (95% CI: 25%–41%). In ADvocate 2, 40% of subjects treated with Ebglyss achieved this level of improvement versus 12% in the placebo group, representing a 28% difference (95% CI: 20%–37%).

Responders at Week 16 were re-randomized to continue treatment through Week 52. In ADvocate 1, 76% of Q2W subjects maintained IGA 0 or 1 versus 47% for placebo, and 79% maintained EASI-75 versus 61% for placebo. In ADvocate 2, 65% maintained IGA 0 or 1 with Q2W compared to 50% for placebo, while 77% maintained EASI-75 versus 72% for placebo. The Q4W regimen showed similar or slightly better results than Q2W in both trials.

The ADhere trial, which assessed Ebglyss in combination with topical corticosteroids (TCS), demonstrated consistent results with the monotherapy trials. Subjects receiving Ebglyss plus TCS showed significant improvements in IGA and EASI scores compared to those receiving TCS alone, further supporting Ebglyss's efficacy in treating moderate-to-severe atopic dermatitis.

Exclusivity and Patents

No exclusivities or patents listed.

Ensacove™

Ensartinib capsules, for oral use

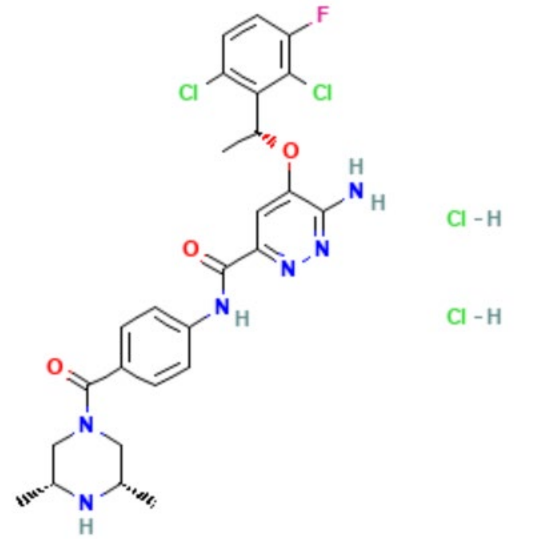
Fast Facts	
NDA Holder	Xcovery Holdings, Inc.
Product Presentation	Capsule
Route of Administration	Oral
NDA Approval	December 18, 2024 (New Molecular Entity)
NCE Exclusivity	December 18, 2029
ODE	None
Mechanism of action	ALK kinase inhibitor

Indication

Ensacove is approved for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive locally advanced or metastatic non-small cell lung cancer (NSCLC) who have not received prior ALK inhibitor therapy.

Description

Ensartinib dihydrochloride has a molecular weight of 634.4 g/mol. Its chemical structure is:



Dosage Form and Handling

Ensacove capsules, intended for oral administration, are available in two strengths: 25 mg and 100 mg of ensartinib. They are packaged in HDPE bottles and contain microcrystalline cellulose and stearic acid as inactive ingredients. The capsules should be stored at controlled room temperature between 20ºC and 25ºC, with allowable excursions from 15ºC to 30ºC.

Dosing Regimen

The recommended dosage of Ensacove is 225 mg orally once daily, with or without food.

Mechanism of Action

Ensartinib is a kinase inhibitor that targets anaplastic lymphoma kinase (ALK) along with other kinases, including MET and ROS1. It inhibits ALK phosphorylation and downstream signaling proteins such as AKT, ERK, and S6, thereby disrupting ALK-driven pathways. This inhibition reduces the proliferation of tumor cells harboring ALK fusions or mutations.

Pharmacokinetics

Ensartinib is absorbed with a median Tmax of 3 hours (range: 2 to 8 hours) at steady state, which is reached within 15 days, with an accumulation ratio of 2.7. No clinically significant differences in pharmacokinetics were observed when ensartinib was administered with a high-fat meal compared to fasting conditions.

The drug has an apparent volume of distribution of 1,720 L (CV 42%) and is 91.6% bound to human plasma proteins. Its elimination half-life (t½) at steady state is approximately 30 hours (CV 20%). Ensartinib is primarily metabolized by CYP3A.

Pharmacokinetic parameters were consistent regardless of age, sex, body weight, race, renal impairment, or mild to moderate hepatic impairment. However, pharmacokinetics in patients with severe hepatic impairment have not been evaluated.

In vitro studies indicate that ensartinib neither inhibits nor induces CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, or CYP3A enzymes. It is a substrate of P-glycoprotein (P-gp) but does not inhibit P-gp or breast cancer resistance protein (BCRP). Ensartinib also does not inhibit other transporters, including OATP1B1, OATP1B3, OAT1, OAT3, OCT1, or OCT2.

Clinical Studies

The efficacy of Ensacove was evaluated in the eXALT3 study, an open-label, randomized, active-controlled, multicenter trial conducted in adult patients with locally advanced or metastatic ALK-positive non-small cell lung cancer (NSCLC). Eligible patients had ALK-positive NSCLC with an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2. Patients were eligible if they had received one prior chemotherapy regimen but no prior ALK-targeted therapy. Those with asymptomatic, untreated brain metastases not receiving corticosteroids, or those with asymptomatic, treated brain

metastases on stable or decreasing corticosteroid doses, were eligible. Completion of radiation therapy at least 2 weeks prior or chemotherapy at least 4 weeks prior to enrollment was required. Patients with leptomeningeal disease were excluded.

Patients were randomized 1:1 to receive either Ensacove 225 mg orally once daily or crizotinib 250 mg orally twice daily, administered in 28-day cycles until disease progression or unacceptable toxicity. Randomization was stratified by prior chemotherapy (0 vs. 1), ECOG performance status (0 or 1 vs. 2), presence of baseline central nervous system (CNS) metastases (yes vs. no), and geographic region (Asia vs. rest of the world). Tumor assessments were conducted every 8 weeks.

The primary efficacy endpoint was progression-free survival (PFS), assessed by Blinded Independent Central Review (BICR) per RECIST version 1.1. Secondary endpoints included overall survival (OS), CNS response rate, time to CNS progression, and overall response rate (ORR).

In the eXALT3 study, progression-free survival events occurred in 59 patients (41%) receiving Ensacove and 80 patients (54%) receiving crizotinib. Progressive disease was reported in 51 patients (36%) on Ensacove and 77 patients (52%) on crizotinib. Deaths occurred in 8 patients (6%) in the Ensacove group and 3 patients (2%) in the crizotinib group. Median PFS was 25.8 months (95% CI: 21.8, not estimable) for Ensacove compared to 12.7 months (95% CI: 9.2, 16.6) for crizotinib, with a hazard ratio (HR) of 0.56 (95% CI: 0.40, 0.79) and a p-value of 0.0007 based on an unstratified log-rank test.

The overall response rate (ORR) was 74% (95% CI: 66, 81) for Ensacove and 67% (95% CI: 58, 74) for crizotinib. Complete response (CR) rates were 12% for Ensacove and 5% for crizotinib, while partial response (PR) rates were 62% and 61%, respectively. Median

duration of response (DOR) was not estimable (95% CI: 22.0, not estimable) for Ensacove and 27.3 months (95% CI: 12.9, not estimable) for crizotinib.

At the time of the final OS analysis, no statistically significant difference in OS was observed between the two treatment arms (p = 0.4570). Median OS was 63.2 months in the Ensacove arm and 55.7 months in the crizotinib arm, with an HR of 0.88 (95% CI: 0.63, 1.23).

Among patients with baseline measurable CNS disease, CNS ORR was 59% (95% CI: 33, 82) for Ensacove (N=17) and 21% (95% CI: 7, 42) for crizotinib (N=24). Complete response rates were 24% and 8%, respectively, while partial response rates were 35% and 13%. Of these responders, 30% in the Ensacove group and 40% in the crizotinib group had a duration of response ≥12 months.

Exclusivity and Patents

An NCE exclusivity, expiring on December 13, 2029, is listed in the Orange Book.

Exblifep®

Cefepime and enmetazobactam for injection, for intravenous use

Fast Facts	
NDA Holder	Allecra Therapeutics SAS
Product Presentation	Powder (for reconstitution)
Route of Administration	Intravenous
NDA Approval	February 22, 2024 (New Chemical Entity, New Combination)
NCE Exclusivity	February 22, 2029 GAIN exclusivity until February 22, 2034
ODE	None
Mechanism of action	Antibiotic

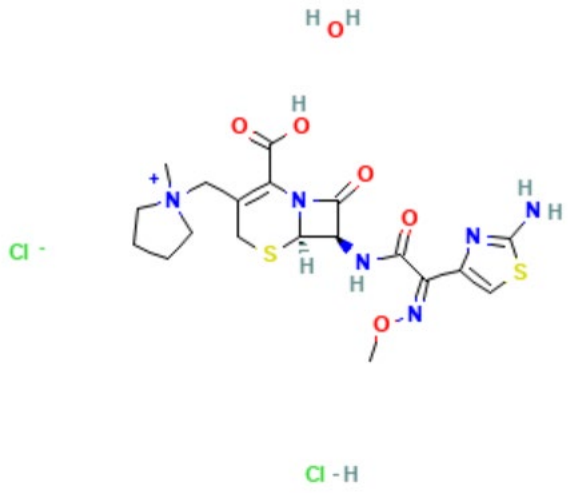
Indication

Exblifep® is approved for adults aged 18 years and older for the treatment of complicated urinary tract infections (cUTIs), including pyelonephritis, caused by susceptible strains of Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Proteus mirabilis, and Enterobacter cloacae complex.

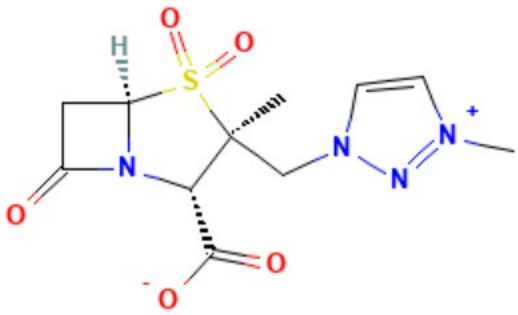
Description

Exblifep® (efepime and enmetazobactam) is a combination intravenous injection comprising cefepime, a cephalosporin antibacterial agent, and enmetazobactam, a beta-

lactamase inhibitor. Cefepime is provided as cefepime hydrochloride monohydrate with a molecular weight of 571.50 g/mol. Its molecular structure is:



Enmetazobactam has a molecular weight of 314.38. Its molecular structure is:



Dosage Form and Handling

Exblifep® 2.5 grams for injection is supplied as a sterile powder for reconstitution in single-dose, clear glass vials. Each vial contains 2 grams of cefepime (equivalent to 2.3 grams of cefepime hydrochloride), 0.5 grams of enmetazobactam, and 1.414 grams of L-arginine.

Vials should be stored refrigerated at 2°C to 8°C, with allowable temperature excursions up to 15°C to 25°C, and protected from light. The powder must be reconstituted and diluted prior to administration.

Dosing Regimen

The recommended dosage of Exblifep® is 2.5 grams (2 grams of cefepime and 0.5 grams of enmetazobactam), administered every 8 hours as an intravenous (IV) infusion over 2 hours. This regimen is indicated for adults aged 18 and older with an estimated glomerular filtration rate (eGFR) between 60 and 129 mL/min. Treatment typically lasts 7 days but may be extended up to 14 days in patients with concurrent bacteremia. Dosage adjustments are required based on renal function.

Mechanism of Action

Antibiotic

Pharmacokinetics

The pharmacokinetics of cefepime and enmetazobactam were evaluated in patients with complicated urinary tract infections (cUTI) and an estimated glomerular filtration rate (eGFR) ≥60 mL/min. Both agents demonstrated similar terminal half-lives—approximately 2.7 hours for cefepime and 2.6 hours for enmetazobactam—and were primarily eliminated renally, with 85% of cefepime and 90% of enmetazobactam excreted unchanged in the urine.

Cefepime exhibits 20% plasma protein binding and has a volume of distribution (Vss) of 20.02 L, while enmetazobactam has negligible protein binding and a Vss of 25.26 L. Drug exposure was approximately dose-proportional following IV administration, with similar

pharmacokinetic profiles observed after single and multiple dosing, indicating no unexpected accumulation.

No clinically significant pharmacokinetic differences were observed based on age, sex, or weight, and hepatic impairment is not expected to affect drug clearance. In patients with renal impairment, systemic exposure increased with declining renal function, reaching a 12-fold increase for cefepime and an 11-fold increase for enmetazobactam in those with severe impairment (CLcr <15 mL/min). In contrast, patients with eGFR ≥130 mL/min showed increased drug clearance, requiring longer infusion durations to achieve comparable exposure.

Drug interaction studies showed no clinically meaningful interactions between cefepime, enmetazobactam, and piperacillin. In vitro, enmetazobactam did not significantly inhibit or induce major CYP450 enzymes, except for CYP2E1 inhibition, and was neither a substrate nor an inhibitor of key membrane transporters. No in vitro drug interaction studies were conducted for cefepime.

Clinical Studies

A multinational, double-blind, noninferiority trial (Trial 1) evaluated the efficacy of Exblifep® (cefepime/enmetazobactam) versus piperacillin/tazobactam in 1,041 adults with complicated urinary tract infections (cUTI), including pyelonephritis. Patients were randomized 1:1 to receive intravenous therapy every 8 hours for 7 days, with treatment extended up to 14 days for those with concurrent bacteremia.

The microbiological modified intent-to-treat (mMITT) population, comprising 345 patients receiving Exblifep® and 333 receiving piperacillin/tazobactam, served as the

primary efficacy group. Baseline characteristics were well balanced between treatment arms.

At the Test of Cure (TOC) visit, conducted 7 days post-treatment, Exblifep® demonstrated superior efficacy, achieving a composite response rate (clinical and microbiological cure) of 79.1%, compared to 58.9% with piperacillin/tazobactam (difference: 21.2%; 95% CI: 14.3, 27.9). Clinical cure rates were slightly higher with Exblifep® (92.5% vs. 88.9%), while microbiological response rates showed a more pronounced benefit (82.7% vs. 64.9%). Among patients with bacteremia, the composite response rate was 71% for Exblifep® versus 50% for piperacillin/tazobactam.

Efficacy was consistent across Gram-negative pathogens, with Exblifep® showing higher response rates for Escherichia coli (83% vs. 59%), Pseudomonas aeruginosa (31% vs. 36%), Klebsiella pneumoniae (68% vs. 56%), Proteus mirabilis (79% vs. 53%), and Enterobacter cloacae complex (86% vs. 33%). Among patients infected with extended-spectrum β-lactamase (ESBL)-producing E. coli and K. pneumoniae (approximately 50% of cases), Exblifep® achieved a 74% composite response rate, compared to 52% with piperacillin/tazobactam.

Exclusivity and Patents

Exblifep® is granted one New Chemical Entity (NCE) exclusivity in the FDA Orange Book, set to expire on November 22, 2029. Additionally, it is listed with one GAIN (Generating Antibiotic Incentives Now) exclusivity, which extends until February 22, 2034. The patents associated with Exblifep® and listed in the Orange Book are summarized in Table 5 (Appendix A).

Flyrcado™

Flurpiridaz F 18 injection, for intravenous use

Fast Facts	
NDA Holder	GE Healthcare
Product Presentation	Solution
Route of Administration	Intravenous
NDA Original Approval	September 27, 2024
NCE Exclusivity	September 27, 2029
ODE	No
Mechanism of action	Imaging agent

Indication

Flycardo™ is approved for use in positron emission tomography (PET) myocardial perfusion imaging (MPI), performed either at rest or during stress, whether pharmacologically induced or through exercise. It is indicated for adult patients with known or suspected coronary artery disease (CAD) to assist in the detection of myocardial ischemia and infarction.

Dosage Form and Handling

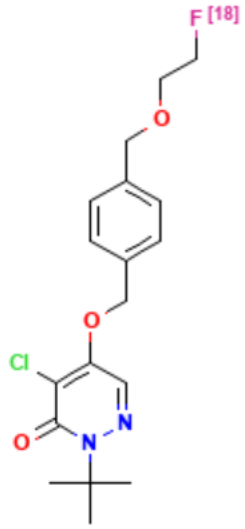
Flycardo™ (flurpiridaz F 18) injection is a clear, colorless to yellow solution containing 190 MBq/mL to 2,050 MBq/mL (5 mCi/mL to 55 mCi/mL) of flurpiridaz F 18 at the end of synthesis. It is supplied in a shielded, multiple-dose vial (NDC 0407-8787-01) with a fill volume of up to 30 mL.

Flycardo™ should be stored at temperatures between 2°C and 30°C, with allowable excursions to -20°C for up to 2 hours or up to 50°C for a maximum of 8 hours. It must remain within appropriate radiation shielding. The product contains no preservatives and should not be used beyond 8 hours post-synthesis or once its radioactivity falls below the specified level—whichever occurs first. The expiration date and time are provided on the shield label. Disposal must comply with applicable federal, state, local, and institutional regulations. Use of this product is restricted to individuals licensed by the U.S. Nuclear Regulatory Commission or an Agreement State regulatory authority.

Flycardo™ may be aseptically diluted with 0.9% Sodium Chloride Injection, USP. It must be used within 8 hours after synthesis or before its radioactivity falls below the required level, whichever occurs first. Administer via intravenous bolus injection over less than 10 seconds, followed immediately by a flush with 0.9% Sodium Chloride Injection, USP. The minimum interval between rest and stress dose administration is 30 minutes for pharmacologic stress and 60 minutes for exercise-induced stress.

Description

Flycardo™ (flurpiridaz F 18) injection is a radioactive diagnostic agent for intravenous administration, with a molecular mass of 367.8 g/mol. Fluorine-18 decays via positron (β^+) emission and has a half-life of 109.8 minutes. The primary photons used in diagnostic imaging are 511 keV gamma rays, produced when the emitted positron annihilates with an electron.



Dosing Regimen

The recommended administered activities of Flycardo™ for myocardial perfusion imaging (MPI) vary according to protocol duration and stress method. In the 1-day protocol, rest imaging requires 93–111 MBq (2.5–3 mCi), while stress imaging requires 222–241 MBq (6–6.5 mCi) for pharmacologic stress and 333–352 MBq (9–9.5 mCi) for exercise stress, maintaining a minimum of twice the rest dose for pharmacologic stress and three times for exercise stress to ensure optimal image quality.

In the 2-day protocol, both rest and stress imaging use the same dose of 93–111 MBq (2.5–3 mCi), regardless of the stress method. If a combined exercise/pharmacologic protocol is employed, the pharmacologic stress dose should be administered.

Each patient receives two intravenous injections — one for rest imaging and one for stress imaging — with a maximum total daily volume of 6.1 mL. Patients should remain well-hydrated, drink fluids, and void frequently after administration to minimize radiation exposure.

Mechanism of Action

Flurpiridaz F-18 is a pyridaben analog and a mitochondrial complex 1 (MC-1) inhibitor. It is extracted by the myocardium in proportion to blood flow and selectively binds to heart tissue with biologically active mitochondria. As a result, radioactivity accumulates more in viable myocardium than in infarcted tissue.

Pharmacokinetics

The pharmacokinetics of flurpiridaz F 18 were studied in healthy subjects, with blood radioactivity peaking at 2.3 minutes post-administration. This was followed by a rise and plateau at approximately 3% of the administered 296 MBq (8 mCi) dose, which remained stable for up to 7 hours after injection. During the first 15 minutes, radioactivity in the blood was primarily associated with flurpiridaz; after this period, it was mainly linked to its metabolites.

Following administration, flurpiridaz F 18 distributed to various organs, including the liver (19%), kidneys (9%), brain (8%), and heart wall (3%) within 10 minutes. Radioactivity in the heart wall remained detectable for up to 1 hour post-administration. The drug and its metabolites were cleared from the blood within 48 hours, undergoing biotransformation into multiple polar metabolites.

Excretion studies using ^{3}H-radiolabeled flurpiridaz showed that 63% of the administered dose was eliminated via urine, with none excreted as unchanged drug, while 30% was recovered in feces, also with no unchanged flurpiridaz detected.

No clinically significant pharmacokinetic differences were observed based on age, sex, body mass index, diabetic status, mild hepatic impairment (Child-Pugh A), or renal

impairment (eGFR 19 to 89 mL/min). However, the effects of moderate to severe hepatic impairment (Child-Pugh B and C) and end-stage renal disease on flurpiridaz F 18 pharmacokinetics have not been evaluated.

Clinical Studies

The clinical evaluation of Flycardo™ PET MPI for detecting coronary artery disease (CAD) was conducted in two prospective, multicenter, open-label studies involving adults with suspected or known CAD. Invasive coronary angiography (ICA) served as the reference standard for diagnosing significant CAD.

Participants received two injections of Flycardo™—one at rest and another during stress (pharmacologic or exercise). PET myocardial perfusion imaging (MPI) was performed using cardiac gating and low-dose CT attenuation correction. Additionally, SPECT MPI was conducted on a separate day using the same stress modality. Study 1 enrolled 578 participants, and Study 2 included 755 participants. Pharmacologic stress was used in 83% of subjects in Study 1 and 71% in Study 2.

Three independent, blinded central readers assessed perfusion and wall motion abnormalities to classify images as normal, ischemia, ischemia plus scar, or scar. For a ≥50% stenosis threshold, Study 1 reported sensitivity ranging from 74% to 89% and specificity from 53% to 70% among the three readers, while Study 2 showed sensitivity from 63% to 77% and specificity from 66% to 86%. At a ≥70% stenosis threshold, Study 1 reported sensitivity from 87% to 97% and specificity from 44% to 62%, whereas Study 2 reported sensitivity from 72% to 85% and specificity from 61% to 80%.

A blinded re-evaluation of 60 randomly selected PET MPI images from Study 1 showed intra-reader agreement (kappa) ranging from 0.71 to 0.93. In Study 2, intra-reader

agreement was assessed in only 10% of images, demonstrating a high agreement rate of 90% to 95%.

For SPECT MPI using a ≥50% stenosis threshold, sensitivity ranged from 61% to 76% in Study 1 and 43% to 58% in Study 2. Specificity ranged from 51% to 65% in Study 1 and 80% to 92% in Study 2. These results indicate that PET MPI outperformed SPECT MPI in detecting CAD, particularly in Study 2.

Exclusivity and Patents

One New Chemical Entity (NCE) exclusivity is listed in the Orange Book, expiring on September 27, 2029. The patents listed in the Orange Book are summarized in Table 6 (Appendix A).

Hympavzi

Marstacimab-hncq injection, for subcutaneous use

Fast Facts	
BLA Holder	Pfizer Inc.
Dosage form	Solution for injection (Prefilled syringe, Prefilled pen)
Route of Administration	Subcutaneous
BLA Approval	October 11, 2024 (New Biological Entity)
ODE	Exclusivity end dates – October 11, 2031
Mechanism of action	A human monoclonal IgG1 antibody that targets the Kunitz domain 2 (K2) of TFPI, neutralizing its activity to enhance coagulation. First-in-class

Indication

Hympavzi is approved for routine prophylaxis to minimize or prevent bleeding episodes in adults and pediatric patients aged 12 years and older with hemophilia A (congenital factor VIII deficiency) without factor VIII inhibitors, or hemophilia B (congenital factor IX deficiency) without factor IX inhibitors.

Description

Marstacimab-hncq is a tissue factor pathway inhibitor (TFPI) antagonist and a human IgG1 monoclonal antibody. It is produced using recombinant DNA technology in CHO cells and has a molecular mass of approximately 146 kDa.

Dosage Form and Handling

Hympavzi (marstacimab-hncq) is a solution for subcutaneous injection available in two formats: prefilled syringe and prefilled pen, each containing 150 mg/mL in a single-dose format.

Each prefilled syringe or pen delivers 1 mL of solution, providing 150 mg of marstacimab-hncq. The formulation also contains inactive ingredients including edetate disodium, histidine, L-histidine monohydrochloride, polysorbate 80, and sucrose in Water for Injection, USP.

Dosing Regimen

The recommended subcutaneous dosage of Hympavzi for patients aged 12 years and older starts with a loading dose of 300 mg (two 150 mg injections), administered at different sites if necessary. Maintenance dosing begins one week later, with 150 mg once weekly on the same day each week. If bleeding control remains inadequate, the dose may be increased to 300 mg weekly for patients weighing ≥50 kg. Multiple injections should always be given at different sites.

Mechanism of Action

Marstacimab-hncq is a human monoclonal IgG1 antibody that targets the Kunitz domain 2 (K2) of TFPI, neutralizing its activity to enhance coagulation. TFPI is the primary inhibitor of the extrinsic coagulation cascade, regulating thrombin generation by inhibiting the FXa/FVIIa/TF complex via its K2 domain.

Pharmacokinetics

Marstacimab-hncq exhibits non-linear absorption, with Cmax and AUC increasing in a greater-than-dose-proportional manner over the 100 mg to 450 mg dose range. Its estimated bioavailability following subcutaneous administration is 71%. The median time to reach peak concentration (Tmax) ranges from 23 to 59 hours. No clinically significant differences in bioavailability were observed based on the site of administration, including the arm, thigh, or abdomen. Marstacimab-hncq demonstrates a steady-state accumulation ratio of approximately 4 to 5, with steady-state concentrations achieved around day 60 (8th or 9th weekly subcutaneous dose).

The drug undergoes both linear and non-linear clearance, with non-linearity attributed to target-mediated drug disposition (TMDD) upon binding to TFPI. Once TFPI is saturated, elimination follows a linear pathway. Approximately 90% of marstacimab-hncq is eliminated within one month after the last dose, with a median half-life of about 7–10 days. The steady-state apparent volume of distribution is 8.6 L in patients with hemophilia. Metabolism occurs via degradation into small peptides and amino acids, following the same catabolic pathways as endogenous IgG.

No clinically significant differences in marstacimab-hncq pharmacokinetics were observed based on race, hemophilia type (A or B), mild renal impairment, or mild hepatic impairment. The effects of moderate to severe hepatic impairment (Child-Pugh B and C) remain unstudied.

Body weight was identified as a significant covariate affecting marstacimab-hncq pharmacokinetics, with exposure increasing as body weight decreases within the 35 to 120 kg range; however, dose adjustment based on body weight is not required.

In pediatric patients, drug clearance (CL) was 29% lower in adolescents (12–18 years) compared to adults. After adjusting for body weight, no significant differences in clearance were observed.

In the 12-month BASIS study, 19.8% (23/116) of ADA-evaluable patients treated with marstacimab-hncq developed anti-drug antibodies (ADAs), with 6 (26%) having neutralizing antibodies (NAbs). Patients with ADAs showed a 24%–50% reduction in steady-state drug concentrations, but no clinically significant impact on safety or efficacy was observed over the treatment period.

Clinical Studies

The BASIS study (NCT0398792) evaluated the efficacy of Hympavzi in 116 adult and pediatric patients (≥12 years, ≥35 kg) with hemophilia A without FVIII inhibitors or hemophilia B without FIX inhibitors. This open-label, multicenter, two-phase study excluded patients with a history of coronary artery disease, thrombosis, or ischemic disease. After a 6-month observation phase, patients were assigned to on-demand treatment (n=33) or routine prophylaxis (n=83) based on their prior factor replacement therapy. Those who completed the 12-month study were eligible to enroll in an open-label extension (NCT05145127).

Patients received an initial 300 mg loading dose, followed by weekly maintenance doses of 150 mg for 12 months. Dose escalation to 300 mg weekly was permitted for patients weighing ≥50 kg who experienced ≥2 breakthrough bleeds, with 14 patients (12%) requiring escalation.

The median annualized bleeding rate (ABR) for treated bleeds was 38.0 in the on-demand cohort compared to 3.18 in the Hympavzi prophylaxis group. Spontaneous bleeds

decreased from 30.93 (on-demand) to 2.44 (Hympavzi prophylaxis), joint bleeds from 32.86 to 2.83, and target joint bleeds from 23.18 to 1.84. Total bleeds (treated and untreated) were also reduced, from 47.76 in the on-demand cohort to 7.39 with Hympavzi prophylaxis.

When comparing Hympavzi prophylaxis to prior routine factor-based prophylaxis, the median ABR for treated bleeds was 7.85 in the prior prophylaxis group versus 5.08 with Hympavzi. Spontaneous bleeds were 5.86 vs. 3.78, joint bleeds were 5.66 vs. 4.13, and target joint bleeds were 3.36 vs. 2.51, respectively. Total bleeds (treated & untreated) were reduced from 8.84 to 2.87 with Hympavzi prophylaxis.

Exclusivity and Patents

One Orphan Drug Exclusivity (ODE) is listed in the Orphan Drug Database and is set to expire on October 11, 2031. This ODE covers the indication for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients 12 years of age and older with hemophilia A (congenital factor VIII deficiency) without factor VIII inhibitors, or hemophilia B (congenital factor IX deficiency) without factor IX inhibitors.

Imdelltra™

Tarlatamab-dlle for injection, for intravenous use

Fast Facts	
BLA Holder	Amgen Inc.
Product Presentation	Powder (for reconstitution)
Route of Administration	Intravenous
BLA Approval	May 16, 2024 (New Biological Entity)* Accelerated Approval
ODE	May 16, 2031
Mechanism of action	A bispecific T-cell engager that targets DLL3 on tumor and other cells and CD3 on T-cells First-in-class

**BLA exclusivity is typically granted for 12 years;

Indication

Imdelltra™ is indicated for adult patients with extensive-stage small cell lung cancer (ES-SCLC) who have experienced disease progression following platinum-based chemotherapy. This indication received accelerated approval based on response rate and duration, with continued approval contingent on confirmatory trials that verify clinical benefit.

Boxed Warnings

Imdelltra™ can cause cytokine release syndrome (CRS), which may be serious or life-threatening. To reduce this risk, initiate treatment with a step-up dosing schedule. If CRS occurs, pause treatment until it resolves or discontinue permanently if the reaction is severe. Imdelltra™ may also cause neurologic side effects, including immune effector cell-associated neurotoxicity syndrome (ICANS), which can be serious or life-threatening. Monitor patients closely for symptoms and provide prompt treatment. Pause treatment until symptoms resolve or discontinue permanently if severe.

Description

Tarlatamab-dlle is a bispecific CD3 T-cell engager targeting DLL3, binding to DLL3 on tumor and other cells as well as CD3 on T cells. It is produced using recombinant DNA technology in CHO cells. The molecule consists of 982 amino acids and has an approximate molecular weight of 105 kilodaltons.

Dosage Form and Handling

Imdelltra™ is supplied as a lyophilized powder in single-use vials for reconstitution and dilution prior to injection. It is available in two dose strengths: a 1 mg package and a 10 mg package. The 1 mg package contains one single-dose vial of 1 mg Imdelltra™ and two 7 mL vials of IV Solution Stabilizer (IVSS). The 10 mg package contains one single-dose vial of 10 mg Imdelltra™ and two 7 mL vials of IVSS. The IV Solution Stabilizer is added to the IV bag to minimize drug adsorption.

Imdelltra™ and IVSS vials should be stored refrigerated at 2°C to 8°C in their original cartons to protect from light until use. Do not freeze. The vials may be kept at room temperature (20°C to 25°C) for up to 24 hours in the original carton to protect from light.

Each 1 mg vial contains tarlatamab-dlle (1 mg), glutamic acid (0.72 mg), polysorbate 80 (0.04 mg), sucrose (37.1 mg), and sodium hydroxide to adjust pH to 4.2. After reconstitution with 1.3 mL of Sterile Water for Injection, the final concentration is 0.9 mg/mL Imdelltra™.

Each 10 mg vial contains tarlatamab-dlle (10 mg), glutamic acid (3.7 mg), polysorbate 80 (0.2 mg), sucrose (194.4 mg), and sodium hydroxide to adjust pH to 4.2. After reconstitution with 4.4 mL of Sterile Water for Injection, the final concentration is 2.4 mg/mL Imdelltra™.

IV Solution Stabilizer (IVSS) is supplied as a sterile, preservative-free, colorless to slightly yellow, clear solution. Each IVSS vial contains citric acid monohydrate (36.75 mg), lysine hydrochloride (1598.8 mg), polysorbate 80 (7 mg), sodium hydroxide to adjust pH to 7.0, and water for injection.

Dosing Regimen

Imdelltra™ is administered using a step-up dosing protocol designed to reduce the risk of cytokine release syndrome (CRS). Recommended pre- and post-medications further minimize CRS risk during the initial treatment cycle.

The dosing schedule begins with a 1 mg step-up dose on Day 1 of Cycle 1, followed by 10 mg doses on Days 8 and 15. In Cycle 2, the 10 mg dose is given on Days 1, 8, and 15, and this continues through Cycles 3 and 4. From Cycle 5 onward, dosing is 10 mg on Days 1 and 15 of each cycle.

To further reduce CRS risk during Cycle 1, concomitant medications are recommended. On Days 1 and 8, patients should receive 8 mg of dexamethasone (or an equivalent corticosteroid) intravenously within one hour prior to Imdelltra™ administration.

Additionally, on Days 1, 8, and 15, 1 liter of normal saline should be administered intravenously over 4 to 5 hours immediately following the Imdelltra™ infusion.

Mechanism of Action

Tarlatamab-dlle is a bispecific T-cell engager that targets DLL3 on tumor and other cells and CD3 on T cells. It induces T-cell activation, cytokine release, and lysis of DLL3-expressing cells. In mouse models of small cell lung cancer (SCLC), Tarlatamab-dlle demonstrated anti-tumor activity.

Pharmacokinetics

Imdelltra™ exposure increases proportionally with doses ranging from 1 mg to 100 mg administered biweekly, reaching steady-state levels by Cycle 2, Day 15. The steady-state volume of distribution is approximately 8.6 L (18.3%). Tarlatamab-dlle is metabolized through catabolic pathways into small peptides, with a median terminal elimination half-life of 11.2 days (range: 4.3 to 26.5 days) and a systemic clearance rate of 0.65 L/day (44%) in patients with small cell lung cancer (SCLC).

The pharmacokinetics of tarlatamab-dlle are not significantly affected by age, body weight, sex, race, mild to moderate renal impairment, or mild hepatic impairment. However, its effects in patients with severe renal impairment, end-stage renal disease, or moderate to severe hepatic impairment remain unknown.

Tarlatamab-dlle induces a transient cytokine release that may suppress CYP450 enzyme expression, potentially increasing exposure to co-administered CYP450 substrates for up to 14 days following cytokine release syndrome (CRS).

In Study DeLLphi-301, 3.2% (4 of 124) of patients receiving the recommended Imdelltra™ dosing tested positive for anti-drug antibodies (ADA), although none developed neutralizing antibodies.

Clinical Studies

The efficacy of Imdelltra™ was evaluated in Study DeLLphi-301 (NCT05060016), an open-label, multicenter, multi-cohort clinical trial involving adult patients with extensive-stage small cell lung cancer (ES-SCLC) whose disease had progressed following platinum-based chemotherapy and, in some cases, prior anti-PD-L1 immunotherapy.

Eligible patients had relapsed or refractory SCLC with disease progression after at least one prior therapy and an ECOG Performance Status of 0 or 1. Patients were required to have at least one measurable lesion, as defined by RECIST v1.1. The trial excluded patients with symptomatic brain metastases, evidence of interstitial lung disease or non-infectious pneumonitis, and active immunodeficiency.

Tumor assessments were performed every 6 weeks for the first 48 weeks and every 12 weeks thereafter. Primary efficacy endpoints included overall response rate (ORR) and duration of response (DOR), assessed by Blinded Independent Central Review (BICR) per RECIST v1.1 criteria.

In Study DeLLphi-301, Imdelltra™ (N = 99) achieved an ORR of 40% (95% CI: 31, 51), with 2% of patients achieving a complete response (CR) and 38% a partial response (PR). The median DOR was 9.7 months (range: 2.7 to 20.7+ months), with 68% of responders maintaining response for at least 6 months and 40% for at least 12 months.

Among 69 patients with platinum sensitivity data, the ORR was 52% (95% CI: 32, 71) in patients with platinum-resistant SCLC and 31% (95% CI: 18, 47) in those with platinum-

sensitive SCLC. Platinum-resistant SCLC was defined as disease progression occurring within 90 days or less after first-line platinum therapy; 42% of patients had platinum-sensitive SCLC.

Exclusivity and Patents

An Orphan Drug Exclusivity (ODE) is listed in the Orphan Drug Database with an expiration date of May 16, 2031.

Iomervu

Iomeprol injection, for intra-arterial or intravenous use

Fast Facts	
NDA Holder	Bracco Diagnostics Inc.
Product Presentation	Solution for injection
Route of Administration	Intravenous or intra-arterial
NDA Approval	November 27, 2024*
NCE Exclusivity	November 27, 2029
ODE	None
Mechanism of action	A radiographic iodinated contrast agent that enhances vessel and tissue visualization by attenuating X-ray photons

*Iomervu is now listed as "discontinued" in the Orange Book.

Indication

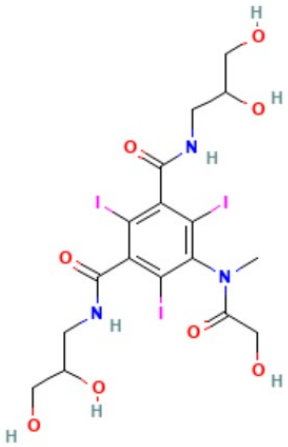
Iomervu is indicated for cerebral arteriography, including intra-arterial digital subtraction angiography (IA-DSA), in both adult and pediatric patients. It is also approved for visceral and peripheral arteriography, as well as aortography—including IA-DSA—in these patient populations. Additionally, Iomervu is indicated for coronary arteriography and cardiac ventriculography in adults, and for radiographic assessment of cardiac chambers and associated arteries in pediatric patients.

Boxed Warnings

Intrathecal administration of Iomervu, whether intentional or accidental, can cause severe and potentially fatal adverse effects, including death, convulsions, cerebral hemorrhage, coma, paralysis, arachnoiditis, acute renal failure, cardiac arrest, seizures, rhabdomyolysis, hyperthermia, and brain edema. Iomervu is strictly intended for intra-arterial or intravenous use only.

Description

Iomervu injection is a tri-iodinated, non-ionic radiographic contrast agent intended for intra-arterial or intravenous administration. It has a molecular weight of 777.09 and an iodine content of 49%. Its chemical structure is:



Dosage Form and Handling

Iomervu injection is a clear, colorless to pale yellow solution supplied in clear glass single-dose vials or bottles. It is available in four iodine concentrations: 250 mg/mL, 300 mg/mL, 350 mg/mL, and 400 mg/mL. Each milliliter of Iomervu contains specific amounts of iomeprol and tromethamine. The 250 mg iodine/mL concentration contains 510 mg of iomeprol, providing 250 mg of bound iodine, along with 1 mg of tromethamine. The 300 mg iodine/mL concentration contains 612 mg of iomeprol, providing 300 mg of bound

iodine, with 1 mg of tromethamine. The 350 mg iodine/mL concentration contains 714 mg of iomeprol, providing 350 mg of bound iodine, and 1 mg of tromethamine. The 400 mg iodine/mL concentration contains 816 mg of iomeprol, providing 400 mg of bound iodine, along with 1 mg of tromethamine. Iomervu is supplied in various packaging configurations. Iomervu should be stored at 20°C to 25°C, in its original carton with the cover closed to protect from light. Freezing is prohibited, as it may compromise the solution's integrity.

Dosing Regimen

Iomervu is used for a variety of intra-arterial and intravenous imaging procedures, with dosage tailored to the procedure type, patient characteristics, and imaging requirements. Strict administration precautions—including hydration, visual inspection, and aseptic handling—must be followed to ensure safety and efficacy.

For adult patients, the recommended dosage of Iomervu varies depending on the imaging procedure and route of administration. In intra-arterial procedures such as cerebral arteriography, visceral and peripheral arteriography, and digital subtraction angiography, a concentration of 300 mg iodine/mL is used. Injection volumes range from 6 to 70 mL, depending on the specific procedure, with a maximum total dose volume of 200 mL. For coronary angiography and cardiac ventriculography, higher concentrations (300, 350, or 400 mg iodine/mL) are used, with injection volumes between 3 and 45 mL (depending on the artery), and a maximum total dose volume ranging from 215 to 286 mL.

For pediatric patients, dosage is based on body weight and the type of intra-arterial procedure. For cerebral arteriography, visceral and peripheral arteriography, and intra-arterial digital subtraction angiography, a concentration of 300 mg iodine/mL is used, with injection volumes ranging from 0.5 to 2 mL/kg per injection. The maximum total dose is 5

mL/kg or the adult maximum dose, whichever is lower. Dosage should be carefully adjusted according to the child's weight, vessel size, blood flow rate, and clinical condition to optimize imaging efficacy and minimize adverse effects. The injection rate should approximate the flow rate of the vessel being injected. For intravenous procedures, dosage should be determined by clinical indication and imaging needs, ensuring volume and rate are appropriate for the pediatric patient's physiology.

For adult intravenous procedures such as CT scans of the head and body, concentrations of 250 or 300 mg iodine/mL are administered at volumes of 100 to 190 mL, with an injection rate of 2 to 4 mL/s. Concentrations of 350 or 400 mg iodine/mL may also be used at volumes of 75 to 150 mL, maintaining the same injection rate. In CT angiography, higher concentrations (300, 350, or 400 mg iodine/mL) are administered at volumes of 80 to 130 mL, with injection rates of 4 to 6 mL/s. Coronary CT procedures require a concentration of 400 mg iodine/mL, with injection volumes of 50 to 90 mL at 4 to 6 mL/s. For CT urography, a concentration of 350 mg iodine/mL is used at volumes of 90 to 120 mL, with an injection rate of 2.5 mL/s. Injection rates should be adjusted to match the vessel's flow rate, ensuring optimal imaging quality and patient safety.

For pediatric intravenous procedures, dosage varies by imaging type and patient weight. For CT scans of the head and body, 250 or 300 mg iodine/mL is administered at 1.5 to 2.5 mL/kg with an injection rate of 1 to 2 mL/s, while 350 or 400 mg iodine/mL is given at 1 to 2 mL/kg, maintaining the same rate. In CT angiography, concentrations of 300, 350, or 400 mg iodine/mL are used at 1 to 2 mL/kg, with injection rates of 2 to 3 mL/s. Coronary CT angiography follows a similar regimen with 300 or 400 mg iodine/mL at 1 to 2 mL/kg, administered at 2 to 3 mL/s. For CT urography, 300 mg iodine/mL is used at 1 to 2 mL/kg

with injection rates of 1 to 2 mL/s. Injection rates should be adjusted according to clinical indications, patient size, and type of intravenous access.

Mechanism of Action

Iomerol is an iodinated radiographic contrast agent that enhances visualization of vessels and tissues by attenuating X-ray photons. It can be administered intravenously or intra-arterially and primarily remains within the vascular system, gradually diffusing into the extravascular space over time. In a normal brain with an intact blood-brain barrier (BBB), Iomerol remains intravascular; however, when the BBB is disrupted, it accumulates extravascularly, thereby highlighting pathological regions. This characteristic facilitates the detection of abnormalities in neurological and other contrast-enhanced radiographic studies.

Pharmacokinetics

Iomerol exhibits dose-proportional pharmacokinetics, with maximum concentration (Cmax) and area under the curve (AUC) increasing proportionally to doses ranging from 250 mg iodine/kg to 1,250 mg iodine/kg body weight. Its volume of distribution is approximately 0.28 L/kg (±0.05 L/kg), indicating that Iomerol remains largely within the vascular space and does not bind to plasma proteins.

The agent is primarily eliminated unchanged, with about 90% of the administered dose excreted in urine within 24 hours. It undergoes minimal metabolism, and elimination relies mainly on renal clearance. In patients with renal impairment, Iomerol clearance declines proportionally to impairment severity: mild impairment results in a 1.6-fold increase in mean half-life, moderate impairment a 2.9-fold increase, and severe impairment a 6.4-fold increase. Additionally, plasma concentrations of Iomerol decreased by approximately 83%

in patients with severe renal impairment undergoing hemodialysis two hours after intravenous administration of a 20,000 mg iodine dose, demonstrating significant dialyzability.

In pediatric patients aged 3 to 17 years, pharmacokinetic parameters are comparable to those in adults, with no clinically significant differences in maximum concentration (Cmax) or plasma levels measured within five minutes post-administration. Like adults, Iomerol is primarily eliminated unchanged, with approximately 90% excreted in urine within 24 hours. Given its minimal metabolism, clearance is highly dependent on renal function and declines substantially with renal impairment.

Clinical Studies

Clinical studies evaluating Iomervu for intra-arterial and intravenous imaging included prospective, randomized, double-blind, multicenter trials. Intra-arterial imaging studies assessed cerebral arteriography, visceral and peripheral arteriography, coronary arteriography, and cardiac ventriculography. Cerebral arteriography was performed in 61 adult patients using a concentration of 300 mg iodine/mL, resulting in 100% visualization adequacy. Visceral and peripheral arteriography were evaluated in 60 patients at the same concentration, with 98% achieving adequate visualization. Additionally, coronary arteriography and cardiac ventriculography were conducted in 118 patients, with half receiving 400 mg iodine/mL and half receiving 300 mg iodine/mL, achieving visualization adequacy ratings between 93% and 100%. Digital subtraction angiography (DSA) demonstrated results comparable to conventional arteriography across the studies.

Intravenous imaging studies evaluated various CT procedures. CT of the head and body involved 118 adult patients receiving either 400 mg or 250 mg iodine/mL, with

visualization adequacy rated between 98% and 100%. CT angiography, conducted with 262 patients using a 400 mg iodine/mL concentration, demonstrated sensitivity and specificity of 99% and 97%, respectively, for detecting stenosis ≥70%, and sensitivity of 91% and specificity of 97% for stenosis >50%. Coronary CT angiography was evaluated in 301 patients administered 400 mg iodine/mL, showing sensitivity ranging from 81% to 94% and specificity from 89% to 94% for stenosis >50%, based on blinded independent reader assessments. Finally, CT urography was performed in 185 patients using 350 mg iodine/mL, achieving good or excellent visualization ratings in 64% to 98% of cases, with mean visualization scores of 4.1 to 4.2 on a 5-point scale.

Exclusivity and Patents

The Orange Book lists one NCE exclusivity with an expiration date of November 27, 2029.

Iqirvo

Elafibranor tablets, for oral use

Fast Facts	
NDA Holder	Ipsen Biopharmaceuticals, Inc.
Product Presentation	Tablet
Route of Administration	Oral
NDA Approval	June 10, 2024 Accelerated Approval
NCE Exclusivity	Exclusivity ending on June 10, 2029
ODE	Yes, Exclusivity end date: June 10, 2031
Mechanism of action	PPAR agonist. inhibition of bile acid synthesis through activation of PPAR-alpha and PPAR-delta. First-in-Class

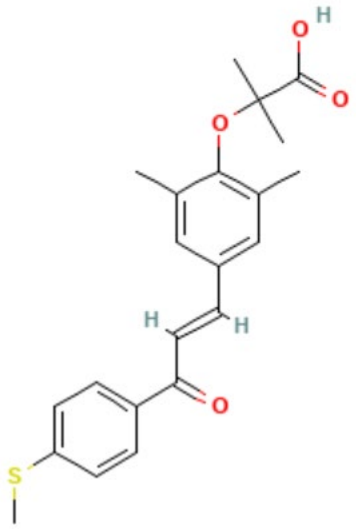
Indication

Iqirvo is approved for the treatment of primary biliary cholangitis (PBC) in adults, either in combination with ursodeoxycholic acid (UDCA) for patients with an inadequate response to UDCA or as monotherapy for those unable to tolerate UDCA.

This indication is approved under accelerated approval based on the reduction of alkaline phosphatase (ALP). Continued approval may be contingent upon verification and demonstration of clinical benefit in confirmatory trial(s).

Description

Elafibranor and its primary active metabolite, GFT1007, are peroxisome proliferator-activated receptor (PPAR) agonists. Elafibranor has a molecular weight of 384.49 g/mol. Its chemical structure is:



Dosage Form and Handling

Iqirvo is supplied as film-coated tablets (80 mg) for oral administration. The inactive ingredients include colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, and povidone. The film coating contains iron oxide red, iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Dosing Regimen

The recommended dosage of Iqirvo is 80 mg taken orally once daily, with or without food. Iqirvo should be administered at least 4 hours before or 4 hours after a bile acid sequestrant, or at the longest possible interval between the two.

Mechanism of Action

Elafibranor and its primary active metabolite, GFT1007, act as peroxisome proliferator-activated receptor (PPAR) agonists, targeting PPAR-alpha, PPAR-gamma, and PPAR-

delta in vitro. However, the exact mechanism by which elafibranor exerts therapeutic effects in primary biliary cholangitis (PBC) remains unclear. Its pharmacological actions, potentially relevant to treatment, include suppression of bile acid synthesis—a process modulated by PPAR-alpha and PPAR-delta activation. Notably, the PPAR-delta signaling pathway is associated with Fibroblast Growth Factor 21 (FGF21)-mediated downregulation of CYP7A1, the key enzyme responsible for converting cholesterol into bile acids.

Pharmacokinetics

With once-daily dosing, elafibranor reached steady state by Day 14, while its active metabolite, GFT1007, did so by Day 7. Increasing the dose from 40 mg to 100 mg (a 2.5-fold increase) resulted in a 3.3-fold increase in $AUC_{0–24h}$ for elafibranor and a 2.6-fold increase for GFT1007. Similarly, raising the dose from 120 mg to 300 mg led to 2.9-fold and 2.2-fold increases in exposure, respectively. At steady state, GFT1007 exposure was 3.2 times greater than that of elafibranor.

In patients with PBC receiving an 80 mg once-daily dose, elafibranor and GFT1007 reached peak plasma concentrations (T_{max}) at a median of 1.25 hours (range: 0.5–2 hours). Administration with a high-fat, high-calorie meal caused minor pharmacokinetic changes that were not clinically significant.

Elafibranor demonstrated high plasma protein binding (99.7%), primarily to albumin, with an apparent volume of distribution (Vd/F) of 4731 L in healthy subjects following a single 80 mg dose under fasted conditions. Its elimination half-life was 70.2 hours (range: 37.1–92.2 hours), compared to 15.4 hours (range: 9.39–21.7 hours) for GFT1007. The mean apparent total clearance (CL/F) of elafibranor was 50.0 L/h. Elafibranor undergoes

extensive metabolism, mainly via PTGR1, CYP2J2, and UGT isoforms (UGT1A3, UGT1A4, UGT2B7), while its major active metabolite, GFT1007, is further metabolized by CYP2C8, UGT1A3, and UGT2B7.

Pharmacokinetics were not significantly affected by sex, BMI, or body weight. In severe renal impairment, elafibranor exposure decreased by 32%, whereas GFT1007 levels remained unchanged. Severe hepatic impairment did not significantly alter total drug exposure but increased unbound elafibranor and GFT1007 levels by twofold and 2.6-fold, respectively.

Elafibranor, GFT1007, and GFT3351 neither inhibit nor induce major CYP enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4), with no evidence of time-dependent CYP inhibition. GFT1007 inhibits UGT1A6, though the clinical relevance is unknown. Elafibranor inhibits the bile salt export pump (BSEP) and breast cancer resistance protein (BCRP), while GFT3351 inhibits MRP2 and MRP3; however, the clinical significance of these interactions remains unclear. None of these compounds inhibit key drug transporters, including P-gp (MDR1), OATP1B1/B3, OCT1/2, OAT1/3, MATE1/2-K, or BSEP.

In clinical drug interaction studies, administration of elafibranor 120 mg with warfarin 15 mg had no clinically significant effect on C_{max}, AUC, or INR (International Normalization Ratio). Co-administration of elafibranor 80 mg with simvastatin 20 mg resulted in a 26% reduction in C_{max} and a 32% decrease in AUC of simvastatin β-hydroxyacid, while atorvastatin 40 mg with elafibranor 180 mg caused a 28% reduction in C_{max} and a 12% decrease in AUC; both changes were considered not clinically meaningful. Sitagliptin (75 mg BID) with elafibranor 120 mg showed no significant impact on plasma glucose or

glucagon-like peptide-1 (GLP-1) levels. Co-administration with indomethacin (a PTGR1 inhibitor) at 75 mg did not significantly alter the pharmacokinetics of elafibranor or GFT1007.

Clinical Studies

Study 1 (NCT04526665) was a multi-center, randomized, double-blind, placebo-controlled trial evaluating Iqirvo in 161 adults with primary biliary cholangitis (PBC) who had an inadequate response to or intolerance of ursodeoxycholic acid (UDCA). Patients were randomized to receive Iqirvo 80 mg (n=108) or placebo (n=53) once daily for at least 52 weeks, with 95% continuing UDCA treatment. Eligibility criteria included an alkaline phosphatase (ALP) level of at least 1.67 times the upper limit of normal (ULN) and a total bilirubin (TB) level no greater than two times the ULN.

The primary endpoint was biochemical response at Week 52, defined as an ALP level below 1.67 times the ULN, a TB level at or below the ULN, and at least a 15% reduction in ALP from baseline. A key secondary endpoint was ALP normalization, defined as ALP levels reaching or dropping below the ULN—set at 129 U/L for males and 104 U/L for females.

Iqirvo demonstrated a higher biochemical response rate at Week 52 compared to placebo: 51% of Iqirvo-treated patients achieved the primary endpoint versus only 4% in the placebo group, reflecting a treatment difference of 47% (95% CI: 32, 57; $p < 0.0001$). Additionally, 52% of Iqirvo-treated patients had ALP levels below 1.67 times the ULN, compared to 9% in the placebo group, while 75% of Iqirvo-treated patients experienced at least a 15% reduction in ALP, compared to 17% of placebo patients.

ALP normalization was achieved by 15% of Iqirvo-treated patients, versus 0% in the placebo group ($p = 0.0019$). The proportion of patients with TB levels at or below the ULN was similar between groups—85% in the Iqirvo group and 83% in the placebo group. ALP levels began to decline as early as Week 4 and remained stable through Week 52. This sustained reduction supports the long-term efficacy of Iqirvo in PBC patients with an inadequate response to or intolerance of UDCA.

Exclusivity and Patents

An NCE exclusivity, expiring on June 10, 2029, and an Orphan Drug Exclusivity, expiring on June 10, 2031, are listed in the Orange Book. The patents associated with the drug are summarized in Table 7 (Appendix A).

Itovebi

Inavolisib tablets, for oral use

Fast Facts	
NDA Holder	Genentech Inc.
Product Presentation	Tablets
Route of Administration	Oral
NDA Original Approval	October 10, 2024
NCE Exclusivity	October 10, 2029
ODE	No
Mechanism of action	A PI3K inhibitor targeting PI3Kα

Indication

Itovebi, in combination with palbociclib and fulvestrant, is indicated for the treatment of adults with endocrine-resistant, PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer. This indication applies to patients whose disease has recurred on or after completing adjuvant endocrine therapy, as determined by an FDA-approved test.

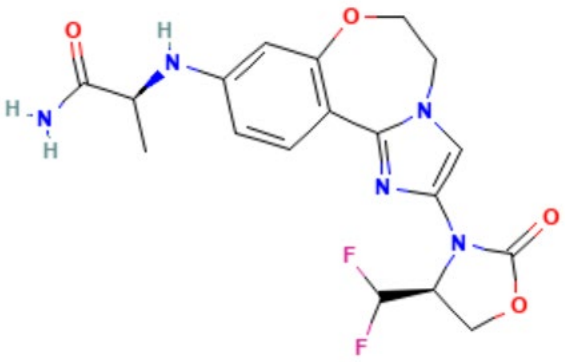
Dosage Form and Handling

Itovebi is available as 3 mg and 9 mg tablets, packaged in bottles of 30 tablets each. It should be stored at 20°C to 25°C, with allowable excursions between 15°C and 30°C. The tablets contain lactose, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate as inactive ingredients. The film coating consists of polyvinyl alcohol (partially

hydrolyzed), titanium dioxide, macrogol/polyethylene glycol, talc, and iron oxide red, with iron oxide yellow included only in the 9 mg tablets.

Description

Itovebi contains inavolisib, a kinase inhibitor, with a molecular weight of 407.37 g/mol. Its chemical structure is:



Dosing Regimen

The recommended dosage of Itovebi is 9 mg taken orally once daily, with or without food, continued until disease progression or unacceptable toxicity occurs.

Mechanism of Action

Inavolisib is a PI3K inhibitor targeting PI3Kα. It degrades mutated PI3K p110α, inhibits AKT phosphorylation, reduces proliferation, and induces apoptosis in PIK3CA-mutated breast cancer cells. In vivo, it suppresses tumor growth in PIK3CA-mutated, estrogen receptor-positive breast cancer models. When combined with palbociclib and fulvestrant, it enhances tumor growth inhibition beyond that achieved by either individual agents or doublet therapies.

Pharmacokinetics

Inavolisib reaches steady-state concentrations by Day 5, exhibiting approximately a 2-fold accumulation. Its steady-state AUC is dose-proportional between 6 and 12 mg (0.7 to 1.3 times the recommended dose). The absolute oral bioavailability is 76%, with a median Tmax of 3 hours (range: 0.5–4 hours). No clinically significant differences in pharmacokinetics were observed when administered with a high-fat meal. The apparent oral volume of distribution is 155 L (26% CV), plasma protein binding is 37%, and the blood-to-plasma ratio is 0.8. Inavolisib is eliminated with a half-life of 15 hours (24% CV) and a total clearance of 8.8 L/hr (29% CV).

Inavolisib is primarily metabolized by hydrolysis, with minimal CYP3A-mediated metabolism. Following oral administration of a single radiolabeled dose, 49% of the dose was recovered in urine (40% unchanged) and 48% in feces (11% unchanged). No clinically significant pharmacokinetic differences were observed based on age, sex, race, body weight, or mild hepatic impairment. The effect of moderate to severe hepatic impairment on inavolisib pharmacokinetics remains unknown. In patients with moderate renal impairment, inavolisib AUC increased by 73% compared to those with normal renal function. No significant differences were noted in mild renal impairment; the impact of severe renal impairment is unknown.

No clinically significant pharmacokinetic differences were observed when inavolisib was co-administered with proton pump inhibitors (PPIs). Inavolisib induces CYP3A and CYP2B6 and acts as a time-dependent inhibitor of CYP3A, but it does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. Regarding transporter systems, inavolisib is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), but not of OATP1B1, OATP1B3, OCT1, OCT2, MATE1, MATE2K, OAT1, or

OAT2. Additionally, it does not inhibit P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, or MATE2K.

Clinical Studies

The INAVO120 trial was a randomized, double-blind, placebo-controlled study evaluating the efficacy of Itovebi in combination with palbociclib and fulvestrant in patients with endocrine-resistant, PIK3CA-mutated, HR-positive, HER2-negative locally advanced or metastatic breast cancer. Eligible patients had disease progression during or within 12 months of completing adjuvant endocrine therapy (ET) and had not received prior systemic therapy for advanced or metastatic disease. To ensure balanced comparisons, patients were stratified by visceral disease status (yes/no), endocrine resistance type (primary/secondary), and geographic region. PIK3CA mutation status was determined using the FoundationOne® Liquid CDx assay at a central laboratory or through validated PCR or next-generation sequencing (NGS) assays at local laboratories.

Patients were randomized to receive Itovebi (9 mg daily, n=161) or placebo (n=164), both in combination with palbociclib (125 mg orally, 21 days on/7 days off) and fulvestrant (500 mg intramuscularly on Cycle 1, Days 1 and 15, then Day 1 of each subsequent 28-day cycle). Treatment continued until disease progression or unacceptable toxicity. Pre/perimenopausal women also received LHRH agonist therapy. The median age was 54 years (range: 27–79), with ECOG performance status 0 in 63% and 1 in 36% of patients. The most common prior adjuvant endocrine therapies were tamoxifen (57%) and aromatase inhibitors (50%). Secondary endocrine resistance was present in 64% of patients, 83% had received prior neo/adjuvant chemotherapy, and 1.2% had prior CDK4/6 inhibitor treatment.

The primary efficacy endpoint was progression-free survival (PFS), assessed by investigators per RECIST version 1.1. Secondary endpoints included overall survival (OS), objective response rate (ORR), and duration of response (DOR). Investigator-assessed PFS results were consistent with blinded independent central review (BICR). At analysis, OS data were immature, with 30% mortality in the overall population. Median PFS was 15.0 months (95% CI: 11.3, 20.5) in the Itovebi + palbociclib + fulvestrant group versus 7.3 months (95% CI: 5.6, 9.3) in the placebo + palbociclib + fulvestrant group (hazard ratio [HR] 0.43; 95% CI: 0.32, 0.59; $p < 0.0001$). PFS events occurred in 51% (82/161) of Itovebi-treated patients versus 69% (113/164) in the placebo group.

The objective response rate (ORR; complete or partial response) was 58% (94/161) in the Itovebi group compared to 25% (41/164) in the placebo group, with 95% confidence intervals of 50–66% and 19–32%, respectively. Median duration of response (DOR) was 18.4 months (95% CI: 10.4, 22.2) with Itovebi versus 9.6 months (95% CI: 7.4, 16.6) with placebo. The Kaplan-Meier survival curve showed early and sustained separation between treatment arms, indicating a longer progression-free survival in the Itovebi group.

Exclusivity and Patents

One New Chemical Entity (NCE) exclusivity is listed in the Orange Book, expiring on October 10, 2029. The patents listed in the Orange Book are summarized in Table 8 (Appendix A).

Kisunla

Donanemab-azbt injection, for intravenous use

Fast Facts	
BLA Holder	Eli Lily and Company
Dosage form	Solution for injection
Route of Administration	Intravenous
BLA Approval	July 2, 2024 (New Biological Entity)*
ODE	None
Mechanism of action	Donanemab-azbt is a humanized IgG1 monoclonal antibody targeting insoluble N-truncated pyroglutamate amyloid beta, reducing amyloid beta plaques

* BLA exclusivity is typically granted for 12 years from date of approval

Indication

Kisunla is an amyloid beta-directed antibody used to treat Alzheimer's disease. It is indicated for patients with mild cognitive impairment or mild dementia and should be initiated at these early stages.

Boxed Warnings

Kisunla, a monoclonal antibody targeting beta-amyloid, may cause amyloid-related imaging abnormalities (ARIA), including ARIA with edema (ARIA-E) and hemosiderin deposition (ARIA-H). While ARIA often occurs early in treatment and is usually

asymptomatic, serious cases—including fatal intracerebral hemorrhages larger than 1 cm—have been reported. ARIA-E can cause neurological deficits resembling ischemic stroke; therefore, clinicians should assess for ARIA before administering thrombolytic therapy.

Patients who are ApoE ε4 homozygotes (approximately 15% of Alzheimer's patients) face a higher risk of ARIA, including symptomatic and severe radiographic cases, compared to heterozygotes and noncarriers. Genetic testing for ApoE ε4 is recommended before treatment to evaluate risk; however, treatment can proceed without testing, although ARIA risk remains uncertain in such cases.

Clinicians should carefully weigh the benefits of Kisunla for Alzheimer's disease against the potential risk of serious ARIA-related events before initiating treatment.

Description

Donanemab-azbt is a humanized IgG1 monoclonal antibody targeting insoluble N-truncated pyroglutamate amyloid beta, with an approximate molecular weight of 145 kDa.

Dosage Form and Handling

Kisunla (donanemab-azbt) injection is a sterile, preservative-free solution supplied in single-dose vials (350 mg/20 mL; 17.5 mg/mL). It should be stored at 2°C to 8°C.

Dosing Regimen

The recommended dosage of Kisunla is 700 mg every four weeks for three doses, followed by 1400 mg every four weeks. It is administered as a 30-minute intravenous infusion and must be diluted prior to administration.

Mechanism of Action

Donanemab-azbt is a humanized IgG1 monoclonal antibody targeting insoluble N-truncated pyroglutamate amyloid beta. The accumulation of amyloid beta plaques in the brain is a hallmark pathophysiological feature of Alzheimer's disease, and donanemab-azbt has been shown in clinical studies to reduce these plaques.

Pharmacokinetics

Minimal accumulation (<1.3-fold) was observed with a dosing interval of every four weeks, and steady-state exposure was achieved after a single dose. When administered at doses ranging from 10 to 40 mg/kg, the maximum plasma concentration (Cmax) and area under the curve (AUC) increased proportionally.

The central volume of distribution (Vd) for Kisunla was determined to be 3.36 liters. Elimination primarily occurs through degradation by proteolytic enzymes, similar to endogenous immunoglobulin G (IgG). The mean terminal half-life of donanemab-azbt is approximately 12.1 days, with a clearance rate of 0.0255 liters per hour.

The pharmacokinetics of donanemab-azbt were not significantly affected by age, sex, or race. While body weight influenced both clearance and volume of distribution, these variations were not considered clinically significant.

No clinical studies specifically evaluated the pharmacokinetics of donanemab-azbt in patients with renal or hepatic impairment. However, since donanemab-azbt is primarily degraded by proteolytic enzymes rather than eliminated renally or metabolized hepatically, significant pharmacokinetic changes in these populations are unlikely.

The incidence of anti-drug antibodies (ADA) varies depending on assay sensitivity and specificity, making cross-study comparisons challenging. In Study 1, 87% of Kisunla-

treated patients developed anti-donanemab-azbt antibodies, all of which were neutralizing. ADA formation was associated with a higher incidence of infusion-related reactions.

ADAs increased donanemab-azbt clearance, resulting in lower serum trough concentrations. Patients with high ADA titers exhibited less amyloid plaque reduction compared to those with low titers. Nevertheless, no clinically significant impact on Kisunla's efficacy was observed over 18 months.

Clinical Studies

The clinical efficacy of Kisunla was evaluated in a double-blind, placebo-controlled study involving 1,736 patients with Alzheimer's disease who had confirmed amyloid pathology and mild cognitive impairment or mild dementia. Participants were randomized to receive either Kisunla (700 mg for the first three doses, followed by 1,400 mg every four weeks) or placebo for up to 72 weeks. Dosing adjustments were made for treatment-emergent amyloid-related imaging abnormalities (ARIA) detected by MRI. Patients could be switched to placebo if amyloid PET scans showed plaque levels below predefined thresholds (<11 Centiloids on a single scan or <25 Centiloids on two consecutive scans).

The primary endpoint was the change in the Integrated Alzheimer's Disease Rating Scale (iADRS) score from baseline to Week 76. Secondary endpoints included the Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB), ADAS-Cog13 (cognitive subscale), and ADCS-iADL (instrumental activities of daily living).

Results showed that Kisunla significantly slowed clinical decline across all primary and secondary endpoints at 76 weeks. For the CDR-SB score, Kisunla-treated patients (n = 860) had a mean adjusted change of +1.72 points compared to +2.42 for placebo (n = 876), representing a 29% reduction in decline ($p < 0.0001$). Similarly, the ADAS-Cog13 scores

demonstrated a 1.33-point (20%) reduction in cognitive decline ($p = 0.0006$), while ADCS-iADL scores showed a 1.70-point (28%) reduction in functional decline ($p = 0.0001$). The efficacy was consistent across low/medium tau populations as well as the combined population. Additionally, amyloid PET scans revealed substantial plaque reductions in Kisunla-treated patients, although plaque levels increased after switching to placebo.

Exclusivity and Patents

No exclusivities or patents currently listed.

Lazcluze™

Lazertinib tablets, for oral use

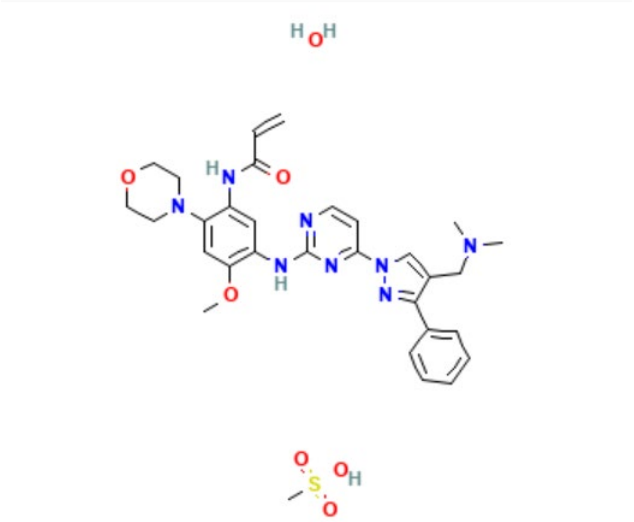
Fast Facts	
NDA Holder	Jansen Biotech Inc.
Product Presentation	Tablet
Route of Administration	Oral
NDA Approval	August 19, 2024
NCE Exclusivity	Exclusivity ending on August 19, 2029
ODE	No
Mechanism of action	Lazertinib is a kinase inhibitor that targets epidermal growth factor receptor (EGFR) mutations, specifically exon 19 deletions and the exon 21 L858R substitution mutation

Indication

Lazcluze, in combination with amivantamab, is indicated as first-line treatment for adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R substitution mutations, as identified by an FDA-approved test.

Description

Lazcluze tablets contain lazertinib, an orally administered kinase inhibitor. Lazertinib is present as lazertinib mesylate hydrate, with a molecular weight of 668.77. Its chemical structure is:



Dosage Form and Handling

Lazcluze (lazertinib) tablets are available in 80 mg and 240 mg strengths and are packaged in HDPE bottles. They should be stored at a controlled temperature of 20°C to 25°C, with allowable excursions between 15°C and 30°C.

The inactive ingredients include croscarmellose sodium, magnesium stearate, mannitol, microcrystalline cellulose, and hydrophobic colloidal silica. The tablet coating contains glycerol monocaprylocaprate type I, iron oxide black and iron oxide red (in the 240 mg tablets), iron oxide yellow (in the 80 mg tablets), macrogol (PEG) polyvinyl alcohol graft copolymer, partially hydrolyzed polyvinyl alcohol, talc, and titanium dioxide.

Dosing Regimen

The recommended dosage of Lazcluze is 240 mg taken orally once daily, administered in combination with amivantamab, with or without food.

Mechanism of Action

Lazertinib is a kinase inhibitor that targets epidermal growth factor receptor (EGFR) mutations, specifically exon 19 deletions and the exon 21 L858R substitution. It inhibits mutant EGFR more effectively at lower concentrations than wild-type EGFR. In mouse models of non-small cell lung cancer (NSCLC) harboring the L858R mutation, treatment with lazertinib combined with amivantamab showed greater antitumor activity than either agent alone.

Pharmacokinetics

Following oral administration, the median time to reach maximum plasma concentration (Cmax) is 2 to 4 hours. Exposure (Cmax and AUC) increases proportionally with dose, and steady state is achieved by Day 15, with a two-fold increase in AUC. A high-fat meal does not significantly affect absorption.

Lazertinib exhibits extensive tissue distribution, with a mean apparent volume of distribution of 2680 L, and is approximately 99.2% bound to plasma proteins. It has a mean terminal half-life of 3.7 days and a mean apparent clearance of 36.4 L/h. Metabolism primarily occurs through glutathione conjugation (both enzymatic and non-enzymatic), with additional metabolism via CYP3A4.

No clinically significant pharmacokinetic differences were observed based on age, sex, body weight, race, or ethnicity. Mild to moderate renal or hepatic impairment had no notable impact, while the effects of severe impairment remain unstudied.

Lazertinib exposure is reduced by CYP3A4 inducers (e.g., rifampin decreased Cmax by 72% and AUC by 83%) and increased by CYP3A4 inhibitors (e.g., itraconazole increased Cmax by 1.2-fold and AUC by 1.5-fold). Gastric acid-reducing agents have no significant effect.

As a perpetrator, lazertinib increases exposure to CYP3A4 substrates (e.g., midazolam Cmax increased by 1.4-fold and AUC by 1.5-fold) and BCRP substrates (e.g., rosuvastatin Cmax increased by 2.2-fold and AUC by 2-fold). It does not significantly affect metformin (OCT1) or raltegravir (UGT1A1). In vitro, it inhibits CYP3A4, UGT1A1, BCRP, and OCT1 but does not induce CYP1A2, CYP2B6, or CYP3A4. No significant differences in safety or efficacy were observed among patients with different GSTM1 genotypes receiving lazertinib with amivantamab.

Clinical Studies

The MARIPOSA trial (NCT04487080) was a randomized, active-controlled, multicenter study evaluating the efficacy of Lazcluze in combination with amivantamab for untreated locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring EGFR exon 19 deletions or exon 21 L858R substitution mutations. Patients were randomized in a 2:2:1 ratio to receive Lazcluze with amivantamab (N=429), osimertinib monotherapy (N=429), or Lazcluze monotherapy (unapproved for NSCLC). Tumor assessments were conducted every eight weeks for the first 30 months, then every 12 weeks until disease progression or unacceptable toxicity. The primary endpoint was progression-free survival (PFS), with secondary endpoints including overall survival (OS), overall response rate (ORR), and duration of response (DOR).

A total of 858 patients were enrolled, 89% with Stage IV disease and 41% with prior brain metastases. EGFR mutations were distributed as 60% exon 19 deletions and 40% exon 21 L858R substitutions, with 97% of biomarker-tested samples confirming EGFR mutations. The combination therapy demonstrated a statistically significant improvement in PFS compared to osimertinib, with a median PFS of 23.7 months versus 16.6 months (HR 0.70,

95% CI: 0.58–0.85). Regarding ORR, Lazcluze plus amivantamab achieved 78% compared to 73% for osimertinib, with a higher proportion of complete responses (5% vs. 3%) and longer DOR (86% vs. 85% for responses lasting ≥ 6 months).

An exploratory analysis of intracranial responses showed ORRs of 68% (55 complete responses) for the combination therapy and 69% (52 complete responses) for osimertinib. However, the combination demonstrated greater durability, with 66 patients maintaining responses for ≥ 12 months compared to 59 with osimertinib, and 35 patients sustaining responses for ≥ 18 months versus 23 in the osimertinib group. These findings highlight the extended benefit of the combination therapy in patients with intracranial lesions and brain metastases.

Exclusivity and Patents

An NCE exclusivity, expiring on June 10, 2029, is listed in the Orange Book. The patents referenced in the Orange Book are summarized in Table 9 (Appendix A).

Leqselvi™

Deuruxolitinib tablets, for oral use

Fast Facts	
NDA Holder	Sun Pharmaceutical Industries, LLC.
Product Presentation	Tablet
Route of Administration	Oral
NDA Approval	July 25, 2024 (New Molecular Entity)
NCE Exclusivity	July 29, 2029
ODE	No
Mechanism of action	A Janus kinase (JAK) inhibitor that targets JAK-mediated signaling pathways involved in cytokine and growth factor signaling

Indication

Leqselvi™ is indicated for the treatment of \adults with severe alopecia areata.

Boxed Warning

The boxed warning for Leqselvi™ highlights serious risks, including severe infections—bacterial, fungal, viral, and opportunistic (such as tuberculosis)—necessitating TB screening and ongoing monitoring. JAK inhibitors are associated with an increased risk of all-cause mortality, particularly cardiovascular deaths, compared to TNF blockers, although Leqselvi™ is not approved for rheumatoid arthritis (RA).

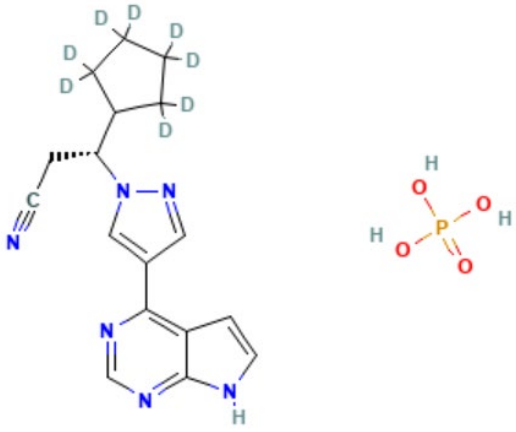
The warning also notes an increased risk of malignancies, including lymphoma and lung cancer, as well as major adverse cardiovascular events (MACE) such as heart attack and stroke. Additionally, patients face increased risks of venous and arterial thrombosis, including deep vein thrombosis (DVT) and pulmonary embolism. Close monitoring is essential to mitigate these risks.

Dosage Form and Handling

Leqselvi™ is supplied as 8 mg immediate-release tablets packaged in high-density polyethylene (HDPE) bottles. Each bottle contains a 1 g silica-gel canister. The tablets contain the following inactive ingredients: colloidal silicon dioxide, lactose monohydrate, low-substituted hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, and povidone. The tablet film coating includes carmine, FD&C Blue No. 2 aluminum lake, glyceryl mono- and dicaprylocaprate, polyvinyl alcohol, sodium lauryl sulfate, talc, and titanium dioxide.

Description

Deuruxolitinib is a deuterated formof ruxolitinib phosphate, with a molecular weight of 412.42 g/mol. Its chemical structure is:



Dosing Regimen

The recommended dosage of Leqselvi™ for treating severe alopecia areata is 8 mg taken orally twice daily, with or without food

Mechanism of Action

Deuruxolitinib is a Janus kinase (JAK) inhibitor that disrupts signaling pathways mediated by JAKs, which regulate cytokine and growth factor activity involved in hematopoiesis and immune system function. These pathways involve the recruitment of STAT (signal transducer and activator of transcription) proteins to cytokine receptors, followed by their activation and translocation to the nucleus to regulate gene transcription. In vitro kinase assays show that deuruxolitinib inhibits JAK1, JAK2, and TYK2 more potently than JAK3. However, the clinical significance of JAK inhibition regarding its therapeutic effect has not been established.

Pharmacokinetics

Deuruxolitinib exhibits dose-proportional pharmacokinetics across the 8–48 mg range, achieving steady-state plasma concentrations within 1 to 2 days of twice-daily dosing, with minimal accumulation. It has a high oral bioavailability of 90%, reaching peak plasma levels approximately 1.5 hours post-administration. Food intake, including high-fat, high-calorie meals, does not significantly affect its pharmacokinetic profile.

The drug shows a steady-state volume of distribution of approximately 50 L, with 91.5% plasma protein binding and a blood-to-plasma concentration ratio of about 1.3. It is primarily metabolized by CYP2C9 (76%) and CYP3A4 (21%), with a minor contribution from CYP1A2 (3%). Its two main metabolites are an order of magnitude less pharmacologically active than the parent compound. Deuruxolitinib has an average

elimination half-life of roughly 4 hours. Following a radiolabeled dose, no unchanged drug is detected in urine or feces, indicating complete metabolism before excretion.

No significant differences in deuruxolitinib pharmacokinetics were observed based on race, ethnicity, age, or body weight. Similarly, no differences were noted in individuals with mild to moderate renal or hepatic impairment. However, the effects of severe renal or hepatic impairment on the drug's pharmacokinetics remain unknown.

Effect of Other Drugs on Deuruxolitinib

Co-administration of deuruxolitinib with rifampin, a strong CYP3A4 and moderate CYP2C9 inducer, resulted in a 78% reduction in AUC and a 41% decrease in Cmax. Predictive modeling suggests that strong CYP2C9 inhibition may cause a 200% increase in AUC and a 25% increase in Cmax, indicating a substantial reduction in metabolic clearance. Similarly, co-administration with fluconazole, a moderate CYP2C9 and CYP3A4 inhibitor, led to a 140% increase in AUC and a 21% increase in Cmax, suggesting enhanced systemic exposure due to enzyme inhibition.

No clinically significant changes in deuruxolitinib pharmacokinetics were observed when administered concomitantly with itraconazole, a strong CYP3A4 inhibitor, or efavirenz, a moderate CYP3A4 inducer.

Effect of Deuruxolitinib on Other Drugs

Deuruxolitinib did not significantly affect the pharmacokinetics of midazolam (a CYP3A4-sensitive substrate) or oral contraceptives (ethinyl estradiol and levonorgestrel), indicating minimal impact on CYP3A4 metabolism.

In vitro, deuruxolitinib is an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4, but not of CYP2D6 or CYP2E1. It does not induce CYP1A2, CYP2B6, or CYP3A4.

Clinical Studies

The clinical efficacy of Leqselvi was evaluated in two multicenter, randomized, double-blind, placebo-controlled Phase 3 trials (AA-1 and AA-2), involving 1,209 adult subjects with alopecia areata (AA) who had at least 50% scalp hair loss for more than six months. Participants were randomized to receive Leqselvi 8 mg, deuruxolitinib 12 mg twice daily, or placebo for 24 weeks. Deuruxolitinib 12 mg is not approved. Subjects were aged 18 to 65 years, with a broad demographic distribution. The average duration of hair loss at baseline was approximately four years, with 59% of participants experiencing near-total hair loss (≥95% scalp hair loss). Eyebrow and eyelash involvement was observed in 73% and 70% of subjects, respectively.

The primary efficacy endpoint was the proportion of subjects achieving significant scalp hair regrowth (≥80% scalp hair coverage, SALT score ≤20) at Week 24. Secondary endpoints included patient satisfaction (measured by the Satisfaction of Hair Patient-Reported Outcome [SPRO], defined as reporting "satisfied" or "very satisfied") and scalp hair regrowth at earlier time points. Clinical response assessments showed that at Week 24, 29% (n=351) and 32% (n=249) of subjects receiving Leqselvi in trials AA-1 and AA-2, respectively, achieved a SALT score ≤20, compared to only 1% in the placebo groups (n=140 and n=127, respectively). The common risk difference from placebo was 28% (95% CI: 23%, 33%) in AA-1 and 31% (95% CI: 25%, 37%) in AA-2. Additionally, 20%

to 24% of Leqselvi-treated subjects achieved near-complete hair regrowth (SALT score ≤10), compared to 0% in placebo groups.

Patient satisfaction with hair coverage was significantly higher among Leqselvi-treated subjects. In trial AA-1, 42% of subjects reported being "satisfied" or "very satisfied," compared to 5% in the placebo group. In trial AA-2, 46% of Leqselvi-treated subjects reported satisfaction, compared to 2% in the placebo group.

Clinical response over time demonstrated progressive hair regrowth in Leqselvi-treated subjects, with notable improvements beginning as early as Week 8 and continuing through Week 24. Subgroup analyses showed consistent efficacy across age, gender, and body weight categories. The response was also robust across different baseline hair loss severities. Among subjects with 50% to 94% scalp hair loss at baseline, 46% achieved a SALT score ≤20 at Week 24 with Leqselvi compared to 2% with placebo. In subjects with more severe hair loss (95% to 100% scalp hair loss), 20% of Leqselvi-treated subjects achieved a SALT score ≤20, compared to none in the placebo group.

Exclusivity and Patents

The patents listed in the Orange Book are summarized in Table 10: Orange Book patents for Leqselvi(Appendix A).

Letybo

Letibotulinumtoxin A-wlbg for injection, for intramuscular use

Fast Facts	
BLA Holder	Hugel Inc.
Dosage form	Powder for solution
Route of Administration	Intramuscular
BLA Approval	February 29, 2024 (New Biological Entity)*
ODE	No
Mechanism of action	Inhibits acetylcholine release at the neuromuscular junction

*BLA exclusivity is typically granted for 12 years from date of approval

Indication

Letybo is indicated for the temporary improvement of moderate to severe glabellar lines in adults by targeting corrugator and procerus muscle activity.

Blackbox Warning

Letybo, like other botulinum toxin products, may spread from the injection site and cause serious, potentially life-threatening effects such as swallowing and breathing difficulties. Cases have been reported from hours to weeks after injection. Letybo is approved only for glabellar lines and not for other conditions.

Description

LetibotulinumtoxinA-wlbg is a 900 kDa botulinum toxin type A that acts as an acetylcholine release inhibitor and neuromuscular blocking agent. It is produced by the fermentation of Clostridium botulinum.

Dosage Form and Handling

Letybo is supplied as a sterile, white, freeze-dried powder in single-dose vials containing either 50 or 100 Units. It should be stored at 2°C to 8°C in the original carton, protected from light, and must not be frozen. Prior to intramuscular injection, Letybo should be reconstituted with preservative-free 0.9% Sodium Chloride Injection, USP, to a final concentration of 4 Units per 0.1 mL. Human albumin and sodium chloride are included as inactive ingredients.

Dosing Regimen

The recommended dose of Letybo is 20 Units per session, administered as five intramuscular injections of 4 Units each—two injections in each corrugator muscle and one in the procerus muscle.

Mechanism of Action

Letybo inhibits acetylcholine release at the neuromuscular junction by cleaving SNAP25, thereby reducing muscle function in a dose-dependent manner.

Pharmacokinetics

Letybo was undetectable in peripheral blood following intramuscular injection at the recommended doses.

Clinical Studies

Letybo was evaluated in three randomized, placebo-controlled Phase 3 trials (BLESS I, II, and III) for the temporary improvement of moderate to severe glabellar lines at

maximum frown. A total of 1,276 subjects aged 19 to 75 years were randomized in a 3:1 ratio to receive Letybo (957 subjects) or placebo (319 subjects). Of these, 1,271 were included in the full analysis set (FAS) for efficacy evaluation. Most subjects were women (91%) and White (91%).

Subjects received a total dose of 20 Units, administered via intramuscular injections at five sites: one injection in the procerus muscle and two in each corrugator supercilii muscle. The Glabellar Line Scale (GLS), used to evaluate severity, is a 4-point scale where 0 = none, 1 = mild, 2 = moderate, and 3 = severe.

At Week 4, efficacy was assessed based on achieving a GLS score of 0 or 1 and at least a 2-point improvement from baseline, as determined by both the investigator and the subject. The proportion of subjects meeting this primary endpoint ranged from 47% to 65% in the Letybo groups and 0% to 2% in the placebo groups. Investigator assessments showed response rates of 66% to 79%, while subject assessments ranged from 55% to 69%.

Exclusivity and Patents

No exclusivities or patents are listed.

Livdelzi®

Seladelpar capsules, for oral use

Fast Facts	
NDA Holder	Gilead Sciences Inc.
Product Presentation	Capsule
Route of Administration	Oral
NDA Approval	August 14, 2024 (New Molecular Entity) Accelerated approval
NCE Exclusivity	August 14, 2029
ODE	Yes, exclusivity ending August 14, 2031
Mechanism of action	A PPAR-delta (δ) agonist that helps regulate bile acid production

Indication

Livdelzi is indicated for the treatment of primary biliary cholangitis (PBC) in adults who have an inadequate response to ursodeoxycholic acid (UDCA) or as monotherapy in those unable to tolerate UDCA. It may be administered in combination with UDCA when additional therapeutic benefit is needed. Livdelzi is a peroxisome proliferator-activated receptor (PPAR)-delta agonist.

This indication has received accelerated approval based on its ability to reduce alkaline phosphatase (ALP) levels.

The use of Livdelzi is not recommended in patients with decompensated cirrhosis or in those who develop it (e.g., ascites, variceal bleeding, hepatic encephalopathy).

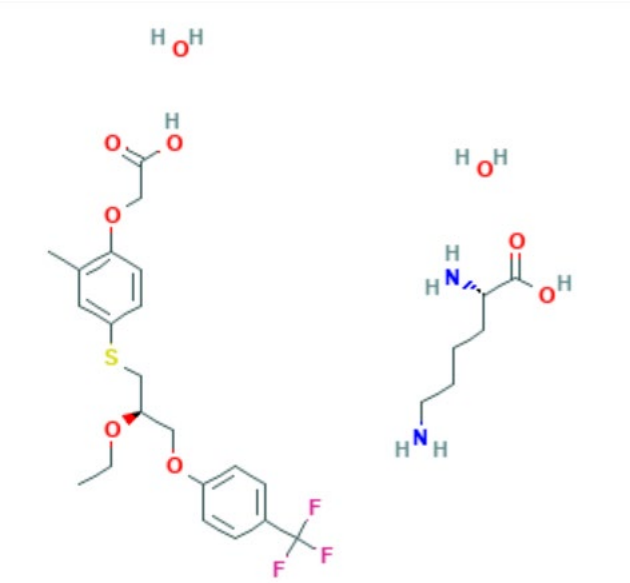
Dosage Form and Handling

Livdelzi (seladelpar) capsules are supplied as 10 mg hard gelatin capsules in HDPE bottles. The product should be stored at 20°C to 25°C, with permitted temperature excursions between 15°C and 30°C

Each capsule contains 14.1 mg of seladelpar lysine and the following inactive ingredients: butylated hydroxytoluene, colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, mannitol, microcrystalline cellulose, and hard gelatin shells.

Description

Livdelzi capsules contain seladelpar lysine dihydrate, which has a molecular weight of 626.7 g/mol. The molecular structure is:



Dosing Regimen

The recommended dosage of Livdelzi is 10 mg taken orally once daily and can be administered with or without food.

Mechanism of Action

Seladelpar is a PPAR-delta (δ) agonist that helps regulate bile acid production, which may contribute to its therapeutic effects. It activates PPARδ, a receptor present in various tissues, including the liver. Research indicates that this activation reduces bile acid synthesis by increasing Fibroblast Growth Factor 21 (FGF21), which subsequently downregulates CYP7A1—the enzyme responsible for converting cholesterol into bile acids. This mechanism helps maintain bile acid balance and may promote liver health.

Pharmacokinetics

Following a single dose, seladelpar systemic exposure increased proportionally from 2 mg to 15 mg (1.5 times the recommended dose). With once-daily dosing, steady-state pharmacokinetics were achieved by Day 4, with less than a 30% increase in AUC. Seladelpar has a median time to peak concentration (Tmax) of 1.5 hours. Administration with a high-fat meal did not produce clinically significant changes in pharmacokinetics. The steady-state apparent volume of distribution is approximately 133.2 L, and plasma protein binding exceeds 99%.

The apparent oral clearance is 12 L/h. In healthy subjects, the mean elimination half-life following a 10 mg dose was 6 hours, whereas in patients with primary biliary cholangitis (PBC), it ranged from 3.8 to 6.7 hours. Seladelpar is primarily metabolized via CYP2C9, with minor contributions from CYP2C8 and CYP3A4, generating three major inactive metabolites: seladelpar sulfoxide (M1), desethyl-seladelpar (M2), and desethyl-seladelpar sulfoxide (M3). Excretion occurs mainly via urine as metabolites.

Seladelpar is a substrate for multiple transporters, including BCRP, P-gp, and OAT3, but not for MATE1, MATE2-K, OAT1, OATP1B1, OATP1B3, OCT1, or OCT2, influencing its drug interaction profile and systemic disposition.

Pharmacokinetics were consistent across demographic groups such as age, BMI, weight, sex, and race, with no clinically significant differences. In patients with renal impairment, pharmacokinetics varied by severity: after a 10 mg dose, AUCinf increased by 10% in mild, 54% in moderate, and was comparable in severe impairment relative to normal renal function. Cmax differences remained under 18%. Pharmacokinetics in patients requiring hemodialysis have not been studied.

In hepatic impairment, seladelpar exposure increased with severity. After a single 10 mg dose, AUC increased 1.1-fold, 2.5-fold, and 2.1-fold in patients with mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment, respectively. Similarly, Cmax increased by 1.3-fold, 5.2-fold, and 5-fold, respectively.

Among PBC patients with hepatic impairment, those with portal hypertension showed.exhibited higher exposure. Compared to PBC patients with mild hepatic impairment (Child-Pugh A) without portal hypertension, exposures were 1.7 to 1.8-fold higher in patients with portal hypertension and 1.6 to 1.9-fold higher in those with moderate hepatic impairment (Child-Pugh B). Despite this, accumulation ratios remained modest (<1.2-fold) after 28 days of once-daily 10 mg dosing.

Seladelpar interacts with several CYP enzymes and transporters, resulting in increased exposure when co-administered with inhibitors such as fluconazole, cyclosporine, or probenecid, and reduced exposure with inducers like carbamazepine. However, seladelpar

itself has minimal impact on the pharmacokinetics of other drugs, indicating a low potential for perpetrating drug-drug interactions.

Clinical Studies

The efficacy of Livdelzi was evaluated in a 12-month, randomized, double-blind, placebo-controlled trial (Trial 1, NCT04620733) involving 193 adult patients with primary biliary cholangitis (PBC) who had an inadequate response or intolerance to ursodeoxycholic acid (UDCA). Eligible patients had alkaline phosphatase (ALP) levels ≥1.67 times the upper limit of normal (ULN) and total bilirubin (TB) ≤2 times ULN. Participants were randomized to receive either Livdelzi 10 mg once daily (N=128) or placebo (N=65). Most Livdelzi-treated patients (94%) received the drug in combination with UDCA, while 6% received Livdelzi as monotherapy.

By Month 12, 62% of Livdelzi-treated patients met the primary biochemical response criteria, compared to 20% in the placebo group, resulting in a treatment difference of 42% (95% CI: 28%, 53%). Among key response components, 66% of Livdelzi patients achieved ALP <1.67 times ULN versus 31% in the placebo group, and 84% had an ALP reduction of at least 15%, compared to 32% of placebo patients. Additionally, ALP normalization (≤ULN) was observed in 25% of Livdelzi patients, whereas no placebo patients achieved this outcome. The least-squares mean change in ALP over 12 months was –134 U/L (95% CI: –151, –117) in the Livdelzi group, versus –41 U/L (95% CI: –59, –22) in the placebo group, reflecting a sustained reduction in ALP levels throughout the study.

Livdelzi also demonstrated a clinically meaningful improvement in pruritus, a common PBC symptom. Among patients with baseline pruritus scores ≥4 on the Numerical Rating Scale (NRS), Livdelzi significantly reduced itching severity. By Month 6, the mean reduction in pruritus scores was –3.2 ± 0.3 with Livdelzi, versus –1.7 ± 0.4 with placebo,

yielding a treatment difference of –1.5 (95% CI: –2.5, –0.5; p=0.0051). This reduction indicates a meaningful improvement in patient-reported quality of life, further supporting Livdelzi's clinical benefits in PBC management.

Exclusivity and Patents

One New Chemical Entity (NCE) exclusivity is listed in the Orange Book, expiring on August 14, 2029. Additionally, one Orphan Drug Exclusivity (ODE) is listed for indication ODE-486*, expiring on August 14, 2031. The patents listed in the Orange Book are summarized in Table 11: Orange Book patents for Livdelzi (Appendix A).

*ODE-486: Treatment of primary biliary cholangitis (PBC) in adults who have had an inadequate response to ursodeoxycholic acid (UDCA), or in patients unable to tolerate UDCA..

Lumisight™

Pegulicianine for injection, for intravenous use

Fast Facts	
NDA Holder	Lumicell
Product Presentation	Powder for Injection
Route of Administration	Intravenous
NDA Approval	April 17, 2024 (New Molecular Entity) Accelerated approval
NCE Exclusivity	Exclusivity ending April 17, 2029
ODE	No
Mechanism of action	Imaging agent

Indication

Lumisight is used for fluorescence imaging in adults with breast cancer to assist in detecting cancerous tissue within the resection cavity after removal of the primary specimen during lumpectomy surgery.

Dosage Form and Handling

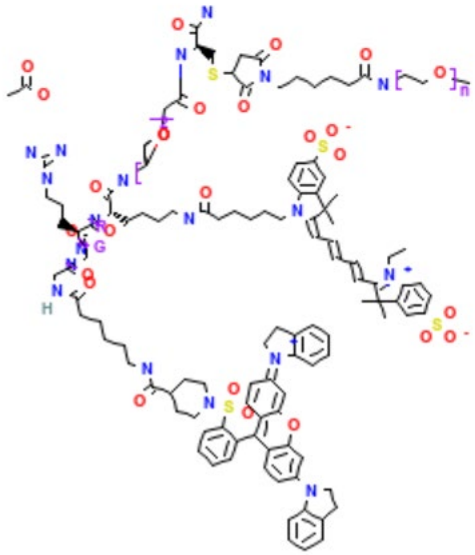
Lumisight (pegulicianine) for injection is supplied as a sterile, preservative-free, lyophilized powder in single-dose vials containing 20 mg of pegulicianine. It is packaged in cartons with one 20 mg vial each. The product should be stored at 2°C to 8°C, protected from light, and kept in the original carton until use. Do not freeze. Prior to administration, Lumisight must be reconstituted with 1.6 mL of sterile water for injection. Inactive

ingredients include mannitol, disodium hydrogen phosphate dihydrate, and citric acid monohydrate.

Description

Lumisight is used with the Lumicell Direct Visualization System (DVS) or other FDA-approved fluorescence imaging devices specifically indicated for use with pegulicianine in the target patient population. The device provides illumination that excites the fluorescent components of pegulicianine and captures images of its fluorescence emission. Areas suspected of containing cancerous tissue are highlighted as positive signals on the Lumicell DVS display.

The molecular formula of pegulicianine acetate is $C_{116}H_{147}N_{19}O_{23}S_4(C_2H_4O)_n$, where n is approximately 450, corresponding to a molecular weight of 20–25 kDa. The chemical structure of the monomeric unit is:



Dosing Regimen

The recommended dose of Lumisight is 1 mg/kg of actual body weight, administered by intravenous injection over 3 minutes, 2 to 6 hours prior to imaging.

Mechanism of Action

Pegulicianine is an optically inactive prodrug that becomes fluorescent upon enzymatic cleavage by cathepsins and matrix metalloproteases (MMPs), enzymes that are more abundant in tumor and tumor-associated cells. This enzymatic cleavage produces two optically active metabolites, Fragment 2 and Fragment 3, which absorb light at 650 nm and fluoresce at 675 nm.

Pharmacokinetics

Pegulicianine is cleaved by tumor-associated proteases, including cathepsins and matrix metalloproteases (MMPs), into the active metabolites fragment 2 and fragment 3. It undergoes minimal hepatic metabolism in vitro.

The excretion pathway of pegulicianine in humans remains unknown; however, the observed blue/green urine discoloration (chromaturia) in subjects suggests possible renal excretion of pegulicianine and/or its metabolites.

Mild renal impairment (RI) does not have a clinically significant effect on the pharmacokinetics, safety, or efficacy of pegulicianine and Fragment 3 (Fragment 2 data are unavailable). The effects of moderate to severe RI on the pharmacokinetics, safety, or efficacy of pegulicianine, fragment 2, and fragment 3 have not been evaluated.

Clinical Studies

The efficacy and safety of Lumisight (pegulicianine) for intraoperative detection of residual cancerous tissue within the lumpectomy cavity were evaluated in a randomized, multicenter, intra-patient controlled trial (NCT03686215). The study enrolled 406 adult patients diagnosed with invasive breast cancer, ductal carcinoma in situ (DCIS), or both. All patients received a single intravenous dose of 1 mg/kg Lumisight administered 2 to 6

hours prior to surgery, followed by intraoperative imaging using the Lumicell DVS system. Patients who had undergone neoadjuvant chemotherapy or radiotherapy were excluded.

After standard-of-care (SOC) lumpectomy, the surgical cavity was divided into six anatomically defined regions, each of which was imaged for fluorescence. When fluorescence signals were detected, up to two fluorescence-guided shaves were excised per region and submitted for histopathologic evaluation. If no guided shaves were taken, margin status was inferred from the corresponding surface of the lumpectomy specimen. Among the 357 patients who underwent Lumisight-guided imaging, 46% (166 patients) had at least one guided shave, and 27 patients (7.6%) had residual cancer confirmed histologically in a fluorescence-guided shave.

Across 2,346 evaluable images, Lumisight demonstrated a sensitivity of 49.1% (95% CI: 36.4%, 61.9%) and specificity of 86.5% (95% CI: 84.5%, 88.3%). Among patients, 43% (155/357) had at least one false positive image, while 8% (28/357) had at least one false negative image. The average volume of Lumisight-guided shaves was 22 cm^3 ± 20 cm^3, representing approximately 20% ± 15% of the total resection volume.

Before Lumisight-guided tissue removal, 17% (62/357) of patients had at least one cancer-positive margin. Following Lumisight-guided resection, 15% (9/62) of these patients achieved complete margin clearance, while 2 of the remaining 295 patients (1%) were reclassified from negative to positive margin status. These findings suggest that Lumisight may aid in identifying residual cancer that is not detected by standard visual inspection and palpation during lumpectomy.

Exclusivity and Patents

An NCE exclusivity expiring on April 17, 2029, is listed in the Orange Book. The patents included in the Orange Book are summarized in Table 12: Orange Book patents for Lumisight (Appendix A).

Miplyffa™

Arimoclomol capsules, for oral use

Fast Facts	
NDA Holder	Zevra Therapeutics, Inc
Product Presentation	Capsule
Route of Administration	Oral
NDA Original Approval	September 20, 2024
NCE Exclusivity	September 20, 2029
ODE	Yes, exclusivity ending September 20, 2031
Mechanism of action	Not known
	First-in-class

Indication

Miplyffa, used in combination with miglustat, is indicated for treating neurological manifestations of Niemann-Pick disease type C (NPC) in adults and pediatric patients aged 2 years and older.

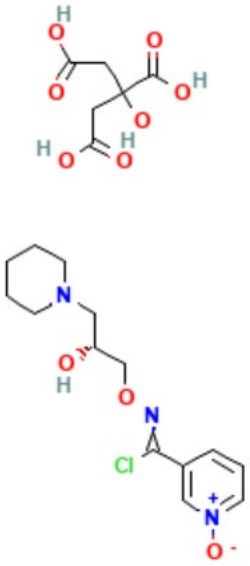
Dosage Form and Handling

Miplyffa (arimoclomol) capsules are available in four strengths—47 mg, 62 mg, 93 mg, and 124 mg—and are packaged in high-density polyethylene (HDPE) bottles containing 90 capsules, each equipped with a child-resistant closure. Miplyffa should be stored at 20°C to 25°C, with permitted temperature excursions between 15°C and 30°C, in its original

container and protected from light. The inactive ingredients include microcrystalline cellulose (MCC) and magnesium stearate.

Description

Miplyffa capsules contain arimoclomol citrate, which has a molecular weight of 505.90 g/mol. The chemical structure is as follows:



Dosing Regimen

The recommended oral dosage of Miplyffa, when used in combination with miglustat, is based on the patient's actual body weight. For patients weighing between 8 kg and 15 kg, the recommended dose is 47 mg three times daily. Those weighing more than 15 kg up to 30 kg should receive 62 mg three times daily. Patients weighing more than 30 kg up to 55 kg require 93 mg three times daily, while those over 55 kg should take 124 mg three times daily. Miplyffa may be administered with or without food.

Mechanism of Action

The exact mechanism of action is unknown.

Pharmacokinetics

Arimoclomol exhibits linear and dose-proportional pharmacokinetics following oral administration of doses ranging from 62 mg to 372 mg, equivalent to three times the maximum recommended dose administered three times daily. The median time to reach maximum plasma concentration (Tmax) is approximately 0.5 hours. No clinically significant differences in arimoclomol pharmacokinetics were observed following administration with a high-fat meal.

At steady state in healthy adults, the apparent volume of distribution is approximately 211 L, and plasma protein binding is about 10%. Arimoclomol undergoes limited metabolism, primarily via glutathionation, O-glucuronidation, and NO-oxime cleavage. It does not inhibit or induce cytochrome P450 (CYP) enzymes or major transporters at clinically relevant concentrations. Arimoclomol is primarily eliminated by the kidneys. The elimination half-life is approximately 4 hours, and the mean apparent clearance is estimated at 34 L/h.

In pediatric patients with Niemann-Pick disease type C (NPC) aged 2 years and older receiving the recommended dose, serum concentrations were comparable to those observed in adults.

In a renal impairment study, subjects with moderate to severe renal impairment exhibited approximately a two-fold increase in arimoclomol exposure (AUC) compared to those with normal renal function. No clinically meaningful difference in exposure was observed in

patients with an eGFR ≥ 50 mL/min. Miplyffa has not been studied in patients with an eGFR < 15 mL/min.

In patients with mild to moderate hepatic impairment (Child-Pugh A or B), no clinically relevant differences in pharmacokinetics were observed. Arimoclomol has not been studied in patients with severe hepatic impairment (Child-Pugh C).

Clinical Studies

The efficacy of Miplyffa was evaluated in a randomized, double-blind, placebo-controlled clinical trial involving 50 patients aged 2 to 18 years with a confirmed diagnosis of Niemann-Pick disease type C (NPC). Patients were randomized in a 2:1 ratio to receive weight-based doses of Miplyffa (31 mg to 124 mg) or placebo three times daily for 12 months. Miglustat use was balanced across both groups, with 76% of patients in the Miplyffa group and 81% in the placebo group receiving miglustat.

Efficacy was assessed using the 4-Domain NPC Clinical Severity Scale (4D-NPC-CSS) every three months over the 12-month period. This scale evaluates disease progression based on ambulation, speech, swallowing, and fine motor skills, with higher scores indicating greater severity. At Month 12, the least squares (LS) mean change from baseline in the 4D-NPC-CSS was -0.2 in the Miplyffa group (n = 22) and 2.0 in the placebo group. The placebo-subtracted difference in mean change from baseline was -2.2 (95% CI: -3.8, -0.6). Two patients in the Miplyffa group discontinued the study: one due to withdrawal of consent, and another due to a disease-related adverse event.

There were insufficient data to determine the effectiveness of Miplyffa without miglustat in treating neurological manifestations of NPC.

Exclusivity and Patents

One New Chemical Entity (NCE) exclusivity is listed in the Orange Book, expiring on September 20, 2029. In addition, an Orphan Drug Exclusivity (ODE) is granted for the treatment of neurological manifestations of Niemann-Pick disease type C (NPC) in adult and pediatric patients aged 2 years and older, with an expiration date of September 20, 2031. Patents associated with Miplyffa and listed in the Orange Book are summarized in Table 13 (Appendix A).

Nemluvio®

Nemolizumab-ilto for injection, for subcutaneous use

Fast Facts	
BLA Holder	Galderma Laboratories, L.P.
Dosage form	Powder for injection Prefilled dual-chamber pen with lyophilized powder in one chamber and diluent in the other chamber.
Route of Administration	Subcutaneous
BLA Approval	August 12, 2024 (New Biological Entity)*
ODE	None
Mechanism of action	A humanized IgG2 monoclonal antibody that inhibits IL-31 signaling by selectively binding to IL-31 RA

* BLA exclusivity is typically granted for 12 years from date of approval.

Indication

Nemluvio is an interleukin-31 receptor antagonist indicated for the treatment of prurigo nodularis in adults.

Description

Nemolizumab-ilto, an interleukin-31 receptor alpha (IL-31RA) antagonist, is a humanized monoclonal modified immunoglobulin G (IgG) antibody with an approximate molecular weight of 144 kDa. It is produced using recombinant DNA technology in CHO cells.

Dosage Form and Handling

Nemluvio (nemolizumab-ilto) is supplied as a sterile, preservative-free, white lyophilized powder in a single-dose, dual-chamber prefilled pen. Each pen contains 30 mg of nemolizumab-ilto in one chamber and water for injection as the diluent in the other. After reconstitution, the pen delivers 30 mg/0.49 mL of solution. The inactive ingredients include arginine hydrochloride, poloxamer 188, sucrose, trometamol, and tris hydrochloride. For storage, Nemluvio should be refrigerated at 2°C to 8°C in its original carton to protect it from light. It may also be stored at room temperature (up to 25°C) for a single period of up to 90 days. After reconstitution, the product must be used within 4 hours or discarded. Nemluvio should not be frozen or exposed to heat or direct sunlight.

Dosing Regimen

For adult patients weighing less than 90 kg, the recommended dosage of Nemluvio begins with an initial dose of 60 mg, administered as two 30 mg injections, followed by a maintenance dose of 30 mg every four weeks (Q4W). For patients weighing 90 kg or more, the initial dose remains 60 mg, but the maintenance dose increases to 60 mg every four weeks (Q4W).

Mechanism of Action

Nemolizumab-ilto is a humanized IgG2 monoclonal antibody that inhibits IL-31 signaling by selectively binding to the IL-31 receptor alpha (IL-31RA). IL-31 is a naturally occurring cytokine involved in pruritus, inflammation, epidermal dysregulation, and fibrosis. By

targeting IL-31RA, nemolizumab-ilto blocks IL-31-induced responses, including the release of proinflammatory cytokines and chemokines.

Pharmacokinetics

The pharmacokinetics of nemolizumab-ilto demonstrate a proportional increase in drug exposure across subcutaneous doses ranging from 0.03 to 3 mg/kg. For doses up to 30 mg, exposure remains approximately dose-proportional, although bioavailability decreases slightly—by 9% at a 60 mg dose and by 15% at a 90 mg dose. The volume of distribution is estimated at 7.67 liters.

After multiple doses, steady-state levels are reached by week 4 in individuals weighing less than 90 kg, and by week 12 in those weighing 90 kg or more. Nemolizumab-ilto is expected to be degraded via catabolic pathways into small peptides, similar to endogenous IgG. Its terminal elimination half-life is approximately 18.9 days, with systemic clearance around 0.263 L/day.

Age does not significantly affect the pharmacokinetics of nemolizumab-ilto. No notable changes have been observed in patients with mild to moderate renal or hepatic impairment, although effects in severe impairment have not been studied. Body weight influences drug exposure, with higher body weight associated with lower systemic concentrations. This variability affects skin lesion improvement, as measured by the Investigator Global Assessment (IGA) response, but does not impact pruritus relief.

No dedicated drug interaction studies have been conducted with nemolizumab-ilto. However, treatment with Nemluvio may alter serum cytokine levels, potentially influencing cytochrome P450 (CYP450) enzyme activity. Therefore, when initiating or discontinuing Nemluvio in patients taking medications that are CYP450 substrates—

especially those with a narrow therapeutic index—monitoring may be necessary. This could include evaluating therapeutic effects (e.g., warfarin) or measuring drug concentrations (e.g., cyclosporine), with dosage adjustments made as needed.

Clinical Studies

The clinical evaluation of Nemluvio was conducted in two randomized, double-blind, placebo-controlled trials—OLYMPIA 1 and OLYMPIA 2—which enrolled a total of 560 adult subjects with prurigo nodularis (PN). Disease severity was assessed using the Investigator's Global Assessment (IGA) scale, ranging from 0 (clear) to 4 (severe), and the peak pruritus numeric rating scale (PP-NRS), an 11-point scale from 0 (no itch) to 10 (worst itch imaginable). Eligible participants had an IGA score of ≥3, a PP-NRS score of ≥7, and at least 20 nodular skin lesions. The efficacy of Nemluvio was evaluated over 16 weeks, with an extension to 24 weeks in OLYMPIA 1.

Subjects weighing less than 90 kg received an initial subcutaneous dose of 60 mg at Week 0, followed by 30 mg every 4 weeks. Subjects weighing 90 kg or more received 60 mg every 4 weeks starting at Week 0. At baseline, the mean PP-NRS score was 8.5. Among all participants, 58% had an IGA score of 3 (moderate PN), and 42% had an IGA score of 4 (severe PN).

Efficacy was assessed by the proportion of subjects achieving a ≥4-point improvement from baseline in PP-NRS, and by the proportion achieving an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-point improvement from baseline. At Week 16, 56% of Nemluvio-treated subjects in OLYMPIA 1 and 49% in OLYMPIA 2 achieved a ≥4-point reduction in PP-NRS scores, compared to 16% in the placebo groups of both trials. For IGA scores of 0 or 1 with the required improvement, 26% of Nemluvio-treated subjects in

OLYMPIA 1 and 38% in OLYMPIA 2 responded, compared to 7% and 11% in their respective placebo groups.

Exclusivity and Patents

No entries listed.

Niktimvo™

Axatilimab-csfr injection, for intravenous use

Fast Facts	
BLA Holder	Incyte Corporation
Dosage form	Solution for injection
Route of Administration	Intravenous
BLA Approval	August 14, 2024 (New Biological Entity)*
	First-in-class
ODE	Yes, exclusivity end date August 14, 2031
Mechanism of action	a CSF-1R–blocking antibody

* BLA exclusivity is typically granted for 12 years from date of approval.

Indication

Niktimvo is a monoclonal antibody targeting the colony-stimulating factor-1 receptor (CSF-1R), approved for use in adults and children weighing 40 kg or more with chronic graft-versus-host disease (cGVHD) who have failed to respond to at least two prior systemic treatment regimens.

Description

Axatilimab-csfr is a CSF-1R–blocking, humanized IgG4 (kappa light chain) monoclonal antibody produced in CHO cells, with an approximate molecular weight of 150 kDa.

Dosage Form and Handling

Niktimvo (axatilimab-csfr) is provided as a solution for injection. It is supplied in a carton containing a single-dose vial at a concentration of 50 mg/mL. Each vial contains 50 mg of axatilimab-csfr in 1 mL of solution. The formulation also includes citric acid monohydrate (3.6 mg), glycine (9.38 mg), polysorbate 80 (0.5 mg), sodium citrate (8.49 mg), sucrose (42.79 mg), and Water for Injection, USP. The pH of the solution is 5.0. Niktimvo should be stored in its original carton at 2°C to 8°C, protected from light. Axatilimab-csfr must be diluted prior to administration.

Dosing Regimen

For patients weighing 40 kg or more, administer Niktimvo at 0.3 mg/kg (up to a maximum of 35 mg) by intravenous infusion over 30 minutes every two weeks, continuing until disease progression or unacceptable toxicity occurs.

Mechanism of Action

Axatilimab-csfr is a monoclonal antibody that blocks CSF-1R, thereby reducing circulating proinflammatory and profibrotic monocytes as well as monocyte-derived macrophages. Additionally, it inhibits the activity of pathogenic macrophages within tissues.

Pharmacokinetics

The area under the curve (AUC) of axatilimab-csfr exhibited a greater-than-dose-proportional increase following a single dose ranging from 0.15 mg/kg to 3 mg/kg (0.5 to 10 times the approved dose) in healthy subjects. No systemic accumulation was observed at the approved dosage. The volume of distribution (Vd) was 6.06 L (16.3% CV). Elimination occurred via both linear and non-linear pathways, with a total clearance rate of 0.07 L/h (38.8% CV). The median time to achieve a 97% reduction in plasma concentration post-infusion was 4.0 days (range: 2.3 to 7.2 days). Clearance decreased

from 2.32 mL/h/kg at lower doses to 0.21 mL/h/kg at higher doses, while the terminal half-life increased from 10.7 hours to 108 hours, indicating dose-dependent pharmacokinetics. The drug is metabolized into small peptides through catabolic pathways.

No clinically significant differences in drug exposure were observed based on age, sex, body weight, or race in patients aged 12 to 81 years. Patients with mild to moderate renal impairment and mild hepatic impairment showed similar drug exposures at the recommended dose. The effects of severe renal impairment and moderate to severe hepatic impairment have not been evaluated. In pediatric patients weighing ≥ 40 kg, drug exposure was comparable to that in adults receiving the approved dose.

In a study of 276 patients with chronic GVHD treated with Niktimvo, 33.7% (93 patients) developed treatment-emergent anti-drug antibodies (ADAs), with neutralizing antibodies (NAbs) detected in 47 of these patients. No clinically meaningful impact of ADAs or NAbs on pharmacokinetics, pharmacodynamics, or efficacy was observed; however, NAbs were associated with hypersensitivity reactions. Cross-study comparisons are limited due to differences in ADA assay methodologies.

Clinical Studies

The AGAVE-201 trial (NCT04710576) was a randomized, open-label study evaluating Niktimvo in patients with recurrent or refractory chronic graft-versus-host disease (cGVHD) after failure of at least two prior systemic therapies. Patients with uncontrolled infections were excluded. Niktimvo (0.3 mg/kg IV every 2 weeks) was administered until disease progression, lack of efficacy (≤9 months), or unacceptable toxicity.

The primary efficacy endpoint, overall response rate (ORR), was assessed at Cycle 7, Day 1, using the 2014 NIH criteria for cGVHD. The ORR was 75% (59 of 79 patients; 95% CI: 64%–84%), with all responses being partial; no complete responses were observed.

The median time to first response was 1.5 months (range: 0.9–5.1 months). The median duration of response was 1.9 months (95% CI: 1.6–3.5 months). Among responders, 60% (95% CI: 43%–74%) experienced no death or need for new systemic therapy for at least 12 months.

Exploratory analyses supported the ORR results, with 56% of patients (95% CI: 44%–67%) reporting a ≥7-point reduction in the modified Lee Symptom Scale by Cycle 7, Day 1, indicating reduced symptom burden.

Exclusivity and Patents

One Orphan Drug Exclusivity (ODE) is listed in the Orphan Drug Database, expiring on August 14, 2031, for the treatment of chronic graft-versus-host disease (cGVHD) in adults and pediatric patients weighing 40 kg or more who have failed at least two prior lines of systemic therapy.

Ohtuvayre

Ensifentrine inhalation suspension, for oral inhalation use

Fast Facts	
NDA Holder	Verona Pharma
Product Presentation	Suspension for inhalation
Route of Administration	Oral inhalation
NDA Approval	June 26, 2024 (New Molecular Entity)
NCE Exclusivity	Exclusivity ending on June 26, 2029
ODE	No
Mechanism of action	A PDE3 and PDE4 inhibitor

Indication

Ohtuvayre, a dual phosphodiesterase 3 and 4 (PDE3/4) inhibitor, is indicated for the maintenance treatment of chronic obstructive pulmonary disease (COPD) in adults.

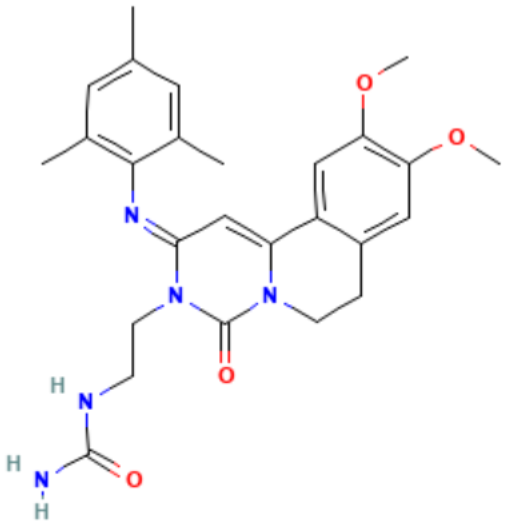
Dosage Form and Handling

Ohtuvayre Inhalation Suspension (3 mg/2.5 mL) is a sterile aqueous suspension supplied in low-density polyethylene unit-dose ampules, each sealed within a foil pouch. Each ampule contains 3 mg of ensifentrine in a pH 6.7 solution with dibasic sodium phosphate, monobasic sodium phosphate, polysorbate 20, sodium chloride, sorbitan monolaurate, and water for injection. Shake vigorously before nebulization. Oral inhalation is administered using a standard jet nebulizer over approximately 5 to 7 minutes. Store in the foil pouch at 20°C–25°C, with excursions permitted from 15°C–30°C.

Description

The molecular weight of ensifentrine is 477.56 g/mol. Its molecular structure is:

as follows:



Dosing Regimen

The recommended dosage of Ohtuvayre is 3 mg twice daily once in the morning and once in the evening administered by oral inhalation using a standard jet nebulizer with a mouthpiece.

Mechanism of Action

Ensifentrine is a dual inhibitor of the enzymes phosphodiesterase 3 (PDE3) and phosphodiesterase 4 (PDE4). PDE3 primarily degrades the intracellular signaling molecules cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), while PDE4 selectively hydrolyzes cAMP. By inhibiting both PDE3 and PDE4, ensifentrine increases intracellular concentrations of cAMP and/or cGMP. This elevation

of second messengers triggers a range of downstream signaling effects believed to contribute to its therapeutic activity.

Pharmacokinetics

Ensifentrine exposure increased 1.4-fold above dose proportionality following a dose three times the recommended amount, with steady-state achieved by Day 3 during twice-daily (BID) dosing. Accumulation ratios for Cmax and AUC ranged from 1.3 to 1.4 in healthy individuals and from 1.4 to 1.5 in COPD patients. Bioavailability in COPD patients was approximately 35% lower than in healthy subjects.

Ensifentrine is rapidly absorbed after inhalation, reaching Cmax within 0.6 to 1.5 hours, with roughly 90% absorption through the lungs. The apparent volume of distribution (Vd) is greater in COPD patients (8,150 L central, 5,490 L peripheral) compared to healthy individuals (2,700 L central, 1,820 L peripheral). Plasma protein binding is approximately 90%.

The drug is eliminated with a terminal half-life ranging from 10.6 to 12.6 hours following BID administration for six days. Ensifentrine undergoes metabolism primarily through oxidation (hydroxylation and O-demethylation), followed by glucuronidation. The major circulating plasma compound is unchanged ensifentrine, with metabolism mainly mediated by CYP2C9 and, to a lesser extent, CYP2D6. Excretion occurs predominantly via feces, with minimal renal clearance (≤0.3% of the dose). Pharmacokinetic profiles showed no significant variation based on age, sex, or ethnicity.

A 25% reduction in apparent clearance was observed in patients with moderate renal impairment; however, data are not available for patients with severe renal impairment or end-stage renal disease.

In patients with moderate hepatic impairment, Cmax and AUCinf increased 2.3-fold and 2.2-fold, respectively. In those with severe hepatic impairment, Cmax increased 1.2-fold and AUCinf increased 2.3-fold. No significant impact on liver function markers (ALT, AST, bilirubin, ALP) was noted.

Co-administration of Ohtuvayre with the CYP2C9 inhibitor fluconazole increased ensifentrine Cmax and AUCinf by 1.4-fold and 1.6-fold, respectively. In vitro studies indicate that ensifentrine is a substrate of BCRP but not of P-gp, OATP1B1, or OATP1B3. At therapeutically relevant concentrations, it does not inhibit major CYP enzymes, efflux transporters (BCRP, P-gp), or uptake transporters, suggesting a low potential for drug-drug interactions.

Clinical Studies

The efficacy and safety of Ohtuvayre in moderate to severe COPD were evaluated in two 24-week, randomized, double-blind, placebo-controlled trials: ENHANCE-1 (n=763) and ENHANCE-2 (n=790). Patients were randomized in a 5:3 ratio to receive 3 mg Ohtuvayre via nebulizer or placebo. The study population had a mean age of 65 years, with 90–95% White participants and 55–57% current smokers. Baseline lung function was severely impaired, with a mean post-bronchodilator FEV1 approximately 52% of predicted and an FEV1/FVC ratio of 0.52. Most patients were receiving concurrent COPD medications, including LAMA, LABA, and ICS combinations.

The primary efficacy endpoint was the change from baseline in FEV1 $AUC_{0–12}$h (mL) at Week 12, measuring lung function over 12 hours post-dose. In ENHANCE-1, Ohtuvayre demonstrated an 87 mL improvement over placebo (95% CI: 55, 118), while in ENHANCE-2, the improvement was 94 mL (95% CI: 65, 124), both statistically

significant. Trough FEV1 at Week 12 increased by 35 mL (95% CI: 14, 68) in ENHANCE-1, reaching statistical significance. In ENHANCE-2, the increase was 49 mL (95% CI: 19, 80), but this did not achieve statistical significance due to failure higher in the testing hierarchy.

Quality of life was assessed using the St. George's Respiratory Questionnaire (SGRQ). In ENHANCE-1, 58.2% of patients treated with Ohtuvayre reported a clinically meaningful improvement in SGRQ score (≥4-point reduction) compared to 45.9% in the placebo group, with an odds ratio of 1.49 (95% CI: 1.07, 2.07), indicating statistical significance. In ENHANCE-2, 45.4% of Ohtuvayre-treated patients improved compared to 50.3% with placebo, with an odds ratio of 0.92 (95% CI: 0.66, 1.29), which was not statistically significant.

Exclusivity and Patents

One New Chemical Entity (NCE) exclusivity is listed in the Orange Book, expiring on June 26, 2029. The patents listed in the Orange Book are summarized in Table 14 (Appendix A).

Ojemda

Tovorafenib tablets, for oral use

Fast Facts	
NDA Holder	Day One Biopharmaceuticals
Product Presentation	Tablet, Powder for Oral Suspension
Route of Administration	Oral
NDA Approval	April 23, 2024 (New Molecular Entity) Accelerated Approval
NCE Exclusivity	Exclusivity ending on April 23, 2029
ODE	Exclusivity ending on April 23, 2031
Mechanism of action	A Type II RAF kinase inhibitor of mutant BRAF V600E, wild-type BRAF, and wild-type CRAF kinases

Indication

Ojemda is indicated for the treatment of patients aged six months and older with relapsed or refractory pediatric low-grade glioma (LGG) harboring a BRAF fusion, rearrangement, or BRAF V600 mutation.

Dosage Form and Handling

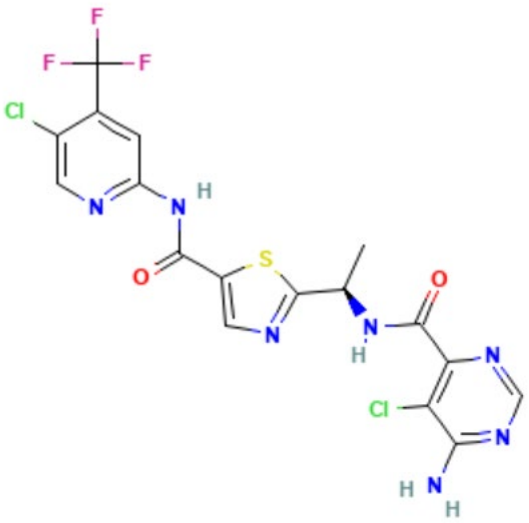
Ojemda tablets are supplied as film-coated tablets of 100 mg strength, packaged in blister cards within a carton. Inactive ingredients include copovidone, colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, and a film coating

containing hypromellose, titanium dioxide, iron oxide yellow, macrogol, polyvinyl alcohol, and talc (Opadry® Orange). The drug product should be stored at 20°C to 25°C, with permitted excursions between 15°C and 30°C.

Ojemda for oral suspension is supplied as a white to off-white powder in a clear glass bottle, co-packaged with a press-in bottle adaptor and a 20 mL oral dosing syringe. Each mL of the reconstituted strawberry-flavored tovorafenib suspension contains 25 mg of tovorafenib. Each bottle delivers 300 mg of tovorafenib in 12 mL. Inactive ingredients include artificial strawberry flavor, colloidal silicon dioxide, copovidone, maltodextrin, mannitol, microcrystalline cellulose, simethicone, sodium lauryl sulfate, and sucralose. Store the glass bottle containing Ojemda for oral suspension at 20°C to 25°C in the original carton to protect from moisture.

Description

Ojemda contains tovorafenib, a kinase inhibitor. Tovorafenib has a molecular weight of 506.29 g/mol. Its chemical structure is:



Dosing Regimen

The recommended dosage of Ojemda is based on body surface area (BSA) at 380 mg/m² orally once weekly, with a maximum weekly dose of 600 mg. It may be taken with or without food, either as a tablet or an oral suspension.

For patients with a BSA between 0.30 and 0.89 m², Ojemda should be administered as an oral suspension according to specific dosing guidelines. Those with a BSA of 0.90 to 1.12 m² should receive 400 mg once weekly, while patients with a BSA of 1.13 to 1.39 m² should receive 500 mg once weekly. For patients with a BSA of 1.40 m² or greater, the recommended dose is 600 mg once weekly.

Ojemda oral suspension is dosed once weekly based on BSA, with individualized doses ranging from 125 mg to 600 mg (equivalent to 5 to 24 mL of suspension). Specific dose volumes corresponding to narrow BSA ranges are detailed in the prescribing information.

Mechanism of Action

Tovorafenib is a Type II RAF kinase inhibitor targeting mutant BRAF V600E, wild-type BRAF, and wild-type CRAF kinases.

Pharmacokinetics

Tovorafenib exhibits dose-proportional pharmacokinetics, with a median Tmax of 3 hours following a single oral dose. Steady-state concentrations are reached within 12 days, with no significant drug accumulation. Food intake delays Tmax to 6.5 hours but does not significantly affect drug exposure, including Cmax or AUC.

The drug has a volume of distribution of 60 L/m² and is 97.5% bound to plasma proteins. It is primarily metabolized by aldehyde oxidase and CYP2C8, with minor contributions from CYP3A, CYP2C9, and CYP2C19. The terminal half-life is approximately 56 hours, with an apparent clearance of 0.7 L/h/m².

Excretion occurs mainly via feces (65%), with 6.8% of the dose excreted unchanged. Approximately 27% is eliminated in urine, with 0.2% unchanged. No clinically significant pharmacokinetic differences were observed based on age, sex, race, mild hepatic impairment, or mild-to-moderate renal impairment.

Regarding drug interactions, tovorafenib may reduce exposure of CYP3A4 substrates by approximately 20%, and it inhibits CYP2C8, CYP2C9, CYP2C19, and CYP3A at clinically relevant concentrations. It does not inhibit CYP1A2, CYP2B6, or CYP2D6 at clinically relevant concentrations. Tovorafenib also induces CYP3A, CYP2C8, CYP1A2, CYP2B6, CYP2C9, and CYP2C19 at clinically relevant concentrations. It is not a substrate for BCRP, P-gp, or OATP1B1/1B3 transporters, thereby minimizing the risk of transporter-mediated drug interactions.

Clinical Studies

The FIREFLY-1 clinical trial evaluated the efficacy of Ojemda, an investigational treatment for relapsed or refractory pediatric low-grade glioma (LGG) harboring a BRAF alteration. This open-label, single-arm study enrolled 76 patients, all of whom had previously received systemic therapy and exhibited documented radiographic progression. Patients were administered Ojemda at approximately 420 mg/m² once weekly, with a recommended dosage of 380 mg/m². Tumor assessments were conducted every 12 weeks. The primary efficacy endpoint was the overall response rate (ORR), which was 51% (95% CI: 40, 63) based on RAPNO-LGG criteria. Responses included 28 patients (37%) with partial responses (PR) and 11 patients (14%) with minor responses (MR); no complete responses were observed. The median duration of response (DoR) was 13.8 months, with 85% of responders maintaining their response for at least 6 months and 23% for at least 12

months. ORR was consistent across subgroups, with a 52% ORR in patients with BRAF fusion/rearrangement and 50% in those with the BRAF V600E mutation. Patients who had received prior MAPK-targeted therapy had an ORR of 49%, compared to 55% in those without prior MAPK inhibitor treatment.

The study population had a median age of 8.5 years (range 2–24), and the most common tumor locations were the optic pathway (51%), deep brain structures (12%), and brainstem (8%). Most patients (74%) had a KIAA1549-BRAF fusion, while the remainder had a BRAF V600E mutation or other BRAF alterations.

Exclusivity and Patents

One New Chemical Entity (NCE) exclusivity is listed in the Orange Book, expiring on June 26, 2029. Additionally, one Orphan Drug Exclusivity (ODE) is also listed for the indication ODE-478*, expiring on June 26, 2031. The patents listed in the Orange Book are summarized in Table 15 (Appendix A).

*ODE-478 — Treatment of patients aged 6 months and older with relapsed or refractory pediatric low-grade glioma (LGG) harboring a BRAF fusion or rearrangement, or BRAF V600 mutation.

Orlynvah™

Sulopenem etzadroxil and probenecid tablets, for oral use

	Fast Facts
NDA Holder	Iterum Therapeutics
Product Presentation	Tablet
Route of Administration	Oral
NDA Original Approval	October 25, 2024 (New Molecular Entity and New Combination)
NCE Exclusivity	October 25, 2029
ODE	Yes, ODE expiring October 25, 2029 and ODE GAIN expiring on October 25, 2031
Mechanism of action	A penem antibacterial drug in combination with probenecid to inhibit renal clearance and increase its plasma concentrations

Indication

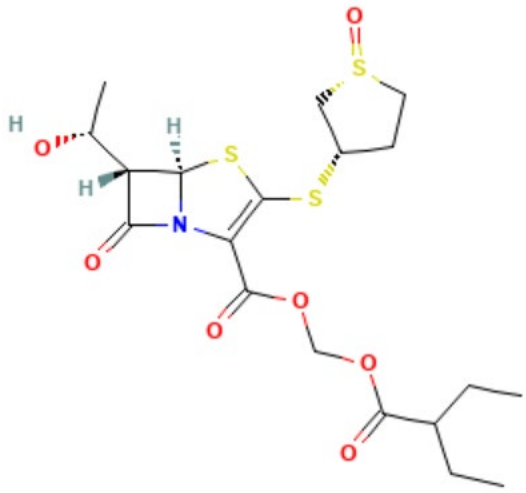
Orlynvah is approved for the treatment of uncomplicated urinary tract infections (uUTIs) in adult women when other oral antibacterial options are unavailable or limited. However, it should not be used for complicated UTIs (cUTIs), complicated intra-abdominal infections (cIAIs), or as step-down therapy following intravenous antibacterial treatments for these conditions.

Dosage Form and Handling

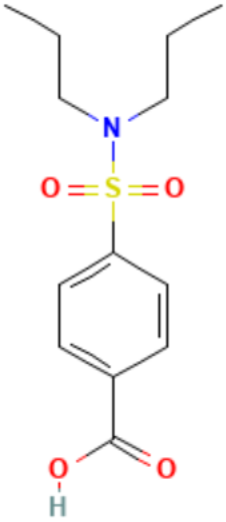
Orlynvah (sulopenem etzadroxil 500 mg and probenecid 500 mg) is supplied as a film-coated, fixed-dose bilayer combination tablet. It should be stored at 20°C to 25°C, with allowable temperature excursions between 15°C and 30°C. Inactive ingredients include croscarmellose sodium, hydroxypropylcellulose, lactose monohydrate, magnesium stearate, and microcrystalline cellulose. The film coating contains carmine, lecithin, polyvinyl alcohol, talc, titanium dioxide, and xanthan gum.

Description

Orlynvah (sulopenem etzadroxil and probenecid) tablets contain sulopenem etzadroxil, a penem antibacterial agent, and probenecid, a renal tubular transport inhibitor. The molecular weight of sulopenem etzadroxil is 477.61 g/mol. Its chemical structure is:



The molecular weight of probenecid is 285.36 g/mol. Its chemical structure is:



Dosing Regimen

The recommended dosage of Orlynvah is one tablet, containing 500 mg of sulopenem etzadroxil and 500 mg of probenecid, taken orally twice daily for 5 days. It is recommended to take Orlynvah with food.

Mechanism of Action

Orlynvah contains sulopenem etzadroxil, a penem antibacterial agent, and probenecid, a renal tubular transport inhibitor. Probenecid inhibits OAT3-mediated renal clearance of sulopenem, thereby increasing its plasma concentrations.

Pharmacokinetics

The pharmacokinetics of Orlynvah were evaluated in healthy subjects following a single oral dose of 500 mg sulopenem etzadroxil and 500 mg probenecid. Sulopenem was rapidly absorbed, reaching a median peak plasma concentration (Tmax) of 1.0 hour under fasted conditions and 2.0 hours when fed, whereas probenecid's Tmax ranged from 3.0 hours (fasted) to 2.0 hours (fed). Food significantly increased sulopenem exposure, raising Cmax by 45% and AUC by 48%, whereas it reduced probenecid Cmax by 27% and AUC by 8%.

The bioavailability of sulopenem was 40% under fasted conditions and 64% under fed conditions. Probenecid bioavailability has not been reported.

Sulopenem exhibited an apparent volume of distribution (Vd) of 134 L under fasted conditions and 92.09 L under fed conditions, suggesting extensive tissue penetration. Plasma protein binding for sulopenem was 11%, while probenecid's protein binding remains unknown. The drug is primarily eliminated via feces (44.3%) and urine (40.8%), with only 3.1% excreted unchanged in urine. Probenecid inhibits OAT3-mediated renal clearance, thereby increasing sulopenem plasma concentrations. Sulopenem undergoes hydrolysis to form the active compound, followed by further metabolism via hydrolysis and dehydrogenation, while probenecid's metabolic pathway remains unclear. The elimination half-life ($t_{1/2}$) of sulopenem was approximately 1.18 hours under fasted conditions and 1.28 hours under fed conditions, whereas probenecid exhibited a longer half-life of 2.93 hours (fasted) and 3.83 hours (fed).

No clinically significant differences in sulopenem pharmacokinetics were observed based on age, sex, or weight, though the effect of hepatic impairment is unknown. In patients with renal impairment, sulopenem AUCinf increased by 2-fold in mild impairment (CrCL 60–89 mL/min), 3-fold in moderate impairment (CrCL 30–59 mL/min), and 7.4-fold in severe impairment (CrCL 15–29 mL/min) after a 1000 mg oral dose, which is not a recommended regimen. The impact of kidney failure (CrCL <15 mL/min) or hemodialysis on sulopenem pharmacokinetics remains unknown, indicating caution in severe renal dysfunction.

Drug interaction studies demonstrated that co-administration of Orlynvah with itraconazole (a P-gp inhibitor), pantoprazole, or aluminum hydroxide had minimal effect

on sulopenem pharmacokinetics. However, multiple doses of 500 mg sulopenem etzadroxil with valproic acid reduced valproic acid's AUCinf by 25% and Cmax by 19%. When valproic acid was administered with Orlynvah, the reduction was less pronounced (AUC∞ decreased by 8.4% and Cmax by 7%), suggesting probenecid may counteract sulopenem's effect on valproic acid concentrations.

In vitro studies confirmed that sulopenem neither inhibits nor induces major CYP enzymes, including CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5, indicating a low potential for CYP450-mediated drug interactions. Sulopenem is primarily a substrate of OAT3 but does not inhibit transporters such as BCRP, P-gp, BSEP, OCT1, or OCT2. Probenecid, however, is a substrate of BCRP and an inhibitor of OAT1 and OAT3, contributing to increased sulopenem plasma concentrations, but it does not inhibit BSEP, P-gp, or MRP2. These findings highlight Orlynvah's limited drug interaction potential and reliance on renal transport mechanisms for clearance.

Clinical Studies

Trial 1: Uncomplicated Urinary Tract Infections (uUTI) – Orlynvah vs. Amoxicillin/Clavulanate

A randomized, double-blind trial (NCT05584657) compared Orlynvah (sulopenem etzadroxil 500 mg + probenecid 500 mg, BID for 5 days) with amoxicillin/clavulanate (875 mg/125 mg, BID for 5 days) in 2,222 adult women with uUTIs. A total of 2,214 patients received trial medication. The microbiological modified intent-to-treat (micro-MITT) population included 990 patients who had $\geq 10^5$ CFU/mL of at least one uropathogen at baseline and received ≥1 dose of study drug.

Composite response (microbiological response + clinical cure) was assessed at the test-of-cure (TOC) visit (Day 12 post-randomization) in the overall micro-MITT population and two subgroups:

Micro-MITTS (with baseline amoxicillin/clavulanate susceptible pathogens; MIC ≤8/4 µg/mL):

Composite response: Orlynvah 61.7% (296/480) vs. Amox/Clav 55% (243/442)

Clinical cure: Orlynvah 77.3% (371/480) vs. Amox/Clav 76.7% (339/442)

Microbiological response: Orlynvah 75.2% (361/480) vs. Amox/Clav 66.7% (296/442)

Micro-MITTR (with baseline amoxicillin/clavulanate non-susceptible pathogens; MIC ≥16/8 µg/mL):

Composite response: Orlynvah 52.4% (22/42) vs. Amox/Clav 68.0% (17/25)

Clinical cure: Orlynvah 61.9% (26/42) vs. Amox/Clav 72.0% (18/25)

Microbiological response: Orlynvah 69.0% (29/42) vs. Amox/Clav 80.0% (20/25)

Trial 2: Uncomplicated Urinary Tract Infections (uUTI) – Orlynvah vs. Ciprofloxacin

A multinational, randomized, double-blind trial (NCT03753349) compared Orlynvah (sulopenem etzadroxil 500 mg + probenecid 500 mg, BID for 5 days) with ciprofloxacin (250 mg BID for 3 days) in 1,660 adult women with uUTIs. The micro-MITT population consisted of 1,108 patients with ≥10^5 CFU/mL of at least one uropathogen at baseline and who received ≥1 dose of study drug. Composite response was evaluated at the TOC visit (Day 12) in two subgroups:

Micro-MITTR (baseline ciprofloxacin non-susceptible pathogens; MIC ≥2 µg/mL):

Composite response: Orlynvah 48.1% (78/162) vs. Ciprofloxacin 32.9% (49/149) ($p = 0.006$)

Clinical cure: Orlynvah 84.0% (136/162) vs. Ciprofloxacin 46.3% (69/149)

Microbiological response: Orlynvah 56.8% (92/162) vs. Ciprofloxacin 44.3% (66/149)

Micro-MITTS (baseline ciprofloxacin susceptible pathogens; MIC ≤1 μg/mL):

Composite response: Orlynvah 60.4% (227/376) vs. Ciprofloxacin 71.8% (300/418)

Clinical cure: Orlynvah 81.1% (205/376) vs. Ciprofloxacin 84.0% (351/418)

Microbiological response: Orlynvah 69.7% (262/376) vs. Ciprofloxacin 80.4% (336/418)

Trials 3 & 4: Lack of Efficacy in Complicated Infections

In Trial 3 (NCT03357614), evaluating complicated urinary tract infections (cUTI), and Trial 4 (NCT03358576), evaluating complicated intra-abdominal infections (cIAI), Orlynvah (IV sulopenem followed by oral sulopenem etzadroxil + probenecid) was compared to IV ertapenem followed by oral standard therapies. Both were randomized, double-blind, multicenter Phase 3 studies.

Orlynvah did not demonstrate efficacy for the primary endpoints in either trial. Therefore, Orlynvah is not indicated for the treatment of complicated urinary tract infections (cUTI) or complicated intra-abdominal infections (cIAI).

Exclusivity and Patents

A New Chemical Entity (NCE) exclusivity is listed in the Orange Book, expiring on October 25, 2029. An additional GAIN (Generating Antibiotic Incentives Now) exclusivity is also listed in the Orange Book, expiring on October 25, 2031.

Piasky

Crovalimab-akkz injection, for intravenous or subcutaneous use

Fast Facts	
BLA Holder	Genentch
Dosage form	Solution for injection
Route of Administration	Intravenous and Subcutaneous
BLA Approval	June 20, 2024 (New Biological Entity)*
ODE	Yes, exclusivity end date June 20, 2031
Mechanism of action	Crovalimab-akkz is a monoclonal antibody that binds to complement protein C5, inhibiting its cleavage and preventing membrane attack complex (MAC) formation. Reduces terminal complement-mediated intravascular hemolysis in PNH.

* BLA exclusivity is typically granted for 12 years from date of approval

Indication

Piasky, a monoclonal antibody that inhibits complement protein C5, is indicated for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) in adults and adolescents aged 13 years and older who weigh at least 40 kilograms.

Boxed Warning

Piasky increases the risk of serious meningococcal infections caused by Neisseria meningitidis. Meningococcal vaccination should be completed at least two weeks before

initiating Piasky treatment, unless delaying therapy poses a greater risk. Patients remain at risk for invasive disease even after vaccination and should be closely monitored for signs of infection. Piasky is available exclusively through the restricted Piasky REMS program to ensure adherence to proper safety measures.

Description

Crovalimab-akkz is a humanized monoclonal antibody that acts as a complement C5 inhibitor. It is based on a human IgG1 framework and is recombinantly produced in Chinese hamster ovary (CHO) cells. The antibody comprises two heavy chains, each consisting of 451 amino acid residues, and two light chains, each with 217 amino acid residues, giving it an approximate molecular weight of 145 kDa.

Dosage Form and Handling

Piasky (crovalimab-akkz) is a sterile, preservative-free solution supplied in single-use vials for intravenous or subcutaneous administration. Intravenous dosing requires prior dilution. Each 2 mL vial contains 340 mg of the active ingredient and is formulated with arginine hydrochloride, histidine, poloxamer 188, and Water for Injection, with the pH adjusted to 5.8 using aspartic acid as needed. The product should be stored refrigerated between 2°C and 8°C in its original packaging to protect it from light. Short-term storage at temperatures up to 30°C is allowed for up to 7 days, provided the vial remains unopened and the total time out of refrigeration does not exceed this limit. The solution must not be frozen or shaken.

Dosing Regimen

The Piasky dosing regimen begins with a loading phase consisting of an intravenous (IV) dose on Day 1, followed by four weekly subcutaneous (SC) doses on Days 2, 8, 15, and

22. The maintenance phase starts on Day 29 and continues every 4 weeks (Q4W) via subcutaneous injection. Dosage is determined based on body weight.

Mechanism of Action

Crovalimab-akkz is a monoclonal antibody engineered to target complement protein C5 with high binding affinity. By blocking the cleavage of C5 into its active fragments, C5a and C5b, it disrupts the formation of the membrane attack complex (MAC). This mechanism effectively suppresses terminal complement activation, helping to control intravascular hemolysis in individuals with paroxysmal nocturnal hemoglobinuria (PNH).

Pharmacokinetics

Crovalimab-akkz exhibits dose-proportional pharmacokinetics over a dose range of 75 mg to 1500 mg when administered as a single intravenous infusion, and from 100 mg to 1020 mg when given subcutaneously. Following the initial intravenous loading dose, steady-state concentrations are reached after approximately 12 weeks with subsequent subcutaneous maintenance dosing according to the recommended regimen.

The absorption profile shows a mean absorption rate constant of 0.126 day^{-1} (90% CI: 0.105–0.176), and the subcutaneous bioavailability is 83.0% (90% CI: 69.6–92.0). Distribution parameters include a central volume of distribution of 3.23 L (90% CI: 3.16–3.29) and a peripheral volume of distribution of 2.32 L (90% CI: 2.02–2.67).

Elimination occurs at a clearance rate of 0.0791 L/day (90% CI: 0.0678–0.0872) in PNH treatment-naïve patients, with a mean terminal half-life of 53.1 days (90% CI: 47.7–58.6). Crovalimab-akkz is metabolized via lysosomal proteolysis into small peptides and amino acids and is not eliminated through renal or hepatic pathways.

Population pharmacokinetic analyses showed no clinically significant differences in crovalimab-akkz exposure based on age (13–85 years), gender, race (Caucasian, Black, or Asian), or body weight. Pediatric patients weighing ≥40 kg exhibited pharmacokinetic exposures comparable to those seen in adults. Piasky has not been studied in pediatric patients weighing less than 40 kg, and limited data in patients under 8 kg preclude definitive conclusions.

No clinically meaningful differences in pharmacokinetics were observed in patients with mild, moderate, or severe renal impairment, or with mild hepatic impairment. Piasky has not been studied in patients with moderate or severe hepatic impairment; therefore, clinical judgment is advised when considering treatment in this population.

In clinical trials, 30% of complement inhibitor–naïve patients and 23% of patients switching from another C5 inhibitor developed anti-drug antibodies (ADAs) to crovalimab-akkz. Although ADA-positive patients experienced reductions in drug concentrations (geometric mean decreases of 39% to 56%), levels remained above the threshold required for terminal complement inhibition in over 80% of these patients. Approximately 1.6% of all treated patients experienced a sustained loss of hemolysis control associated with reduced drug exposure. There was no evidence that ADA positivity impacted the safety profile of Piasky.

Clinical Studies

The efficacy of Piasky in paroxysmal nocturnal hemoglobinuria (PNH) was evaluated in the COMMODORE 2 study (NCT04434092), an active-controlled, open-label, non-inferiority trial involving 204 complement inhibitor–naïve patients weighing ≥40 kg. Participants were randomized 2:1 to receive either Piasky (n = 135) or Eculizumab (n =

69). Additionally, six pediatric patients (aged >12 years, weighing ≥40 kg) received Piasky in a separate non-randomized cohort.

Both treatments demonstrated comparable efficacy in transfusion avoidance, hemolysis control, breakthrough hemolysis, and hemoglobin stabilization. Transfusion avoidance was achieved in 65.7% of Piasky patients versus 68.1% in the Eculizumab group. Hemolysis control was observed in 79.3% of Piasky patients and 79.0% of those receiving Eculizumab, with an odds ratio of 1.02 (95% CI: 0.57, 1.82). Breakthrough hemolysis occurred in 10.4% of Piasky patients compared to 14.5% of Eculizumab patients, a difference of –3.9% (95% CI: –14.8%, 5.3%). Hemoglobin stabilization was seen in 63.4% of Piasky patients versus 60.9% of those on Eculizumab, with a difference of 2.2% (95% CI: –11.4%, 16.3%).

The efficacy of Piasky in pediatric patients weighing ≥40 kg was evaluated across three clinical studies: COMMODORE 2 (n = 7, ages 13–17), COMMODORE 1 (n = 2, ages 13–16), and COMMODORE 3 (NCT04654468, n = 3, ages 15–17). The treatment effects observed in pediatric patients were consistent with those seen in adults.

Exclusivity and Patents

Orphan drug exclusivity for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) was granted for seven years, extending through June 20, 2031.

Rapiblyk

Landiolol for injection, for intravenous use

Fast Facts	
NDA Holder	AOP Orphan Pharmaceuticals
Product Presentation	Powder for solution
Route of Administration	Intravenous
NDA Original Approval	November 22, 2024
NCE Exclusivity	November 22, 2029
ODE	No
Mechanism of action	A selective beta-1 adrenoreceptor antagonist

Indication

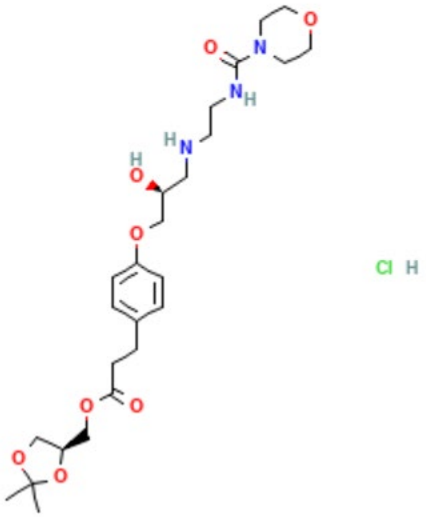
Rapiblyk is approved for the short-term control of ventricular rate in adults with supraventricular tachycardia, including atrial fibrillation and atrial flutter.

Dosage Form and Handling

Rapiblyk is a preservative-free, sterile lyophilized powder supplied in single-dose 50 mL vials, each containing 280 mg of landiolol (equivalent to 300 mg of landiolol HCl) and packaged individually in cartons. The unreconstituted product should be stored at 20°C to 25°C, with allowable excursions between 15°C and 30°C. It is administered by intravenous infusion after reconstitution with 0.9% Sodium Chloride Injection or 5% Dextrose Injection. The formulation contains 300 mg of mannitol as an inactive ingredient, with sodium hydroxide added as necessary to adjust the pH.

Description

The molecular weight of landiolol hydrochloride is 546.06 g/mol. Its chemical structure is as follows:



Dosing Regimen

Rapiblyk is administered as a continuous intravenous infusion, titrated as needed to control heart rate, with limited data available for use beyond 24 hours. The dosing regimen depends on cardiac function. For patients with normal cardiac function, the starting dose is 9 mcg/kg/min, with titration steps of 9 mcg/kg/min every 10 minutes, up to a maximum dose of 36 mcg/kg/min. In patients with impaired cardiac function, the starting dose is significantly lower at 1 mcg/kg/min, with titration steps of 1 mcg/kg/min every 15 minutes; the maximum dose remains 36 mcg/kg/min.

Mechanism of Action

Rapiblyk is a selective beta-1 adrenoreceptor antagonist that counteracts the positive chronotropic effects of catecholamines, epinephrine and norepinephrine, on the heart, where beta-1 receptors are primarily located.

Pharmacokinetics

The pharmacokinetics of landiolol are dose-proportional over the range of 9.3 to 74.6 mcg/kg/min. Steady-state concentrations are achieved approximately 15 minutes after infusion initiation. Peak plasma concentrations (Cmax) differ between healthy volunteers and patients with atrial fibrillation/flutter, with higher levels observed at increased doses.

Landiolol exhibits a short elimination half-life of 4.5 minutes and a steady-state volume of distribution of 0.4 L/kg, with low plasma protein binding (<10%). It is primarily metabolized by pseudocholinesterases and carboxylesterases to an active metabolite, M1, which possesses less than 1/40th of landiolol's pharmacological activity. Renal excretion accounts for 50–75% of the administered dose, mainly as M1; approximately 8% of the parent drug is excreted unchanged in urine within 4 hours, with 89–99% recovered within 24 hours.

In patients with mild hepatic impairment, landiolol AUC and Cmax increase by 44% and 42%, respectively. Data on moderate hepatic impairment (Child-Pugh B) are limited, and effects in severe impairment (Child-Pugh C) are unknown. The impact of renal impairment on landiolol pharmacokinetics has not been established. Additionally, landiolol and its M1 metabolite act as time-dependent inhibitors of CYP2D6 but do not inhibit CYP1A2, CYP2C9, CYP2C19, or CYP3A4..

Clinical Studies

In five randomized, double-blind, placebo-controlled studies, 317 adults with supraventricular tachycardia were treated with landiolol, resulting in a 40–90% reduction in heart rate within 10 minutes, compared to 0–11% in the placebo group. Heart rate

reduction was defined as a decrease greater than 20%, a heart rate below 100 bpm, or intermittent cessation of arrhythmia. The infused landiolol dose ranged from 9.3 to 74.6 mcg/kg/min.

Exclusivity and Patents

New Chemical Entity (NCE) exclusivity is listed in the Orange Book, expiring on November 22, 2029. Currently, no patents are listed in the Orange Book.

Revuforj

Revumenib tablets, for oral use

Fast Facts	
NDA Holder	Syndax Pharmaceuticals, Inc.,
Product Presentation	Tablet
Route of Administration	Oral
NDA Original Approval	November 15, 2024
NCE Exclusivity	November 15, 2029
ODE	Yes, exclusivity ending November, 2031
Mechanism of action	A menin inhibitor that blocks the interaction of wild-type and fusion KMT2A proteins with menin. First-in-class

Indication

Revuforj is indicated for the treatment of relapsed or refractory acute leukemia in adult and pediatric patients aged 1 year and older who have a lysine methyltransferase 2A (KMT2A) gene translocation.

Boxed Warnings

Differentiation syndrome, which can be fatal, has been reported with Revuforj. Symptoms may include fever, dyspnea, hypoxia, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain, peripheral edema, hypotension, and renal dysfunction. If

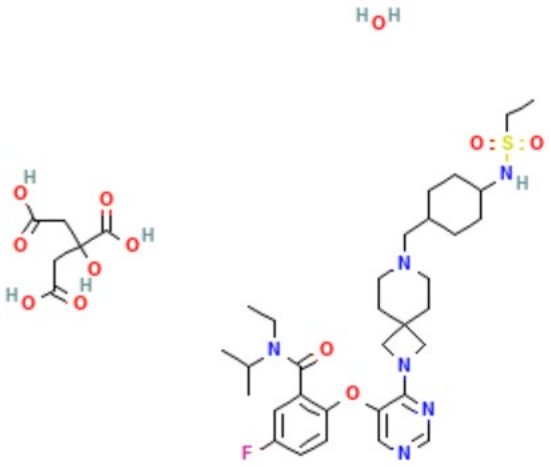
differentiation syndrome is suspected, immediate corticosteroid therapy and hemodynamic monitoring should be initiated until symptoms resolve.

Dosage Form and Handling

Revuforj is available in three tablet strengths—25 mg, 110 mg, and 160 mg—each supplied in 30-count bottles containing a desiccant and equipped with a child-resistant closure. Tablets should be stored at 20°C to 25°C, with excursions allowed between 15°C and 30°C. Each tablet contains revumenib in doses of 25 mg, 110 mg, or 160 mg, corresponding to 33.4 mg, 146.5 mg, and 213.2 mg of revumenib citrate, respectively. All strengths contain the same inactive ingredients: microcrystalline cellulose, dicalcium phosphate, crospovidone, hypromellose, sodium bicarbonate, hydrophobic colloidal silica, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and red iron oxide. Coloring agents differ by strength: the 110 mg tablet contains yellow iron oxide, while the 160 mg tablet includes FD&C Blue #2 (indigo carmine aluminum lake).

Description

Revuforj contains revumenib, a menin inhibitor, presented as revumenib citrate hydrate with a molecular weight of 840.96 g/mol. Its chemical structure is:



Dosing Regimen

The recommended Revuforj dosage depends on patient weight and concomitant use of strong CYP3A4 inhibitors. Treatment should not be initiated if the absolute neutrophil count (ANC) is below 0.5 × 10^9/L and should continue until disease progression or unacceptable toxicity occurs. For patients without disease progression or toxicity, therapy should be maintained for at least 6 months to adequately assess clinical response.

For patients aged 1 year and older weighing 40 kg or more, the standard dose is 270 mg twice daily, unless co-administered with a strong CYP3A4 inhibitor, in which case the dose is reduced to 160 mg twice daily. For patients weighing less than 40 kg, dosing is based on body surface area (BSA), ranging from 220 mg twice daily for a BSA of 1.3 m^2 to 25 mg twice daily for a BSA of 0.3 m^2. If a strong CYP3A4 inhibitor is discontinued, the Revuforj dose should be increased after at least five half-lives of the inhibitor have passed.

Revuforj is recommended to be taken twice daily, either fasting or with a low-fat meal (approximately 400 calories, with no more than 25% fat), at the same time each day. Tablets must be swallowed whole with water and should not be cut, crushed, or chewed.

For patients who have difficulty swallowing, tablets may be dispersed in water and consumed within 2 hours. If a dose is missed, it should be taken as soon as possible, provided there are at least 12 hours before the next scheduled dose. Patients at risk of central nervous system (CNS) relapse should receive standard intrathecal chemotherapy prophylaxis.

Mechanism of Action

Revumenib is a menin inhibitor that blocks the interaction between wild-type and fusion KMT2A proteins and menin. This interaction plays a critical role in KMT2A-rearranged (KMT2Ar) acute leukemias by activating a leukemogenic transcriptional pathway. In nonclinical studies, revumenib modulated the transcription of genes, including differentiation markers, in cells expressing KMT2A fusions. Furthermore, both in vitro and in vivo studies demonstrated its antiproliferative and antitumor effects in leukemia cells harboring KMT2A fusions.

Pharmacokinetics

Revumenib pharmacokinetics were studied in patients with relapsed or refractory acute leukemia following oral administration, both with and without strong CYP3A4 inhibitors. Steady-state concentrations were reached within 2 to 3 days, and the drug demonstrated dose-proportional increases in exposure. The median time to peak concentration (Tmax) was approximately 2 hours when taken with CYP3A4 inhibitors and 1 hour without them. Food had no significant effect on pharmacokinetics, although Cmax and AUC decreased slightly when administered with a low-fat meal.

Revumenib has a large volume of distribution (78 L) and is approximately 90% protein-bound. It is primarily metabolized by CYP3A4, with M1 identified as the active metabolite.

The drug is eliminated via both feces (~49%) and urine (~27%), with only 7% excreted unchanged in each route. The half-life is longer when administered with CYP3A4 inhibitors (7.5 hours) compared to without (3.6 hours), and clearance is reduced in the presence of these inhibitors.

Revumenib pharmacokinetics are not significantly influenced by age, sex, race, or mild to moderate renal impairment. However, its effects in severe renal or severe hepatic impairment remain unknown. Body weight (8–146 kg) affects drug exposure, with lower body weight linked to increased exposure, supporting the use of BSA-based dosing for patients under 40 kg. In pediatric patients, revumenib exposure is comparable to that seen in adults.

Co-administration with strong CYP3A4 inhibitors (e.g., posaconazole, itraconazole, voriconazole) doubles revumenib exposure and Cmax by 2-fold, while cobicistat increases exposure by 2.5-fold. Conversely, strong and moderate CYP3A4 inducers are expected to decrease revumenib exposure while increasing its M1 metabolite levels. No significant pharmacokinetic differences were observed when co-administered with fluconazole or isavuconazole (both moderate CYP3A4 inhibitors).

In *in vitro* studies, revumenib inhibits CYP3A4 but does not affect other major CYP enzymes such as CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6, nor does it induce CYP1A2, CYP2B6, or CYP3A4. Regarding transporters, revumenib inhibits OCT1, OCT2, OAT1, OAT3, and MATE1 but does not inhibit P-gp, BCRP, OATP1B1, OATP1B3, or MATE-2K. The M1 metabolite inhibits MATE1 but does not significantly affect OAT1, OAT3, OCT2, or other major transporters.

Clinical Studies

The efficacy of Revuforj was evaluated in a single-arm, open-label, multicenter trial in adult and pediatric patients (≥30 days old) with relapsed or refractory (R/R) acute leukemia harboring a KMT2A translocation. Patients with an 11q23 partial tandem duplication were excluded, and eligibility required a QTcF < 450 msec at baseline. Patients received Revuforj at 160 mg twice daily with a strong CYP3A4 inhibitor or 276 mg twice daily without a strong CYP3A4 inhibitor. Treatment continued until disease progression, unacceptable toxicity, failure to achieve a morphological leukemia-free state by four treatment cycles, or hematopoietic stem cell transplantation (HSCT). Of the 104 treated patients, 24 (23%) underwent HSCT following treatment.

Most patients had acute myeloid leukemia (AML) (83%), while acute lymphoblastic leukemia (ALL) (15%) and mixed-phenotype acute leukemia (MPAL) (2%) were also represented. The most common KMT2A translocations were t(9;11) (22%), t(11;19) (19%), and t(6;11) (10%). Eighty-three patients (80%) had relapsed disease, while 21 (20%) had primary refractory disease.

Efficacy was assessed based on complete remission (CR) plus CR with partial hematologic recovery (CRh), the duration of response (DOR), and conversion from transfusion dependence to transfusion independence. The combined CR + CRh rate was 21.2% (22/104 patients), with a median duration of 6.4 months. The CR rate alone was 12.5% (13/104 patients), with a median duration of 4.3 months, while the CRh rate was 8.7% (9/104 patients), with a median duration of 6.4 months. Among the 22 patients who achieved CR or CRh, the median time to response was 1.9 months (range, 0.9 to 5.6 months).

Among 83 patients who required red blood cell (RBC) and/or platelet transfusions at baseline, 12 (14.5%) became independent of both RBC and platelet transfusions during a

56-day post-baseline period. Of the 21 patients who were transfusion-independent at baseline, 10 (47.6%) remained transfusion-independent during this period.

Exclusivity and Patents

The following exclusivities apply: New Chemical Entity (NCE) exclusivity, expiring on November 15, 2029, and three Orphan Drug Exclusivities (ODEs), each expiring on November 15, 2031, for the following protected indications:

Treatment of relapsed or refractory acute myeloid leukemia (AML) with a lysine methyltransferase 2A (KMT2A) gene translocation in adult and pediatric patients aged 1 year and older.

Treatment of relapsed or refractory mixed-phenotype acute leukemia (MPAL) with a KMT2A gene translocation in adult and pediatric patients aged 1 year and older.

Treatment of relapsed or refractory acute lymphocytic leukemia (ALL) with a KMT2A gene translocation in adult and pediatric patients aged 1 year and older.The patents listed in the Orange Book are summarized in Table 16 (Appendix A).

Rezdiffra

Resmetirom tablets, for oral use

Fast Facts	
NDA Holder	Madrigal Pharmaceuticals
Product Presentation	Tablet
Route of Administration	Oral
NDA Approval	March 14, 2024 (New Molecular Entity) Accelerated Approval
NCE Exclusivity	Exclusivity ending on March 14, 2029
ODE	No
Mechanism of action	A partial agonist of the thyroid hormone receptor-beta (THR-β) thereby reducing intrahepatic triglycerides First-in-class

Indication

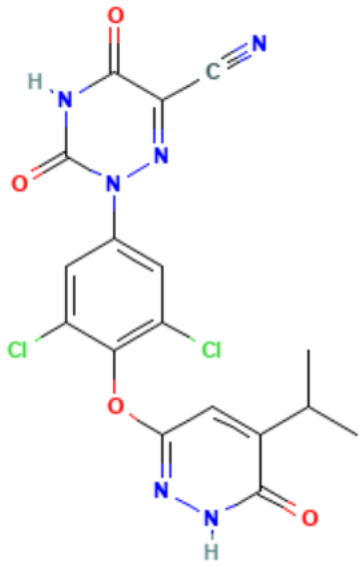
Rezdiffra is indicated as an adjunct to diet and exercise for the treatment of adults with noncirrhotic nonalcoholic steatohepatitis (NASH) exhibiting moderate to advanced liver fibrosis (stages F2 to F3).

Dosage Form and Handling

Rezdiffra is supplied as film-coated tablets in strengths of 60 mg, 80 mg, and 100 mg. Tablets should be stored at 20°C to 25°C, with allowable excursions between 15°C and 30°C. Inactive ingredients include microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, hypromellose, titanium dioxide, polyethylene glycol, and iron oxide yellow.

Description

Rezdiffra (resmetirom) tablets contain resmetirom, a thyroid hormone receptor-beta (THR-β) agonist, with a molecular weight of 435.22. The chemical structure is as follows:



Dosing Regimen

The recommended dosage of Rezdiffra is based on the patient's actual body weight. Patients weighing less than 100 kg should take 80 mg orally once daily, while those weighing 100 kg or more should take 100 mg orally once daily, with or without food.

Mechanism of Action

Resmetirom is a partial agonist of thyroid hormone receptor-beta (THR-β), the predominant isoform expressed in the liver. By selectively activating THR-β, resmetirom reduces intrahepatic triglyceride levels. In contrast, thyroid hormone receptor-alpha (THR-α) primarily mediates thyroid hormone effects in tissues outside the liver, such as the heart and bones.

Pharmacokinetics

Resmetirom reaches steady-state concentrations within 3 to 6 days of once-daily dosing. Systemic exposure increases dose-proportionally between 40 mg and 100 mg, but exceeds proportionality between 100 mg and 200 mg. With repeated dosing, exposure increases 1.5- to 3-fold, while its major metabolite does not accumulate. At steady state, systemic exposure is comparable in patients with stage F2 and F3 fibrosis.

After multiple daily doses of 80 mg or 100 mg, the median time to peak concentration (Tmax) is approximately 4 hours. A high-fat meal does not produce clinically meaningful pharmacokinetic differences, though food reduces Cmax by 33%, AUC by 11%, and delays Tmax by about 2 hours compared to fasting conditions.

The apparent volume of distribution (Vd/F) at steady state is 68 L, with >99% protein binding. Resmetirom is primarily metabolized by CYP2C8 and not significantly by other CYP enzymes. The median terminal half-life (t½) is 4.5 hours, and the steady-state apparent clearance (CL/F) is 17.5 L/h.

Following a single 100 mg radiolabeled dose, 67% of the dose was excreted in feces (mainly as metabolites), and 24% in urine. Unchanged resmetirom was not detected in feces and accounted for only 1% in urine.

No clinically significant pharmacokinetic differences were observed by age, sex, or race. Mild to moderate renal impairment had no significant impact, while data in severe renal impairment are lacking. In hepatic impairment, systemic exposure increased with severity: Cmax and AUC increased by 1.2-fold and 1.3-fold in mild, 1.7-fold and 2.7-fold in moderate, and 8.1-fold and 19-fold in severe hepatic impairment, respectively.

Resmetirom interacts with several drugs, particularly those involving CYP2C8 and transporters such as OATP1B1, OATP1B3, and BCRP. Co-administration with clopidogrel (a moderate CYP2C8 inhibitor) increased resmetirom Cmax by 1.3-fold and AUC by 1.7-fold. With pioglitazone (a CYP2C8 substrate), Cmax remained unchanged while AUC increased by 1.5-fold.

Resmetirom affected the pharmacokinetics of various statins. When administered with a single 20 mg dose of simvastatin, Cmax and AUC increased by 1.4-fold and 1.7-fold, respectively. For rosuvastatin (10 mg), Cmax increased 2.9-fold and AUC 1.9-fold. Pravastatin (40 mg) showed Cmax and AUC increases of 1.3-fold and 1.4-fold. Atorvastatin (20 mg) showed no change in Cmax but a 1.4-fold AUC increase, while the 80 mg dose led to a 2.0-fold Cmax increase and 1.8-fold AUC increase.

No significant pharmacokinetic changes were observed when co-administered with R-warfarin or S-warfarin.

In vitro, resmetirom inhibits CYP2C8, UGT1A1, and UGT1A4; however, the clinical relevance of UGT inhibition is unknown. Resmetirom is a substrate of BCRP and inhibits OATP1B1, OATP1B3, and BCRP, though the clinical significance of these transporter interactions remains undetermined.

Clinical Studies

The efficacy of Rezdiffra was evaluated in Trial 1 (NCT03900429), a 54-month, randomized, double-blind, placebo-controlled study. The trial enrolled patients with noncirrhotic NASH, fibrosis stage 2 or 3, and a NAFLD Activity Score (NAS) of ≥4. The co-primary endpoints were (1) resolution of steatohepatitis without worsening of fibrosis and (2) improvement in fibrosis without worsening of steatohepatitis, both assessed at Month 12 by liver biopsy.

A total of 888 patients were randomized 1:1:1 to receive placebo (n = 294), Rezdiffra 80 mg once daily (n = 298), or Rezdiffra 100 mg once daily (n = 296), in addition to standardized lifestyle counseling. All participants remained on stable doses of background medications for diabetes, dyslipidemia, and hypertension.

Histopathologic evaluations at Month 12 were independently performed by two pathologists (designated A and B). Rezdiffra demonstrated statistically significant improvement over placebo for both primary endpoints. For steatohepatitis resolution without fibrosis worsening, response rates were 27% (80 mg) and 36% (100 mg) per Pathologist A, and 26% (80 mg) and 24% (100 mg) per Pathologist B, compared to 13% and 9% with placebo, respectively. The absolute differences in response versus placebo ranged from +14% to +23% (Pathologist A) and +15% to +17% (Pathologist B).

For fibrosis improvement without worsening of steatohepatitis, response rates were 23% (80 mg) and 28% (100 mg) per Pathologist A, and 23% (80 mg) and 24% (100 mg) per Pathologist B, compared to 15% and 13% with placebo, respectively. The absolute differences versus placebo ranged from +8% to +13%.

Between Month 3 and Month 12, patients treated with Rezdiffra exhibited greater reductions in serum ALT and AST levels compared to placebo. Subgroup analyses revealed

no clinically meaningful differences in treatment response based on age, sex, diabetes status, or fibrosis stage (F2 vs. F3). The study population was predominantly White (89%), limiting the ability to evaluate efficacy across other racial groups.

Exclusivity and Patents

The NCE exclusivity is valid until March 14, 2029. The patents listed in the Orange Book are summarized in Table 17 (Appendix A).

Rytelo

Imetelstat for injection, for intravenous use

Fast Facts	
NDA Holder	Geron Corporation
Product Presentation	Powder for solution
Route of Administration	Intravenous
NDA Approval	June 6, 2024
NCE Exclusivity	Not listed*
ODE	Yes, exclusivity ending June 6, 2031
Mechanism of action	Imetelstat binds to the RNA template region of human telomerase (hTR), blocking telomerase activity and preventing telomere binding

*Typically lasts for 5 years from the date of approval. Not listed in the Orange Book at present.

Indication

Rytelo is indicated for the treatment of adults with low- to intermediate-1 risk myelodysplastic syndromes (MDS) who have transfusion-dependent anemia, requiring at least four units of red blood cells over eight weeks. It is intended for patients who have not responded to, have lost response to, or are ineligible for erythropoiesis-stimulating agents (ESAs).

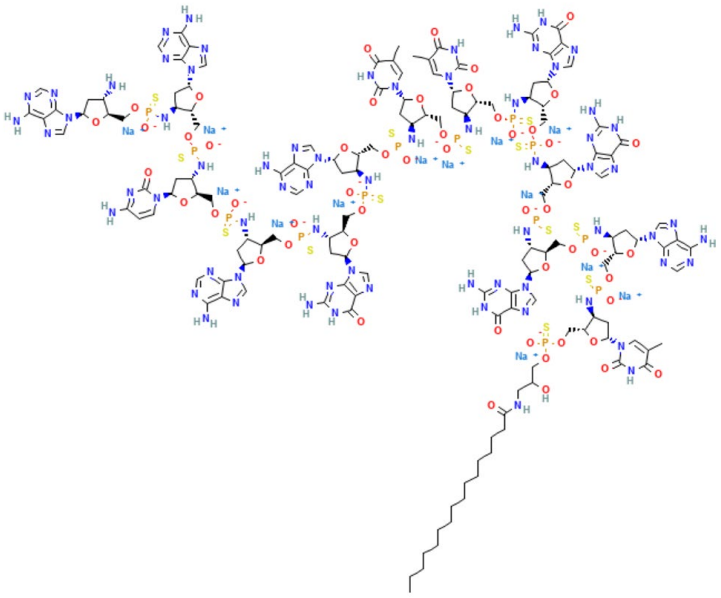
Dosage Form and Handling

Rytelo (imetelstat) for injection is a sterile, preservative-free, lyophilized powder intended for intravenous infusion after reconstitution and dilution. Each single-dose vial contains either 47 mg of imetelstat (equivalent to 50 mg of imetelstat sodium) or 188 mg of imetelstat (equivalent to 200 mg of imetelstat sodium). The formulation includes the following inactive ingredients: sodium carbonate anhydrous (for the 47 mg vial), sodium carbonate monohydrate (for the 188 mg vial), and hydrochloric acid to adjust the pH to 7.0–8.5.

Storage: Store vials refrigerated at 2°C to 8°C in the original carton. Do not freeze.

Description

Rytelo for injection contains imetelstat, an oligonucleotide telomerase inhibitor for intravenous administration. Its molecular weight as the sodium salt is 4896 g/mol.



Dosing Regimen

The recommended dosage of Rytelo is 7.1 mg/kg, administered as a 2-hour intravenous infusion every 4 weeks. Treatment should be discontinued after 24 weeks (6 doses) if there

is no reduction in red blood cell transfusion burden or if unacceptable toxicity occurs at any point.

Mechanism of Action

Imetelstat is an oligonucleotide human telomerase inhibitor that binds to the template region of the RNA component of human telomerase (hTR), thereby blocking telomerase enzymatic activity and preventing telomere elongation. Elevated telomerase activity and increased expression of human telomerase reverse transcriptase (hTERT) RNA have been observed in MDS as well as in malignant stem and progenitor cells.

Pharmacokinetics

Imetelstat does not accumulate between treatment cycles. Following a single intravenous infusion of 7.1 mg/kg over 2 hours in patients with MDS, the volume of distribution (Vd) is approximately 14.1 L (CV% 27.2%), indicating moderate tissue distribution. Additionally, imetelstat is approximately 94% bound to plasma proteins.

Elimination occurs with a plasma half-life (t½) of about 4.9 hours (CV% 43.2%) at the recommended dose. The drug is primarily metabolized by nucleases, which degrade it into nucleotides of varying lengths.

No clinically significant pharmacokinetic differences were observed based on age, sex, or race. Mild to moderate renal and hepatic impairment do not appear to significantly affect metabolism; however, the impact of severe renal impairment, end-stage renal disease, or severe hepatic impairment remains unknown.

In the IMerge study, 17% (28/166) of evaluable low/intermediate-1 risk MDS patients developed anti-drug antibodies (ADA) to imetelstat, with a median onset of 38 weeks.

Across Phases 2 and 3, the median treatment duration was 35 weeks. No clinically significant effects of ADA on pharmacokinetics, safety, or efficacy were observed.

Clinical Studies

A randomized, double-blind, placebo-controlled, multicenter trial (IMerge; NCT02598661) was conducted to evaluate the efficacy of Rytelo in 178 patients with low- or intermediate-1 risk myelodysplastic syndromes (MDS). These patients were transfusion-dependent, requiring at least four red blood cell (RBC) units over an eight-week period during the 16 weeks before randomization. Patients were required to have failed, lost response to, or been ineligible for erythropoiesis-stimulating agents (ESAs). Additional inclusion criteria included an absolute neutrophil count of at least 1.5×10^9/L and a platelet count of at least 75×10^9/L. Patients with the del(5q) cytogenetic abnormality or prior treatment with lenalidomide or hypomethylating agents were ineligible for the study. Participants were randomized in a 2:1 ratio, with 118 patients receiving Rytelo (7.1 mg/kg intravenously) and 60 patients receiving a placebo. Treatment was administered in 28-day cycles and continued until disease progression, unacceptable toxicity, or withdrawal from the study. Randomization was stratified based on prior RBC transfusion burden and International Prognostic Scoring System (IPSS) risk group. All patients received supportive care, including RBC transfusions as needed. Efficacy was assessed over a median follow-up of 19.5 months (range: 1.4 to 36.2 months) in the active group and 17.5 months (range: 0.7 to 34.3) in the placebo group. In the Rytelo group, 47 out of 118 patients (39.8%) achieved 8-week RBC transfusion independence (TI), compared to 9 out of 60 patients (15.0%) in the placebo group. The percent difference in response rate was 24.8% (95% CI: 9.9 – 36.9%), with a p-value of <0.001.

Additionally, 33 out of 118 patients (28.0%) in the Rytelo group achieved 24-week RBC TI, compared to 2 out of 60 patients (3.3%) in the placebo group, yielding an absolute difference of 24.6% (95% CI: 12.6 – 34.2%, $p < 0.001$). The 8-week RBC TI rate was based on the absence of RBC transfusions during any consecutive 8-week period from randomization until the initiation of subsequent anti-cancer therapy.

Exclusivity and Patents

An Orphan Drug Exclusivity (ODE) is granted, expiring on June 6, 2031, for the treatment of adult patients with low- to intermediate-1 risk myelodysplastic syndromes (MDS) who have transfusion-dependent anemia requiring four or more red blood cell units over eight weeks and who have not responded to, lost response to, or are ineligible for erythropoiesis-stimulating agents (ESAs). The patents listed in the Orange Book are summarized in Table 18 (Appendix A).

Sofdra

Sofpironium topical gel

Fast Facts	
NDA Holder	BOTANIX SB Inc.
Product Presentation	Metered gel
Route of Administration	Topical
NDA Approval	June 18, 2024
NCE Exclusivity	Exclusivity ending on June 20, 2029
ODE	No
Mechanism of action	Anticholinergic agent

Indication

Sofdra is approved for the treatment of primary axillary hyperhidrosis (excessive underarm sweating) in adults and pediatric patients aged 9 years and older.

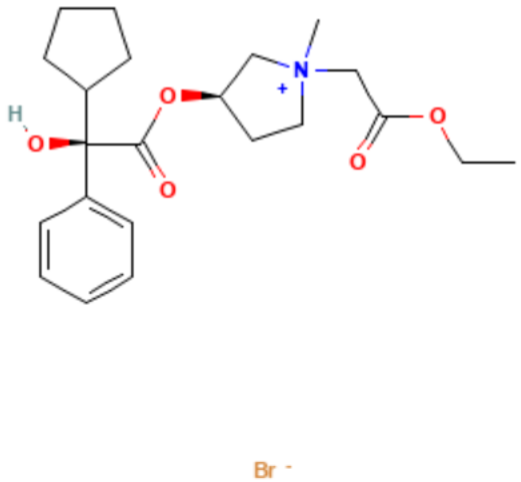
Dosage Form and Handling

Sofdra is supplied as a topical gel (12.45%, w/w) of sofpironium in a 50 mL bottle with a metered dose pump and applicator. One full pump delivers 72 mg sofpironium in 0.67 mL of gel. The inactive ingredients are citric acid, 77.2% v/v dehydrated alcohol, hexylene glycol, hydroxypropyl cellulose, and isopropyl myristate.

Storage instructions: store upright at 20°C to 25°C; excursions permitted to 15°C to 30°C.

Description

Sofpironium bromide, the drug substance, has a molecular weight of 470.4 g/mol. Its chemical structure is:



Dosing Regimen

Sofdra should be applied once daily at bedtime to clean, dry underarm skin. One pump actuation is dispensed onto the top of the supplied applicator and evenly spread over one underarm. This process is then repeated with a second pump actuation for the other underarm. The application must be allowed to dry completely before dressing.

Mechanism of Action

Sofpironium bromide competitively inhibits acetylcholine receptors found on specific peripheral tissues, including sweat glands. By blocking stimulation of these receptors, it indirectly reduces the rate of sweating.

Pharmacokinetics

The pharmacokinetics of sofpironium were evaluated in adults with primary axillary hyperhidrosis following once-daily topical application to the underarms. No drug accumulation was observed. Peak plasma concentration occurred approximately 5.3 hours post-application, with sofpironium demonstrating moderate plasma protein binding (34.8–

37.8%). It is primarily metabolized via nonenzymatic hydrolysis and enzymatic oxidation mediated by CYP2D6 and CYP3A4. In plasma, unchanged sofpironium represented 38% of the total drug dose, while its major metabolite, BBI-4010, accounted for 20%. Renal elimination of both the parent compound and its metabolite was minimal, with less than 0.5% of the dose excreted in urine.

In pediatric patients aged 9 years and older, systemic exposure and metabolism were comparable to adults, and no accumulation was detected after repeated dosing. Drug interaction studies revealed no significant changes in sofpironium pharmacokinetics when co-administered with inhibitors of CYP3A4, OCT2, MATE1, or MATE2-K. However, co-administration with the strong CYP2D6 inhibitor paroxetine approximately doubled sofpironium exposure (Cmax and AUC), as demonstrated in a clinical interaction study.

Clinical Studies

Two randomized, vehicle-controlled multicenter trials, CARDIGAN 1 (NCT03836287) and CARDIGAN 2 (NCT03948646), evaluated the efficacy of Sofdra in 701 subjects aged 10 years and older with primary axillary hyperhidrosis. Eligibility criteria included at least six months of hyperhidrosis symptoms, sweat production of ≥50 mg per axilla (total ≥150 mg over 5 minutes), and a Hyperhidrosis Disease Severity Measure-Axillary (HDSM-Ax-7) score of ≥3. Participants aged 12 and older rated their underarm sweating severity using the HDSM-Ax Adult instrument, where higher scores indicated greater severity. Baseline HDSM-Ax-7 scores averaged 3.5 in CARDIGAN 1 and 3.6 in CARDIGAN 2. Subjects were randomized to receive either Sofdra or vehicle, applied once daily at bedtime to each axilla, and assessed at Day 43 for improvements in sweating severity and sweat production.

At Day 43, a greater proportion of Sofdra-treated subjects achieved a ≥2-point improvement in HDSM-Ax-7 scores compared to vehicle. In CARDIGAN 1, 49% of subjects in the Sofdra group improved, compared to 29% in the vehicle group, with a treatment difference of 18% (95% CI: 8%, 29%). In CARDIGAN 2, 64% of Sofdra-treated subjects improved, compared to 48% in the vehicle group, with a treatment difference of 17% (95% CI: 6%, 27%). At baseline, median gravimetric sweat production (GSP) was 214 mg (Sofdra) versus 229 mg (vehicle) in CARDIGAN 1, and 208 mg (Sofdra) versus 231 mg (vehicle) in CARDIGAN 2. By Day 43, median reduction (mg/5 min) in GSP were greater in the Sofdra groups, with decreases of -128 mg versus -100 mg in CARDIGAN 1, and -143 mg versus -134 mg in CARDIGAN 2.

Exclusivity and Patents

One NCE exclusivity, expiring on June 20, 2029, is listed in the Orange Book. The patents listed in the Orange Book are summarized in Table 19 (Appendix A).

Tevimbra™

Tislelizumab-jsgr injection, for intravenous use

Fast Facts	
BLA Holder	BeiGene
Dosage form	Solution for injection
Route of Administration	Intravenous
BLA Approval	March 13, 2024 (New Biological Entity)
ODE	Granted for two indications Exclusivity end dates – March 13, 2031 (for esophageal cancer) and TBD for gastric cancer**
Mechanism of action	Binds to PD-1 and blocks its interaction with PD-L1 and PD-L2, thereby releasing PD-1 pathway-mediated inhibition of the immune response

* BLA exclusivity is typically granted for 12 years from date of approval

Indication

Tevimbra (tislelizumab jsgr), administered as monotherapy, is indicated for adult patients with unresectable or metastatic esophageal squamous cell carcinoma who have previously received systemic chemotherapy excluding PD-(L)1 inhibitors.

Description

Tislelizumab-jsgr is a humanized IgG4 kappa monoclonal antibody, Fc-engineered to block the programmed death receptor-1 (PD-1). It has an approximate molecular weight of 147 kilodaltons.

Dosage Form and Handling

Tevimbra (tislelizumab-jsgr) is supplied as a clear to slightly opalescent solution containing 100 mg per 10 mL (10 mg/mL) in a single-dose vial. Each vial contains the following excipients: citric acid monohydrate (4.2 mg), histidine (17.2 mg), L-histidine hydrochloride monohydrate (8.2 mg), sodium citrate (59.3 mg), polysorbate 20 (2 mg), trehalose (650.4 mg), and Water for Injection, USP. The solution has an approximate pH of 6.5.

Prior to administration, 200 mg of tislelizumab-jsgr should be diluted in an IV bag containing 0.9% Sodium Chloride Injection, USP, to achieve a final concentration of 2–5 mg/mL, corresponding to a total volume of approximately 40–100 mL. The diluted solution should be gently mixed by inversion; do not shake.

Unopened vials should be stored refrigerated at 2°C to 8°C and protected from light. Do not freeze. The diluted solution may be stored at room temperature for up to 4 hours (including infusion time) or refrigerated at 2°C to 8°C for up to 20 hours. Do not freeze the diluted solution.

Dosing Regimen

The recommended dose of Tevimbra is 200 mg administered by intravenous infusion every three weeks, continued until disease progression or unacceptable toxicity occurs.

Mechanism of Action

Tislelizumab-jsgr binds to the PD-1 receptor, blocking its interaction with ligands PD-L1 and PD-L2, thereby reversing PD-1–mediated immune inhibition and enhancing the anti-tumor immune response.

Pharmacokinetics

Pharmacokinetics of tislelizumab-jsgr have been evaluated over a dose range of 0.5 to 10 mg/kg, demonstrating dose-proportional increases in both peak concentration (Cmax) and overall exposure (AUC). The drug exhibits a total clearance of 0.153 L/day (CV: 29.5%) and a terminal elimination half-life of approximately 24 days (CV: 31%).

Steady-state concentrations are achieved after roughly 12 weeks of dosing every three weeks, with a systemic accumulation factor of 2.14. The volume of distribution at steady state is 6.42 L (CV: 32.6%).

Pharmacokinetics of tislelizumab-jsgr are not significantly influenced by age, body weight, or race. Mild to moderate renal or hepatic impairment does not meaningfully affect drug exposure; however, pharmacokinetics in patients with severe hepatic or renal impairment, including those with end-stage renal disease, remain unestablished.

No significant impact of anti-drug antibodies (ADA) on tislelizumab-jsgr pharmacokinetics has been observed. The clinical consequences of ADA regarding drug activity, safety, or therapeutic outcomes are yet to be fully determined.

Clinical Studies

RATIONALE-302 (NCT03430843) was a multicenter, randomized (1:1), open-label trial involving 512 adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC) who had progressed after prior systemic chemotherapy.

Patients were excluded if they had previously received immune checkpoint inhibitors, had symptomatic or treated brain or leptomeningeal metastases, active autoimmune disease, required systemic steroids or immunosuppressants, or had tumor invasion into nearby organs around the esophagus.

Patients were randomized (1:1) to receive either Tevimbra 200 mg every three weeks or investigator's choice chemotherapy (ICC), which included paclitaxel (135–175 mg/m² every three weeks or 80–100 mg/m² weekly), docetaxel (75 mg/m² every three weeks), or irinotecan (125 mg/m² on Days 1 and 8 of each 3-week cycle). Treatment continued until disease progression per investigator assessment or unacceptable toxicity. Tumor assessments occurred every six weeks for the first six months and every nine weeks thereafter until progression. The primary efficacy endpoint was overall survival (OS) in the intent-to-treat (ITT) population. Secondary endpoints included progression-free survival (PFS), objective response rate (ORR), and duration of response (DOR) per RECIST v1.1 criteria.

A total of 512 patients were randomized evenly between Tevimbra (n=256) and ICC (n=256). In the ITT population, 197 (77%) patients in the Tevimbra group and 213 (83.2%) in the ICC group had died at the time of OS analysis. Median OS was 8.6 months (95% CI: 7.5, 10.4) with Tevimbra and 6.3 months (95% CI: 5.3, 7.0) with ICC, yielding a hazard ratio (HR) of 0.7 (95% CI: 0.57, 0.85; p=0.0001).

For PFS, 223 (87.1%) patients in the Tevimbra group and 180 (70.3%) in the ICC group experienced disease progression or death. Median PFS was 1.6 months (95% CI: 1.4, 2.7) for Tevimbra and 2.1 months (95% CI: 1.5, 2.7) for ICC, with a hazard ratio of 0.83 (95% CI: 0.67, 1.01).

The ORR was 15.2% (95% CI: 11.1, 20.2) in the Tevimbra arm and 6.6% (95% CI: 3.9, 10.4) in the ICC arm. Complete responses (CR) were observed in 5 (2%) patients receiving Tevimbra and 1 (0.4%) patient receiving ICC, while partial responses (PR) occurred in 34 (13.3%) patients on Tevimbra and 16 (6.3%) on ICC. Median duration of response (DOR) was 10.3 months (95% CI: 6.5, 13.2) with Tevimbra and 6.3 months (95% CI: 2.8, 8.5) with ICC.

Exclusivity and Patents

Two Orphan Drug Exclusivities (ODEs) are listed in the Orphan Drug Database for the following indications:

Treatment of esophageal cancer (exclusivity end date: March 13, 2031)

Treatment of gastric cancer, including gastroesophageal junction cancer (exclusivity end date: to be determined)

Tryngolza

Olezarsen injection, for subcutaneous use

Fast Facts	
NDA Holder	Ionis Pharmaceuticals Inc.
Product Presentation	Solution for Injection (autoinjector)
Route of Administration	Subcutaneous
NDA Approval	December 19, 2024 (New Molecular Entity)
NCE Exclusivity	Not listed*
ODE	Yes, exclusivity ending date TBD**
Mechanism of action	An ASO-GalNAc$_3$ conjugate that binds to apoC-III mRNA and promotes its degradation

*Not listed in the Orange Book. Typically 5 years from date of approval. **ODE typically 7 years from date of approval

Indication

Tryngolza is approved to reduce triglyceride levels in adults with familial chylomicronemia syndrome (FCS) when used in conjunction with dietary modifications.

Dosage Form and Handling

Tryngolza is supplied as a sterile, preservative-free injectable solution intended for subcutaneous use. Each single-use autoinjector delivers 80 mg of olezarsen in 0.8 mL. The formulation contains buffering and tonicity agents, including disodium hydrogen phosphate, sodium chloride, and sodium dihydrogen phosphate, in water for injection, with a pH maintained between 6.9 and 7.9. It should be refrigerated in its original carton (2°C

to 8°C) but may be stored at room temperature (15°C to 30°C) for up to 6 weeks if kept in the original packaging.

Description

Olezarsen is an antisense oligonucleotide (ASO) that inhibits Apolipoprotein C-III (apoC-III) mRNA to reduce its expression. It is conjugated to a ligand containing three N-acetylgalactosamine (GalNAc) residues, enabling targeted delivery to hepatocytes. The molecular weight is 9,124.48 daltons.

Dosing Regimen

The standard dosing regimen for Tryngolza is an 80 mg subcutaneous injection administered once monthly.

Mechanism of Action

Olezarsen is an ASO-$GalNAc_3$ conjugate that binds to apoC-III mRNA, facilitating its degradation and consequently lowering serum apoC-III protein levels. This reduction improves the clearance of plasma triglycerides (TG) and very low-density lipoproteins (VLDL).

Pharmacokinetics

Olezarsen pharmacokinetics are dose-proportional across a dose range of 10 to 120 mg, with no accumulation detected after repeated dosing. Following subcutaneous administration, peak plasma concentration (Tmax) is reached in approximately 2 hours.

The distribution of olezarsen involves a central volume of distribution of 91.9 L and a peripheral volume of 2960 L. It exhibits extensive plasma protein binding, with over 99% bound in vitro. After administration, olezarsen primarily distributes to the liver and kidneys.

Elimination is relatively slow, with a terminal half-life of about 4 weeks. Metabolism occurs hepatically via endo- and exonucleases, breaking the drug down into short oligonucleotide fragments. Less than 1% of the dose is excreted unchanged in urine within 24 hours, indicating minimal renal clearance.

No clinically meaningful pharmacokinetic differences have been observed based on age, body weight, sex, or race. Mild to moderate renal or hepatic impairment does not significantly affect olezarsen pharmacokinetics; however, the impact of severe impairment in these organs is unknown.

In vitro drug interaction studies show that olezarsen neither inhibits nor induces CYP450 enzymes. It is also not a substrate or inhibitor of transporter systems including OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, BCRP, P-gp, and BSEP. Furthermore, olezarsen does not displace warfarin or ibuprofen from plasma protein binding sites.

In Trial 1, during up to 53 weeks of treatment, 42% (18 of 43) of patients treated with TRYNGOLZA developed treatment-related anti-drug antibodies (ADAs). These ADAs did not affect peak plasma concentrations but were associated with increased trough levels. No clear impact on efficacy, safety, or drug activity was observed; however, limited data preclude definitive conclusions.

Clinical Studies

The clinical efficacy of Tryngolza was evaluated in a randomized, placebo-controlled, double-blind trial involving adult patients with genetically identified familial chylomicronemia syndrome (FCS) and fasting triglyceride (TG) levels ≥880 mg/dL (Trial 1; NCT04568434). After a ≥4-week low-fat diet run-in period, patients were randomly

assigned to receive either Tryngolza 80 mg (n=22) or placebo (n=23) via subcutaneous injection every 4 weeks for 53 weeks. Median baseline fasting TG levels for all patients were 2,303 mg/dL.

At study entry, patients in both groups were on other lipid-lowering therapies, including statins (27%), omega-3 fatty acids (42%), fibrates (49%), and other agents (13%).

By month 6, patients receiving Tryngolza showed a 30% reduction in fasting TG levels, while the placebo group experienced a 12% increase, resulting in a treatment difference of -42.5% (95% CI: -74.1, -10.9%).

Non-HDL cholesterol decreased by 18% in the Tryngolza group but increased by 5.7% in the placebo group, yielding a treatment difference of -23.4% (95% CI: -45.3, -1.5%). ApoB-48 levels dropped by 51% with Tryngolza and rose by 25% with placebo, with a treatment difference of -75.9% (95% CI: -149.8, -2.0%). Total ApoB increased by 20% in the Tryngolza group and 9% in the placebo group, with a treatment difference of +11.7% (95% CI: -12.6, 35.9%). LDL cholesterol rose by 64% in the Tryngolza group and 9% in the placebo group; however, 74% of Tryngolza-treated patients remained within the normal LDL-C range (<70 mg/dL).

Throughout the 12-month treatment period, Tryngolza maintained a consistent triglyceride-lowering effect, whereas TG levels in the placebo group fluctuated and generally increased. Furthermore, the incidence of acute pancreatitis was lower in the Tryngolza group (1 patient, 5%) compared to the placebo group (7 patients, 30%), with all cases occurring in patients who had a prior history of pancreatitis within 10 years before screening.

Exclusivity and Patents

The patents listed in the Orange Book are summarized in Table 20 (Appendix A). The Orphan Drug Exclusivity (ODE) expiration date has not yet been determined.

Tryvio™

Aprocitentan, oral tablet

Fast Facts	
NDA Holder	Idorsia Pharmaceuticals Ltd.
Product Presentation	Tablet
Route of Administration	Oral
NDA Original Approval	March 19, 2024
NCE Exclusivity	March 22, 2029
ODE	No
Mechanism of action	An endothelin receptor antagonist (ERA) that blocks the binding of endothelin (ET)-1 to ETA and ETB receptors First-in-class

Indication

Tryvio is indicated for the treatment of high blood pressure in adults who are not adequately controlled with other medications and should be taken in conjunction with other antihypertensive therapies.

Boxed Warning

Tryvio carries a boxed warning for embryo-fetal toxicity, as it can cause major birth defects and is contraindicated during pregnancy. Patients capable of becoming pregnant must confirm they are not pregnant before starting treatment, undergo monthly pregnancy testing

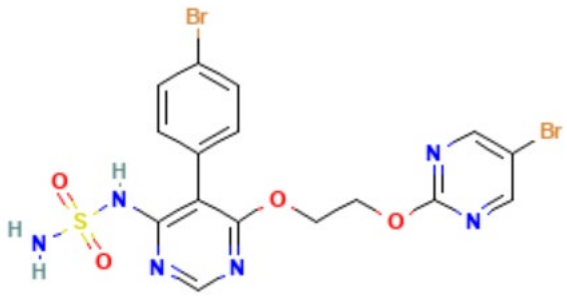
throughout treatment, and continue testing for one month after discontinuing Tryvio. Additionally, effective contraception must be used before, during, and for one month after treatment. Due to these risks, Tryvio is available only through a restricted distribution program called the Tryvio REMS.

Dosage Form and Handling

Tryvio is supplied as 12.5 mg film-coated tablets, available in blister packs and bottles. The tablets should be stored at 20°C to 25°C, with permitted excursions between 15°C and 30°C. Inactive ingredients include croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, and microcrystalline cellulose. The film coating consists of hydroxypropyl cellulose, iron oxides (black, red, and yellow), polyvinyl alcohol, colloidal hydrated silica, talc, titanium dioxide, and triethyl citrate.

Description

The molecular weight of aprocitentan is 546.2 g/mol. Its chemical structure is as follows:



Dosing Regimen

The recommended dose of Tryvio is 12.5 mg taken orally once daily. It may be administered with or without food.

Mechanism of Action

Aprocitentan is an endothelin receptor antagonist (ERA) that inhibits the binding of endothelin-1 (ET-1) to both ETA and ETB receptors. Through these receptors, ET-1 mediates various harmful effects, including vasoconstriction, fibrosis, cell proliferation, and inflammation. In hypertension, ET-1 contributes to endothelial dysfunction, vascular hypertrophy and remodeling, sympathetic activation, and increased aldosterone synthesis.

Pharmacokinetics

Aprocitentan is an endothelin receptor antagonist (ERA) that inhibits the binding of endothelin-1 (ET-1) to both ETA and ETB receptors. Through these receptors, ET-1 mediates various harmful effects, including vasoconstriction, fibrosis, cell proliferation, and inflammation. In hypertension, ET-1 contributes to endothelial dysfunction, vascular hypertrophy and remodeling, sympathetic activation, and increased aldosterone synthesis.Aprocitentan demonstrates dose-proportional increases in plasma concentration up to 100 mg once daily, reaching steady-state levels by day 8 with approximately three-fold accumulation upon daily dosing. Its oral bioavailability is unknown, and following a 25 mg dose, the time to maximum concentration (Tmax)ranges from 4 to 5 hours. Food intake does not significantly affect its pharmacokinetics, even when taken with a high-fat, high-calorie meal. The drug has an apparent volume of distribution of about 20 L and binds extensively to plasma proteins (>99%), primarily albumin, with a blood-to-plasma ratio of 0.63. It exhibits an effective half-life of approximately 41 hours and a plasma clearance near 0.3 L/h.

Aprocitentan is primarily metabolized by UGT1A1- and UGT2B7-mediated N-glucosidation and non-enzymatic hydrolysis. It is mainly excreted via urine (52%), with

less than 0.2% excreted unchanged, while 25% is eliminated in feces, of which 6.8% is unchanged.

No clinically significant pharmacokinetic differences have been observed across populations defined by age, sex, race/ethnicity, or body weight. Similarly, pharmacokinetics are comparable between patients and healthy subjects, including those with mild to severe renal impairment or mild to moderate hepatic impairment. The impact of severe renal failure, dialysis, or severe hepatic impairment remains unknown.

Drug interaction studies indicate that aprocitentan does not significantly affect the pharmacokinetics of midazolam (a CYP3A4 substrate) or rosuvastatin (a BCRP substrate). In vitro, aprocitentan inhibits CYP3A4 and all CYP2C family enzymes but has no effect on CYP1A2, CYP2A6, CYP2B6, CYP2D6, or CYP2E1. It acts as an inducer of CYP3A4 but does not induce CYP1A2 or CYP2C9. Additionally, aprocitentan serves as both a substrate and inhibitor of UGT1A1 and UGT2B7.

Regarding transporter systems, aprocitentan is a substrate of P-glycoprotein (P-gp) and BCRP; however, inhibitors of these transporters are not expected to affect its pharmacokinetics. It inhibits BCRP, bile salt export pump (BSEP), and sodium taurocholate co-transporting polypeptide (NTCP) but does not inhibit P-gp, organic cation transporters (OCT1, OCT2), multidrug and toxin extrusion proteins (MATE1, MATE2K), or organic anion transporters (OAT1, OAT3, OATP1B1, and OATP1B3) at therapeutic concentrations.

Clinical Studies

The efficacy of Tryvio was evaluated in the PRECISION phase 3 multicenter trial (NCT03541174) involving adults with systolic blood pressure (SBP) ≥140 mmHg who

were on at least three antihypertensive medications. The study included a placebo run-in period followed by three treatment phases. Prior to the run-in, all patients were switched to a standardized background antihypertensive regimen consisting of an angiotensin receptor blocker, a calcium channel blocker, and a diuretic, with beta-blockers continued if previously used.

After a 4-week placebo run-in period, 730 patients were randomized equally to receive either 12.5 mg or 25 mg aprocitentan, or placebo once daily during the 4-week double-blind treatment phase (Part 1). Following this, all patients entered a single-blind treatment phase (Part 2), receiving 25 mg aprocitentan once daily for 32 weeks. At the end of this period, patients were re-randomized to either continue 25 mg aprocitentan or switch to placebo once daily during a 12-week double-blind withdrawal phase (Part 3).

The primary efficacy endpoint was the change in sitting systolic blood pressure (SiSBP) from baseline to Week 4, measured by unattended automated office blood pressure (uAOBP). The key secondary endpoint was the change in SiSBP from Week 36 to Week 40, assessing the effect before and after withdrawal.

Compared to placebo, Tryvio 12.5 mg significantly reduced SiSBP at Week 4, with a least squares (LS) mean reduction of -15.4 mmHg (97.5% CI: -17.5, -13.3) versus -11.6 mmHg (97.5% CI: -13.7, -9.5) for placebo. The treatment effect was also consistent for sitting diastolic blood pressure (SiDBP), with Tryvio 12.5 mg reducing SiDBP by -10.4 mmHg (97.5% CI: -11.7, -9.1) compared to -6.4 mmHg (97.5% CI: -7.8, -5.1) for placebo.

The persistence of Tryvio's blood pressure-lowering effect was confirmed in Part 3. After all patients received 25 mg aprocitentan, those re-randomized to placebo experienced an increase in mean SiSBP, indicating loss of treatment effect, while patients continuing 25

mg maintained their SiSBP reduction, demonstrating sustained efficacy. At Week 40, Tryvio remained statistically superior to placebo, with consistent effects on SiDBP.

Most of Tryvio's blood pressure-lowering effect occurred within the first two weeks of treatment. The 25 mg dose is not approved because it did not provide meaningful additional benefit over the 12.5 mg dose and was associated with a higher risk of edema and fluid retention. Tryvio's efficacy was consistent across subgroups, regardless of age, sex, race, BMI, renal function (eGFR, UACR), diabetes history, or blood pressure measurement method (uAOBP and ambulatory BP).

Exclusivity and Patents

The Orange Book lists new chemical entity (NCE) exclusivity for Tryvio expiring on March 22, 2029. The patents listed in the Orange Book are summarized in Table 21 (Appendix A).

Unloxcyt

Cosibelimab-ipdl injection, for intravenous use

Fast Facts	
BLA Holder	Checkpoint Therapeutics
Dosage form	Solution for injection
Route of Administration	Intravenous
BLA Approval	December 13, 2024 (New Biological Entity)*
ODE	None
Mechanism of action	Cosibelimab-ipdl binds to PD-L1, preventing its interaction with PD-1 and B7.1 receptors

*BLA exclusivity is typically granted for 12 years from date of approval.

Indication

Unloxcyt is approved for treating adults with metastatic cutaneous squamous cell carcinoma (mCSCC) or locally advanced cutaneous squamous cell carcinoma (laCSCC) who are not candidates for curative surgery or radiation therapy.

Description

Cosibelimab-ipdl is a human IgG1 lambda monoclonal antibody that blocks programmed death-ligand 1 (PD-L1). It is produced in CHO cells and has an estimated molecular weight of approximately 147 kDa.

Dosage Form and Handling

Unloxcyt (cosibelimab-ipdl) injection for intravenous use is a preservative-free solution intended for infusion after dilution, supplied in single-use vials. Each vial contains 300 mg of Unloxcyt in 5 mL of solution at a pH of 5.3. Each mL contains 60 mg of cosibelimab-ipdl and the following excipients: acetic acid (0.24 mg), mannitol (37.35 mg), polysorbate 80 (1.1 mg), sodium acetate (1.31 mg), sodium chloride (4.09 mg), and Water for Injection, USP.

Dosing Regimen

The recommended dosage of Unloxcyt is 1,200 mg administered as an intravenous infusion over 60 minutes every three weeks, until disease progression or unacceptable toxicity occurs.

Mechanism of Action

Cosibelimab-ipdl binds to PD-L1, blocking its interaction with PD-1 and B7.1 receptors, thereby restoring the anti-tumor immune response.

Pharmacokinetics

Cosibelimab-ipdl exhibits dose-proportional pharmacokinetics over the 800 mg to 1,200 mg dose range. At the recommended dose of 1,200 mg every three weeks, steady-state concentration is reached by week 12. The steady-state volume of distribution is approximately 5.67 L, suggesting limited tissue distribution. The mean half-life of cosibelimab-ipdl is 17.8 days, with a clearance rate of 0.256 L/day. No clinically significant differences in pharmacokinetics were observed based on age, sex, race, mild to moderate renal impairment, or mild hepatic impairment. The effects of severe hepatic impairment remain unknown. Treatment-emergent anti-drug antibodies (ADAs) were detected in 49%

of patients, with neutralizing antibodies found in 3%. The presence of ADAs did not have a clinically meaningful impact on efficacy or safety.

Clinical Studies

The efficacy of Unloxcyt was evaluated in Study CK-301-101 (NCT03212404), a multicenter, multi-cohort, open-label trial involving patients with metastatic cutaneous squamous cell carcinoma (mCSCC) or locally advanced cutaneous squamous cell carcinoma (laCSCC) who were not candidates for curative surgery or radiation.

Patients received Unloxcyt 800 mg intravenously every two weeks until disease progression or unacceptable toxicity. Tumor response was assessed every eight weeks for the first eight months and every 12 weeks thereafter. The primary efficacy endpoints were objective response rate (ORR) and duration of response (DOR).

Among patients with mCSCC (N = 78), the ORR was 47% (95% CI: 36–59%), with 8% achieving a complete response (CR) and 40% achieving a partial response (PR). In patients with laCSCC (N = 31), the ORR was 48% (95% CI: 30–67%), with 10% achieving a complete response and 39% a partial response.

For mCSCC responders (N = 37), the median DOR was not reached (NR), with a range of 1.4+ to 34.1+ months. Among these responders, 84% maintained a response for at least six months, and 54% maintained a response for at least 12 months. In laCSCC responders (N = 15), the median DOR was 17.7 months (range: 3.7+ to 17.7 months), with 87% maintaining a response for at least six months and 20% for at least 12 months.

Exclusivity and Patents

No equivalents or exclusivities are listed in the Purple Book.

Vafseo®

Vadadustat tablets, for oral use

Fast Facts	
NDA Holder	Akebia Therapeutics Inc.
Product Presentation	Tablet
Route of Administration	Oral
NDA Original Approval	March 27, 2024
NCE Exclusivity	March 22, 2029
ODE	No
Mechanism of action	Vafseo is a HIF-PH inhibitor causing an increase in erythropoietin (EPO) production.

Indication

Vafseo is indicated for the treatment of anemia in adults with chronic kidney disease (CKD) who have been receiving dialysis for at least three months.

Boxed Warning

Vafseo increases the risk of thrombotic vascular events, including major adverse cardiovascular events (MACE). Targeting a hemoglobin level above 11 g/dL is associated with an increased risk of death and arterial and venous thrombotic events, similar to erythropoietin-stimulating agents (ESAs) that also raise erythropoietin levels. No clinical trial has established a hemoglobin target, dose, or dosing strategy for Vafseo that avoids

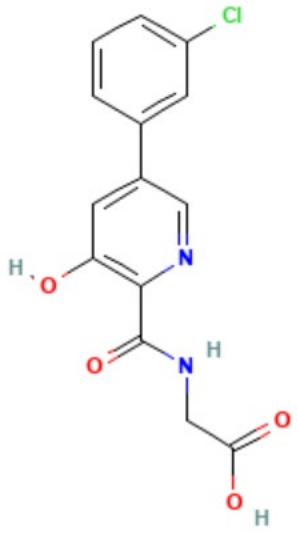
these risks. The lowest effective dose to reduce the need for red blood cell transfusions should be used.

Dosage Form and Handling

Vafseo is available as film-coated, immediate-release tablets in 150 mg, 300 mg, and 450 mg strengths, packaged in HDPE bottles. It should be stored at 20°C to 25°C, with excursions permitted between 15°C and 30°C. The inactive ingredients in the tablet include colloidal silicon dioxide, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The film coating consists of polyvinyl alcohol, polyethylene glycol (PEG), and talc.

Description

Vafseo contains vadadustat, which has a molecular weight of 306.70. Its molecular structure is:



Dosing Regimen

The recommended starting dose of Vafseo is 300 mg orally once daily, with or without food. Hemoglobin levels should be monitored when initiating or adjusting the dose, then

monthly thereafter. Dose increases should not occur more frequently than once every 4 weeks, while dose reductions may be made more frequently as needed. Adjustments should be made in 150 mg increments to maintain hemoglobin levels between 10 g/dL and 11 g/dL, with doses ranging from 150 mg up to a maximum of 600 mg.

Mechanism of Action

Vafseo is a hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitor that stabilizes and promotes the nuclear accumulation of HIF-1α and HIF-2α transcription factors, resulting in increased erythropoietin (EPO) production.

Pharmacokinetics

Vadadustat exhibits dose-proportional pharmacokinetics, with both the area under the curve (AUC) and maximum plasma concentration (Cmax) increasing proportionally across single doses ranging from 80 mg to 1200 mg. Steady-state concentrations are achieved by Day 3 with once-daily dosing, without significant accumulation over time.

The absorption of vadadustat is characterized by a time to peak plasma concentration (Tmax) of approximately 2 to 3 hours. Food intake does not have a clinically significant effect on its pharmacokinetics. Vadadustat is ≥99.5% protein-bound in human plasma and does not distribute into red blood cells.

Vadadustat is primarily metabolized through glucuronidation, mediated by UDP-glucuronosyltransferase (UGT) enzymes. In patients undergoing chronic hemodialysis, the elimination half-life is approximately 9.2 hours. Following administration of a radiolabeled oral dose, 85.9% of the total dose was recovered—58.9% was excreted in urine (<1% as unchanged drug), and 26.9% in feces (9% unchanged).

No clinically significant differences in vadadustat pharmacokinetics have been observed based on age, sex, race/ethnicity, or moderate hepatic impairment (Child-Pugh Class B). However, the effects of severe hepatic impairment (Child-Pugh Class C) remain unknown. In patients with renal impairment, vadadustat clearance decreases as renal function declines, with dialysis-dependent chronic kidney disease (DD-CKD) patients exhibiting approximately two-fold higher exposure compared to healthy individuals. In patients with Stage 5 DD-CKD, no significant differences in Cmax, AUC, or half-life were observed when vadadustat was administered either 4 hours before or 2 hours after dialysis.

Effect of other drugs on vadadustat

Inhibitors: Cyclosporine (a BCRP/OATP1B1 inhibitor) and probenecid (an OAT1/OAT3 inhibitor) increase vadadustat exposure.

pH Modifier: Rabeprazole has minimal impact on vadadustat pharmacokinetics.

Iron Supplements and Iron-Containing Phosphate Binders: Ferrous sulfate, ferric citrate, and sucroferric oxyhydroxide reduce vadadustat exposure.

Non-Iron-Containing Phosphate Binders: Sevelamer carbonate and calcium acetate also decrease vadadustat levels, particularly when vadadustat is administered prior to these binders.

Effect of Timing: Lower vadadustat exposure (AUC and Cmax) is observed when it is taken before phosphate binders, indicating reduced absorption due to drug binding.

Effect of vadadustat on other drugs

Vadadustat has minimal impact on the pharmacokinetics of most co-administered drugs. No significant inhibitory or inductive effects on CYP enzymes, UGT enzymes, or transport

proteins have been observed, indicating a low likelihood of clinically relevant drug–drug interactions

Clinical Studies

The efficacy and safety of Vafseo (vadadustat) for treating anemia in adults with chronic kidney disease on dialysis (DD-CKD) were evaluated in two global, multicenter, randomized, active-controlled, non-inferiority trials (INNO-VATE-1 and INNO-VATE-2), involving a total of 3,923 patients. Participants were randomized 1:1 to receive either Vafseo (300 mg once daily) or darbepoetin alfa (administered subcutaneously or intravenously). Treatment continued for 52 weeks, during which hemoglobin (Hb) levels were adjusted by titrating Vafseo in 150 mg increments, up to a maximum dose of 600 mg. Following the initial 52-week period, patients remained on treatment for long-term safety evaluation, with major adverse cardiovascular events (MACE) serving as the primary safety outcome.

The study included two distinct patient populations. INNO-VATE-1 enrolled patients with incident DD-CKD who had initiated dialysis within the previous 16 weeks and had either no prior ESA exposure or limited prior use. INNO-VATE-2 enrolled patients who had been on maintenance dialysis for more than 12 weeks, including those who transitioned from prior ESA therapy. The median time from dialysis initiation to the start of Vafseo treatment ranged from 0.1 to 2.3 years. Baseline hemoglobin (Hb) ranges were 8–11 g/dL in the United States and 9–12 g/dL in other regions.

Efficacy was assessed based on the mean change in Hb levels from baseline to Weeks 24–36 (primary endpoint) and Weeks 40–52 (secondary endpoint). Major adverse cardiovascular events (MACE)—defined as all-cause mortality, non-fatal myocardial

infarction (MI), and non-fatal stroke—were evaluated in both trials. No significant differences in response to Vafseo were observed across age, sex, race, or geographic region.

In both trials, baseline hemoglobin (Hb) levels were comparable between treatment groups. In INNO-VATE-1, patients started at 9.4 g/dL (Vafseo) versus 9.2 g/dL (darbepoetin alfa), while in INNO-VATE-2, both groups began at 10.3 g/dL.

At Weeks 24–36, Hb levels increased in both groups. The adjusted least squares mean (LSM) change from baseline was 1.3 g/dL (Vafseo) versus 1.6 g/dL (darbepoetin alfa) in INNO-VATE-1, and 0.2 g/dL and 0.4 g/dL for these groups, respectively, in INNO-VATE-2. The treatment difference for Vafseo compared to darbepoetin alfa was –0.3 g/dL (95% CI: –0.5 to –0.1) in INNO-VATE-1 and –0.2 g/dL (95% CI: –0.2 to –0.1) in INNO-VATE-2.

Similar results were observed at Weeks 40–52, with a treatment difference of –0.1 g/dL (95% CI: –0.3 to 0.2) in INNO-VATE-1 and –0.2 g/dL (95% CI: –0.3 to –0.1) in INNO-VATE-2.

In the combined cardiovascular safety analysis, Vafseo was non-inferior to darbepoetin alfa with respect to time to first major adverse cardiovascular event (MACE), which included all-cause mortality, non-fatal myocardial infarction (MI), and non-fatal stroke. The hazard ratio for MACE was 0.96 (95% CI: 0.83 to 1.11), confirming non-inferiority, as the upper bound of the confidence interval remained below the pre-specified margin of 1.25. Results were consistent across all MACE components. The risk of MACE was similar between Vafseo and darbepoetin alfa in both the global study population and the U.S. subgroup, supporting the non-inferiority of Vafseo in terms of cardiovascular outcomes.

Exclusivity and Patents

The Orange Book lists new chemical entity (NCE) exclusivity expiring on March 27, 2029.

The patents listed in the Orange Book are summarized in Table 22 (Appendix A).

Vorangio®

Vorasidenib tablets, for oral use

Fast Facts	
NDA Holder	Servier Pharmaceuticals
Product Presentation	Tablet
Route of Administration	Oral
NDA Original Approval	August 6, 2024
NCE Exclusivity	August 6, 2029
ODE	Yes, exclusivity ending August 6, 2031
Mechanism of action	Inhibitor of wild-type and mutant IDH1/IDH2 including R132H mutation.

Indication

Voranigo is authorized for use in individuals aged 12 years and older, including both adolescents and adults, who have undergone surgery for Grade 2 astrocytoma or oligodendroglioma with a qualifying IDH1 or IDH2 gene mutation. Eligible surgical procedures include biopsy, partial resection, or complete resection

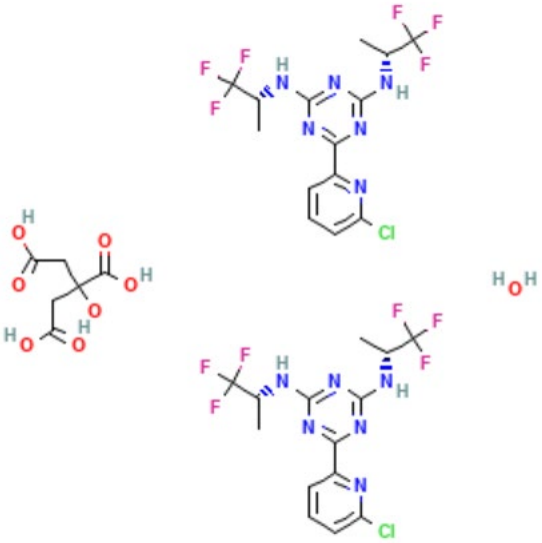
Dosage Form and Handling

Voranigo is available as 10 mg and 40 mg film-coated tablets, packaged in HDPE bottles for oral administration. It should be stored at 20°C to 25°C, with permitted excursions between 15°C and 30°C.

Each tablet core contains the following inactive ingredients: croscarmellose sodium, magnesium stearate, microcrystalline cellulose, silicified microcrystalline cellulose and sodium lauryl sulfate. The tablet coating includes hypromellose, lactose monohydrate, macrogol and titanium dioxide.

Description

Vorasidenib is present as a hemicitric acid hemihydrate co-crystal with a molecular weight of 519.8 g/mol. Its molecular structure is as follows:



Dosing Regimen

The recommended dosage of Voranigo for adult patients is 40 mg taken orally once daily, with or without food, until disease progression or unacceptable toxicity occurs. For pediatric patients aged 12 years and older, dosage is based on body weight: those weighing 40 kg or more receive 40 mg orally once daily, while those weighing less than 40 kg receive 20 mg orally once daily. Treatment should continue until disease progression or unacceptable toxicity, with appropriate monitoring and dose adjustments as needed.

Mechanism of Action

Vorasidenib is a small-molecule inhibitor targeting both wild-type and mutant IDH1/IDH2 enzymes. It reduces 2-hydroxyglutarate (2-HG) production in IDH-mutant tumors and may aid in restoring normal cell differentiation.

Pharmacokinetics

Following oral administration, vorasidenib exhibits linear pharmacokinetics across the 10 to 200 mg dose range, which extends up to four times the maximum approved dose. Drug accumulation at steady state is approximately 4.4-fold, with steady state typically reached within 28 days of daily dosing.

The median time to peak concentration (Tmax) is 2 hours, ranging from 0.5 to 4 hours. Vorasidenib has an absolute oral bioavailability of 34%.

A high-fat, high-calorie meal (800–1,000 kcal; 500–600 kcal from fat) increases Cmax by 3.1-fold and AUC by 1.4-fold. A low-fat, low-calorie meal (400–500 kcal; 100–125 kcal from fat) increases Cmax by 2.3-fold and AUC by 1.4-fold compared to fasting conditions.

Vorasidenib has a large volume of distribution at steady state (mean: 3,930 L; CV: 40%) and is 97% bound to plasma proteins in vitro. It penetrates the brain, exhibiting a tumor-to-plasma ratio of approximately 1.6.

Elimination is slow, with a terminal half-life of about 10 days (CV: 57%). Oral clearance at steady state is 14 L/hour (CV: 56%). The drug is primarily metabolized by CYP1A2, with minor contributions from CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A. Non-CYP pathways may account for up to 30% of total metabolism.

Radiolabeled excretion studies show that 85% of the administered dose is recovered in feces (56% as unchanged drug), while 4.5% is recovered in urine.

No clinically meaningful differences in vorasidenib pharmacokinetics were observed based on age (16–75 years), sex, race, ethnicity, body weight, or mild to moderate hepatic impairment (Child-Pugh Class A or B). Data are lacking for patients with severe hepatic impairment (Child-Pugh Class C), severe renal impairment (CrCl ≤40 mL/min), or those undergoing dialysis. In these populations, monitoring for increased toxicity is recommended, with dose adjustments as needed.

For pediatric patients aged 12 and older, modeled exposure to vorasidenib using body weight–based dosing is expected to fall within the range observed in adults receiving the standard 40 mg daily regimen.

Effect of Other Drugs on Vorasidenib

CYP1A2 inhibitors such as ciprofloxacin (a moderate inhibitor) raise vorasidenib levels moderately (Cmax increased by approximately 1.3-fold; AUC increased by approximately 2.5-fold), while stronger inhibitors like fluvoxamine elevate Cmax and AUC by fivefold or more. CYP1A2 inducers such as phenytoin or rifampicin may reduce vorasidenib levels (Cmax reduced by approximately 30%, AUC reduced by 40%).

Co-administration with omeprazole does not meaningfully change vorasidenib exposure.

Effect of Vorasidenib on Other Drugs

CYP3A substrates: Repeated dosing of vorasidenib may reduce the plasma concentrations of drugs metabolized by CYP3A enzymes.

UGT1A4 substrates: Vorasidenib does not significantly affect lamotrigine exposure when co-administered.

P-gp and BCRP substrates: Vorasidenib has minimal impact on drugs such as digoxin and rosuvastatin.

In vitro studies show that vorasidenib induces CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A, and UGT1A4. It is not a substrate of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), or the hepatic uptake transporters OATP1B1 and OATP1B3. Although vorasidenib inhibits BCRP, it does not inhibit P-gp or OATP1B1.

Clinical Studies

The efficacy of Voranigo was demonstrated in the INDIGO trial (AG881-C-004), a global, randomized, double-blind, placebo-controlled Phase 3 study that enrolled 331 participants with Grade 2 astrocytoma or oligodendroglioma harboring an IDH1 or IDH2 mutation. All patients had undergone prior surgery—biopsy, subtotal resection, or gross total resection—and had measurable, non-enhancing disease. Patients with previous chemotherapy or radiation exposure were excluded. A small subset with minimal, non-nodular enhancement on imaging was eligible if confirmed by central review.

Participants were randomized to receive either Voranigo 40 mg once daily (n=168) or matching placebo (n=163), continuing treatment until disease progression or unacceptable toxicity. Randomization was stratified by 1p19q co-deletion status and baseline tumor diameter (≥2 cm vs. <2 cm). IDH mutation testing was prospectively performed using the Oncomine Dx Target Test.

Among the enrolled patients, the majority harbored IDH1 mutations, with R132H as the most common variant (87%). Less frequent IDH1 variants included R132C (5%), R132G (3%), R132L (1%), and R132S (1%). IDH2 mutations were observed in 3% of patients, comprising R172K (2%) and R172G (1%).

The primary endpoint was progression-free survival (PFS), assessed by independent radiological review using modified RANO-LGG criteria. At the time of analysis, disease progression had occurred in 47 patients (28%) in the Voranigo group and 88 patients (54%) in the placebo group. No deaths were reported in either group. The hazard ratio (HR) for disease progression was 0.39 (95% CI: 0.27 to 0.56), indicating a statistically significant benefit for Voranigo ($p < 0.0001$).

Time to next intervention (TTNI), defined as the interval from randomization to initiation of first subsequent anticancer therapy or death, was evaluated as a key secondary endpoint. The median TTNI was not reached in the Voranigo arm, compared to 17.8 months in the placebo arm. The hazard ratio for TTNI was 0.26 (95% CI: 0.15 to 0.43; $p < 0.0001$), favoring Voranigo

Exclusivity and Patents

The Orange Book lists New Chemical Entity (NCE) exclusivity expiring on August 6, 2029, and Orphan Drug Exclusivity through August 6, 2031. The patents listed in the Orange Book are summarized in Table 23 (Appendix A).

Vodeya™

Danicopan tablets, for oral use

Fast Facts	
NDA Holder	Alexion Pharmaceuticals, Inc
Product Presentation	Tablet
Route of Administration	Oral
NDA Original Approval	March 29, 2024
NCE Exclusivity	March 29, 2029
ODE	Yes, exclusivity ending August 6, 2031
Mechanism of action	A selective Factor D inhibitor blocking the alternative complement pathway First-in-class

Indication

Voydeya is approved as an add-on therapy to ravulizumab or eculizumab for treating extravascular hemolysis (EVH) in adults with paroxysmal nocturnal hemoglobinuria (PNH).

Boxed Warnings

Voydeya increases the risk of serious and potentially life-threatening infections caused by encapsulated bacteria, including Neisseria meningitidis, Streptococcus pneumoniae, and Haemophilus influenzae type B. To reduce this risk, patients should complete or update vaccinations against these bacteria at least two weeks before starting Voydeya, unless the

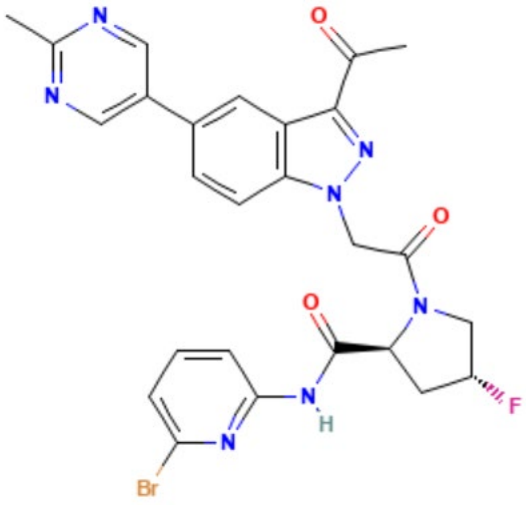
urgency of treatment outweighs the risk of delay. However, even vaccinated patients remain at increased risk for invasive infections and should be closely monitored for early signs of infection, with prompt evaluation if symptoms develop. Due to these risks, Voydeya is available only through the restricted Voydeya REMS program.

Dosage Form and Handling

Voydeya is supplied as 50 mg and 100 mg film-coated oral tablets, packaged in HDPE bottles. Store and dispense Voydeya in its original container at 20°C to 25°C, with permitted excursions between 15°C and 30°C. Inactive ingredients include colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. The film coating contains polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Description

Danicopan has a molecular weight of 580.4 g/mol. Its chemical structure is as follows:



Dosing Regimen

The recommended dosage of Voydeya is 150 mg taken orally three times daily. It can be administered with or without food.

Mechanism of Action

Danicopan is a reversible inhibitor of complement Factor D that selectively targets the alternative complement pathway. By blocking the cleavage of Factor B, it prevents the formation of C3 convertase, thereby reducing C3 fragment opsonization and downstream terminal pathway activation. In patients with paroxysmal nocturnal hemoglobinuria (PNH), Danicopan primarily controls C3-mediated extravascular hemolysis (EVH), while co-administered ravulizumab or eculizumab maintains suppression of membrane attack complex (MAC)-driven intravascular hemolysis (IVH).

Pharmacokinetics

Danicopan exhibits dose-proportional pharmacokinetics, with systemic exposure increasing predictably across the 150 mg to 200 mg dosing range when administered three times daily. Steady-state concentrations are typically reached within approximately two days, with an expected two-fold accumulation compared to a single dose. The median time to peak plasma concentration (Tmax) is 3.7 hours following a 150 mg oral dose in patients with paroxysmal nocturnal hemoglobinuria (PNH). Danicopan has a terminal half-life of 7.9 hours and a clearance rate of 63 L/hour.

The drug undergoes extensive metabolism (96%), primarily via oxidation, reduction, and hydrolysis, with amide hydrolysis being the predominant pathway. Cytochrome P450 (CYP)-mediated metabolism plays a minimal role. Danicopan is mainly excreted via feces (69%), with 25% recovered in urine. Only 3.57% of the administered dose is excreted unchanged in feces, and 0.48% appears unchanged in urine.

Danicopan exhibits consistent pharmacokinetics across sex, age, and racial groups. However, renal impairment increases systemic exposure (AUC) by approximately 52%. In patients with moderate hepatic impairment, Cmax and AUC decrease by 27% and 8%, respectively. The pharmacokinetics of danicopan have not been studied in individuals with severe hepatic impairment.

Food intake influences danicopan's pharmacokinetics. When administered with a high-fat meal, Cmax increases by 93% and AUC by 25%, while the time to peak concentration (Tmax) remains similar—3.0 hours in the fed state versus 2.5 hours in the fasted state.

Drug interaction studies show that danicopan does not meaningfully affect cytochrome P450 (CYP) enzymes, indicating a low potential for CYP-mediated drug interactions. However, it significantly alters transporter-mediated drug exposure. Co-administration with rosuvastatin, a BCRP substrate, results in a 3.3-fold increase in Cmax and a 2.2-fold increase in AUC. Moderate effects are also observed with fexofenadine and tacrolimus, both P-gp substrates. No clinically significant interactions occur with antacids or proton pump inhibitors.

Danicopan is a substrate of P-glycoprotein (P-gp) but not of BCRP, OATP1B1, or OATP1B3. It inhibits BCRP and P-gp, but does not inhibit OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, or MATE2-K. Given its transporter-mediated interaction profile and minimal involvement with CYP enzymes, co-administration with BCRP or P-gp substrates—such as statins or immunosuppressants—requires careful monitoring.

Clinical Studies

A randomized, double-blind, placebo-controlled trial (ALXN2040-PNH-301; NCT04469465) evaluated the efficacy of Voydeya (danicopan) in adults with paroxysmal

nocturnal hemoglobinuria (PNH) and clinically significant extravascular hemolysis (EVH). Clinically significant EVH was defined as anemia (hemoglobin ≤ 9.5 g/dL) with an absolute reticulocyte count ≥ 120 × 10^9/L, with or without transfusion requirements. Eligible participants had been receiving stable treatment with ravulizumab or eculizumab for at least six months prior to enrollment.

Participants received oral Voydeya at 150 mg three times daily, with optional dose escalation to 200 mg three times daily based on clinical response. Meningococcal vaccination was required prior to or at treatment initiation unless recent vaccination status (within three years) was verified. Patients were randomized in a 2:1 ratio to receive Voydeya or placebo for 12 weeks, in combination with background ravulizumab or eculizumab. At Week 12, all participants transitioned to open-label Voydeya plus background therapy up to Week 24, with the option to enter a long-term extension period beyond Week 24. Baseline demographic and disease characteristics were generally balanced across treatment arms.

At Week 12, Voydeya demonstrated significant efficacy across multiple endpoints. The mean hemoglobin increase from baseline was +2.9 g/dL in the Voydeya group versus +0.5 g/dL in the placebo group (treatment difference: 2.4 g/dL; 95% CI: 1.7–3.2; p = 0.0007). A hemoglobin increase of ≥2 g/dL without transfusion was achieved by 59.5% of patients receiving Voydeya, compared to 12.0% in the placebo arm (treatment difference: 46.9%; 95% CI: 29.2–64.7; p < 0.0001).

Transfusion avoidance—defined as no transfusions and not meeting protocol-specified transfusion criteria—was observed in 83.3% of patients on Voydeya versus 38.1% on placebo (treatment difference: 41.7%; 95% CI: 22.7–60.8; p = 0.0004). Improvements in

patient-reported fatigue, as assessed by the FACIT-Fatigue scale, were greater with Voydeya (+5.0 points) than with placebo (–1.9 points), with a treatment difference of 6.1 points (95% CI: 2.3–9.9; p = 0.002). The absolute reticulocyte count decreased by 84 × 10^9/L in the Voydeya arm compared to 87 × 10^9/L in the placebo arm, with a treatment difference of –87 (95% CI: –118 to –57; p < 0.0001).

Exclusivity and Patents

Voydeya is protected by two regulatory exclusivities:

New Chemical Entity (NCE) exclusivity, which expires on March 29, 2029

Orphan Drug Exclusivity (ODE), which extends through March 29, 2031

The ODE protection is for the treatment of extravascular hemolysis (EVH) in adults with paroxysmal nocturnal hemoglobinuria (PNH). The patents listed in the FDA Orange Book are summarized in Table 24(Appendix A).

Vyloy®

Zolbetuximab-clzb for injection, for intravenous use

Fast Facts	
BLA Holder	Astellas Pharma US, Inc.
Dosage form	Solution for injection
Route of Administration	Intravenous
BLA Approval	October 18, 2024 (New Biological Entity)*
ODE	Yes, October 18, 2031
Mechanism of action	Zolbetuximab-clzb is a CLDN18.2-directed cytolytic antibody that depletes CLDN18.2-positive cells First-in-class

*BLA exclusivity is typically granted for 12 years from date of approval

Indication

Vyloy is approved as a first-line treatment for locally advanced, unresectable, or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma in HER2-negative patients. It must be administered in combination with fluoropyrimidine- and platinum-based chemotherapy, and is specifically indicated for patients whose tumors express claudin 18.2 (CLDN18.2), as determined by an FDA-approved test.

Description

Zolbetuximab-clzb is a chimeric monoclonal antibody composed of mouse-derived variable regions targeting human claudin-18 isoform 2 (CLDN18.2), fused to human IgG1 constant regions. The molecule has an approximate molecular weight of 147 kDa.**Dosage Form and Handling**

Vyloy (zolbetuximab-clzb) for injection is a sterile, preservative-free lyophilized powder supplied in single-dose vials, each containing 100 mg of the active ingredient. The powder must be reconstituted and diluted with normal saline prior to administration.

Store refrigerated at 2°C to 8°C in the original carton to protect from light. Do not freeze or shake.

Vyloy is packaged in a carton containing one 100 mg vial.

The inactive ingredients in Vyloy include arginine, polysorbate 80, sucrose, and phosphoric acid (used for pH adjustment).

Dosing Regimen

Vyloy is administered in combination with fluoropyrimidine- and platinum-based chemotherapy. The initial dose is 800 mg/m² given intravenously, followed by maintenance doses of either 600 mg/m² every three weeks or 400 mg/m² every two weeks. Treatment should continue until disease progression or the development of unacceptable toxicity.

Mechanism of Action

Zolbetuximab-clzb is a CLDN18.2-directed cytolytic antibody that eliminates CLDN18.2-positive cells via antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). In mouse tumor models expressing CLDN18.2, the

combination of zolbetuximab-clzb and chemotherapy exhibited greater antitumor activity than either agent alone.

Pharmacokinetics

Following a 2-hour intravenous infusion, zolbetuximab-clzb displays dose-proportional pharmacokinetics across doses ranging from 33 mg/m² to 1000 mg/m². When administered at an initial dose of 800 mg/m² followed by 600 mg/m² every three weeks, steady-state concentrations are achieved within 18 weeks. The estimated steady-state volume of distribution is 14.0 L, and metabolism occurs through degradation into small peptides and amino acids. The drug is primarily cleared at a rate of 0.013 L/h, with an elimination half-life of 41 days.

No clinically significant differences in zolbetuximab-clzb clearance were observed based on age, sex, or race. Additionally, mild to moderate renal or hepatic impairment did not affect drug clearance. However, the effects of severe renal impairment and moderate to severe hepatic impairment remain unknown. Due to limited data, the immunogenicity profile of zolbetuximab-clzb is not well characterized, and its impact on pharmacokinetics, pharmacodynamics, safety, or efficacy is unclear.

Clinical Studies

The SPOTLIGHT trial (NCT03504397) was a double-blind, randomized, multicenter study evaluating the efficacy of Vyloy combined with mFOLFOX6 in patients with locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma. All 565 enrolled patients had CLDN18.2-positive tumors, defined as ≥75% of tumor cells exhibiting moderate to strong CLDN18 staining confirmed by

immunohistochemistry (IHC). Patients with complete or partial gastric outlet syndrome or central nervous system metastases were excluded.

Patients were randomized 1:1 to receive either Vyloy plus mFOLFOX6 (n=283) or placebo plus mFOLFOX6 (n=282). Vyloy was administered intravenously at an initial dose of 800 mg/m² (Cycle 1, Day 1), followed by 600 mg/m² every three weeks. Up to 12 cycles of mFOLFOX6 (oxaliplatin, folinic acid, and fluorouracil) were given over a 42-day cycle. After 12 cycles, patients could continue Vyloy alongside 5-fluorouracil and folinic acid at the investigator's discretion until disease progression or unacceptable toxicity. Tumor assessments were performed every 9 weeks up to Week 54, then every 12 weeks thereafter. The primary efficacy endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS), objective response rate (ORR), and duration of response (DOR), all assessed per RECIST v1.1 by an independent review committee (IRC). Median PFS was 10.6 months (95% CI: 8.9–12.5) in the Vyloy plus mFOLFOX6 group compared to 8.7 months (95% CI: 8.2–10.3) in the placebo plus mFOLFOX6 group (HR: 0.751; 95% CI: 0.598–0.942; p = 0.0066).

Median overall survival (OS) was 18.2 months (95% CI: 16.4–22.9) with Vyloy plus mFOLFOX6 versus 15.5 months (95% CI: 13.5–16.5) with placebo (HR: 0.75; 95% CI: 0.601–0.936; p = 0.0053). The objective response rate (ORR) was 40.3% (95% CI: 34.5–46.3) in the Vyloy group compared to 39.7% (95% CI: 34.0–45.7) in the placebo group. Median duration of response (DOR) was 10.3 months (95% CI: 8.3–10.9) versus 10.5 months (95% CI: 7.7–13.3), respectively.

The GLOW trial (NCT03653507) was a double-blind, randomized, multicenter study evaluating Vyloy in combination with Capox (capecitabine and oxaliplatin) in patients with

locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma. A total of 507 patients with CLDN18.2-positive tumors—defined as ≥75% of tumor cells with moderate to strong CLDN18 staining confirmed by immunohistochemistry—were enrolled. Patients with complete or partial gastric outlet syndrome or central nervous system metastases were excluded.

Patients were randomized 1:1 to receive Vyloy plus Capox (n=254) or placebo plus Capox (n=253). Vyloy was administered intravenously at an initial dose of 800 mg/m² (Cycle 1, Day 1), followed by 600 mg/m² every three weeks. Capox was given for up to 8 cycles, consisting of oxaliplatin (130 mg/m², Day 1) and capecitabine (1000 mg/m², twice daily for 21 days per cycle). After 8 cycles, patients could continue Vyloy and capecitabine at the investigator's discretion until disease progression or unacceptable toxicity. Tumor assessments were performed every 9 weeks up to Week 54, then every 12 weeks thereafter.

The primary efficacy endpoint was progression-free survival (PFS), with overall survival (OS), objective response rate (ORR), and duration of response (DOR) as secondary endpoints, all assessed per RECIST v1.1 by an independent review committee (IRC). Median PFS was 8.2 months (95% CI: 7.5–8.8) in the Vyloy plus Capox group versus 6.8 months (95% CI: 6.1–8.1) in the placebo plus Capox group (HR: 0.687; 95% CI: 0.544–0.866; p = 0.0007). Median OS was 14.4 months (95% CI: 12.3–16.5) with Vyloy plus Capox compared to 12.2 months (95% CI: 10.3–13.7) with placebo (HR: 0.771; 95% CI: 0.615–0.965; p = 0.0118). The ORR was 32.3% (95% CI: 26.6–38.4) in the Vyloy group versus 31.2% (95% CI: 25.6–37.3) in the placebo group. Median DOR was 8.3 months (95% CI: 6.3–11.4) versus 6.2 months (95% CI: 6.0–7.6), respectively.

Exclusivity and Patents

The ODE database lists an exclusivity expiring on October 18, 2031, for the first-line treatment of adults with locally advanced, unresectable, or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors are claudin-18.2 (CLDN18.2) positive, as determined by an FDA-approved test.

Winrevair™

Sotatercept-csrk for injection, for subcutaneous use

Fast Facts	
BLA Holder	Merck Sharp Dohme LLC.
Dosage form	Solution for injection
Route of Administration	Subcutaneous
BLA Approval	March 26, 2024 (New Biological Entity)*
ODE	Yes, exclusivity ending on March 26, 2031
Mechanism of action	An Activin Signaling Inhibitor Regulating Vascular Proliferation First-in-class

* BLA exclusivity is typically granted for 12 years from date of approval.

Indication

Winrevair™ is indicated for the treatment of adults with pulmonary arterial hypertension (PAH) classified as World Health Organization (WHO) Group 1. It is intended to improve exercise capacity, enhance WHO functional class (FC), and reduce the risk of clinical worsening events.

Description

Sotatercept-csrk is a homodimeric recombinant fusion protein comprising the extracellular domain of the human activin receptor type IIA (ActRIIA) fused to the human IgG1 Fc

domain. Based on its amino acid sequence, the molecular weight of sotatercept-csrk as a homodimer is approximately 78 kDa.

Dosage Form and Handling

Winrevair™ is supplied as a sterile, lyophilized cake or powder for subcutaneous injection, available in single-dose vials containing either 45 mg or 60 mg of sotatercept-csrk. Each vial is packaged in a kit that includes a dosing syringe, safety needle, vial adapter(s), alcohol pads, and prefilled syringes of Sterile Water for Injection for reconstitution.

Vials should be stored refrigerated at 2°C to 8°C in the original carton to protect from light. Do not freeze. Kits should remain refrigerated until use. If necessary, an unopened kit may be kept at room temperature (up to 25°C) for a maximum of 24 hours.

The 45 mg vial contains sotatercept-csrk along with citric acid monohydrate (0.40 mg), polysorbate 80 (0.18 mg), sodium citrate (1.84 mg), and sucrose (72 mg), with a pH of 5.8. Reconstitution with 1 mL of Sterile Water for Injection yields a solution with a concentration of 50 mg/mL and a nominal deliverable volume of 0.9 mL.

The 60 mg vial contains sotatercept-csrk along with citric acid monohydrate (0.53 mg), polysorbate 80 (0.24 mg), sodium citrate (2.45 mg), and sucrose (96 mg), also at a pH of 5.8. Reconstitution with 1.3 mL of Sterile Water for Injection provides a final concentration of 50 mg/mL and a nominal deliverable volume of 1.2 mL.

Dosing Regimen

Winrevair™ is administered once every 3 weeks by subcutaneous injection, dosed according to patient body weight. The starting dose is 0.3 mg/kg. After confirming acceptable hemoglobin (Hgb) and platelet counts, increase the dose to the target of 0.7

mg/kg. Continue treatment at 0.7 mg/kg every 3 weeks unless dosage adjustments are needed.

Check Hgb and platelet counts before each dose for the first five doses, or longer if values remain unstable. Thereafter, monitor Hgb and platelet counts periodically.

Mechanism of Action

Sotatercept-csrk is a recombinant fusion protein comprising the extracellular domain of activin receptor type IIA linked to an IgG1 Fc fragment (ActRIIA-Fc). It inhibits activin signaling by binding activin A and other ligands within the TGF-β superfamily. By modulating signaling pathways, it reduces pro-proliferative signaling via ActRIIA/Smad2/3 while enhancing anti-proliferative signals through BMPRII/Smad1/5/8, thereby regulating abnormal vascular cell growth.

Pharmacokinetics

Following subcutaneous administration of Winrevair™ every three weeks in patients with pulmonary arterial hypertension (PAH), both AUC and Cmax increase proportionally with dose. Steady state is reached after approximately 15 weeks of repeated dosing, with an accumulation ratio of 2.2. The absolute bioavailability of sotatercept-csrk after subcutaneous administration is approximately 66%. Median time to peak concentration (Tmax) is around 7 days, with a range of 2 to 8 days, following multiple subcutaneous doses administered every four weeks. The estimated volume of distribution at steady state is approximately 5.3 L (CV 27.3%) in patients with PAH.

The elimination half-life of sotatercept-csrk is approximately 24 days, with a clearance rate of 0.18 L/day. It undergoes catabolic break down into small peptides.

No clinically significant differences in sotatercept-csrk pharmacokinetics (PK) were observed based on age, sex, race, or mild to moderate renal impairment. Patients with end-stage kidney disease on dialysis also showed no significant impact on PK. Severe renal impairment is not expected to affect PK, while the effect of hepatic impairment remains unstudied. Clearance (CL) and central volume of distribution (Vc) increase with body weight; however, this effect is not clinically significant with weight-based dosing of sotatercept-csrk. During the 24-week STELLAR treatment period, 27% of patients treated with sotatercept-csrk developed anti-drug antibodies (ADA), with 27% of these ADA-positive patients testing positive for neutralizing antibodies. The incidence of these antibodies is assay-dependent, limiting comparisons with other studies. No clinical impact on pharmacokinetics, pharmacodynamics, safety, or efficacy was observed during treatment at the recommended dose.

Clinical Studies

The efficacy of Winrevair™ was evaluated in the STELLAR trial (NCT04576988), a global, double-blind, placebo-controlled, multicenter study involving 323 patients with pulmonary arterial hypertension (PAH) classified as WHO Group 1, Functional Class (FC) II or III. Patients were randomized 1:1 to receive Winrevair™ (0.7 mg/kg, n=163) or placebo (n=160), administered subcutaneously every three weeks.

Participants were predominantly female (79%), with a median age of 48 years (range 18–82) and a median body weight of 68 kg (range 38–141). The most common PAH etiologies were idiopathic PAH (59%), heritable PAH (18%), and PAH associated with connective tissue diseases (15%). The trial excluded patients with HIV-associated PAH, portal hypertension-associated PAH, schistosomiasis-associated PAH, and pulmonary veno-

occlusive disease. The mean time from PAH diagnosis to screening was 8.8 years. Most participants were receiving either two (35%) or three (61%) background PAH therapies, and 40% were on prostacyclin infusions. At baseline, 49% of patients had WHO FC II, while 51% had WHO FC III.

The primary efficacy endpoint was the change in 6-Minute Walk Distance (6MWD) from baseline to Week 24. In the Winrevair™ group, the placebo-adjusted median increase in 6MWD was 41 meters (95% CI: 28, 54; $p < 0.001$).

Treatment with Winrevair™ resulted in a 29% improvement in WHO Functional Class at Week 24, compared to 14% in the placebo group ($p < 0.001$). Additionally, Winrevair™ led to an 84% reduction in death from any cause or PAH clinical worsening events compared to placebo. These outcomes were assessed until the last patient completed the Week 24 visit, with a median exposure duration of 33.6 weeks.

Exclusivity and Patents

The Orphan Drug Database lists Orphan Drug Exclusivity (ODE) for Winrevair™, expiring on March 26, 2031. The protected indication is the treatment of adults with pulmonary arterial hypertension (PAH, World Health Organization [WHO] Group 1) to increase exercise capacity, improve WHO functional class (FC), and reduce the risk of clinical worsening events.

Xolremdi™

Mavorixafor capsules, for oral use

Fast Facts	
NDA Holder	X4 Pharmaceuticals, Inc
Product Presentation	Capsule
Route of Administration	Oral
NDA Original Approval	April 26, 2024
NCE Exclusivity	April 26, 2029
ODE	Yes, exclusivity ending April 26, 2031
Mechanism of action	An oral CXC chemokine receptor 4 (CXCR4) antagonist First-in-class

Indication

Xolremdi™ is indicated for patients aged 12 years and older with WHIM syndrome (warts, hypogammaglobulinemia, infections, and myelokathexis) to increase circulating mature neutrophil and lymphocyte counts.

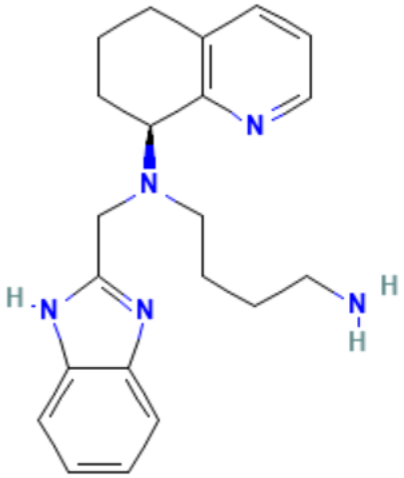
Dosage Form and Handling

Xolremdi™ is supplied as hard gelatin capsules containing 100 mg of mavorixafor as the active ingredient. The capsules are packaged in HDPE bottles and should be stored refrigerated at 2°C to 8°C. Keep the bottle tightly closed and store it in the original container to protect from moisture.

Each capsule contains 100 mg of mavorixafor along with the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, dibasic calcium phosphate dihydrate, microcrystalline cellulose, sodium lauryl sulfate, and sodium stearyl fumarate. The hard gelatin capsule shell is composed of FD&C Blue #2, gelatin, and titanium dioxide. The black ink used for imprinting contains ammonium hydroxide (28%), ferrosoferric oxide/black iron oxide (E172), isopropyl alcohol, n-butyl alcohol, propylene glycol, and shellac glaze in ethanol.

Description

Mavorixafor has a molecular weight of 349.48 g/mol. Its chemical structure is as follows:



Dosing Regimen

The recommended dosage of Xolremdi™ is weight-based. Patients weighing over 50 kg should take 400 mg orally once daily on an empty stomach after an overnight fast, at least 30 minutes before eating. Those weighing 50 kg or less should take 300 mg orally once daily under the same fasting conditions.

Mechanism of Action

Mavorixafor is an orally bioavailable antagonist of CXC chemokine receptor 4 (CXCR4) that blocks the binding of its ligand, stromal-derived factor-1α (SDF-1α)/CXC chemokine ligand 12 (CXCL12). The SDF-1/CXCR4 pathway controls the trafficking and homing of leukocytes between the bone marrow and peripheral circulation. In WHIM syndrome, gain-of-function mutations in the CXCR4 gene increase responsiveness to CXCL12, causing abnormal retention of leukocytes in the bone marrow.

Mavorixafor inhibits CXCL12-mediated signaling in both wild-type and mutant CXCR4 variants linked to WHIM syndrome. By blocking this pathway, it promotes the mobilization of neutrophils and lymphocytes, facilitating their release from the bone marrow into peripheral circulation.

Pharmacokinetics

Mavorixafor reaches peak concentration (Tmax) at a median of 2.8 hours (range: 1.9 to 4 hours) after administration of the highest approved dose. The drug exhibits greater-than-dose-proportional pharmacokinetics, with steady state achieved within approximately 9 to 12 days at this dose. Food intake significantly affects mavorixafor absorption: a high-fat meal reduces Cmax by 66% and AUC by 55%, while a low-fat meal decreases Cmax by 55% and AUC by 51%. Additionally, food delays time to peak concentration by about 4 hours compared to fasting conditions.

Mavorixafor has a volume of distribution of 768 L and is more than 93% bound to human plasma proteins. It has a terminal half-life of 82 hours (CV 34%) and an apparent clearance of 62 L/h (CV 40%). Although mavorixafor shows partial nonlinear clearance, this effect is not clinically significant at the approved dose. Metabolism occurs primarily via cytochrome P450 3A4 (CYP3A4), with CYP2D6 contributing minimally. Following a

single radiolabeled dose, 74.2% of the drug is excreted in feces and 13.3% is eliminated in urine.

Pharmacokinetics remain consistent in patients with mild to moderate renal impairment; however, the effects of severe renal impairment are unknown. The impact of hepatic impairment has not been studied.

Clearance is influenced by body weight, with higher clearance seen in patients weighing over 50 kg; however, this does not require dose adjustments when using weight-based dosing. In pediatric patients aged 12 to 17 years, mavorixafor demonstrates pharmacokinetics comparable to adults after accounting for body weight differences.

Clinical studies indicate that co-administration of mavorixafor with strong CYP3A4 inhibitors, such as itraconazole, approximately doubles mavorixafor exposure. Furthermore, CYP2D6 substrates like dextromethorphan show a sixfold increase in Cmax and an ninefold increase in AUC when administered with mavorixafor 400 mg. Similarly, CYP3A4 substrates such as midazolam show a 1.1-fold increase in Cmax and a 1.7-fold increase in AUC under the same conditions.

Mavorixafor also impacts the pharmacokinetics of other drugs. Digoxin, a P-glycoprotein (P-gp) substrate, displays a 1.5-fold increase in Cmax and a 1.6-fold increase in AUC when co-administered with mavorixafor. Metformin, an OCT2/MATE1 substrate, shows a 35% increase in both Cmax and AUC with 400 mg of mavorixafor. However, no significant pharmacokinetic interactions were observed with caffeine (CYP1A2 substrate), losartan (CYP2C9 substrate), omeprazole (CYP2C19 substrate), furosemide (OAT1 and OAT3 substrate), or oral contraceptives when taken alongside mavorixafor.

In vitro studies show that mavorixafor is a substrate of CYP3A4, CYP2D6, CYP3A5, and CYP2C19, but is not metabolized by CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2E1, or CYP4A11. It acts as a time-dependent inhibitor of CYP3A4, and also inhibits CYP3A5, CYP2D6, CYP2C19, and CYP1A2. Regarding drug transporters, mavorixafor is a substrate of P-glycoprotein (P-gp) and inhibits OATP1B1, OATP1B3, OAT1, OAT3, and MATE1, but does not inhibit BCRP, OATP2B1, OATP3A1, OAT2, MATE2-K, or NTCP.

Clinical Studies

The efficacy of Xolremdi™ was assessed in a 52-week, randomized, double-blind, placebo-controlled trial (NCT03995108) involving patients aged 12 years and older with WHIM syndrome. Participants had a genotype-confirmed CXCR4 variant and a baseline absolute neutrophil count (ANC) of ≤400 cells/μL. Patients were permitted to continue—but not initiate immunoglobulin therapy, while the use of other CXCR4 antagonists was prohibited.

A total of 31 patients were randomized 1:1 to receive either Xolremdi™ (N=14) or placebo (N=17) once daily for 52 weeks. The mean age was 22.1 years in the Xolremdi™ group and 30.9 years in the placebo group, with 50% of Xolremdi™ patients aged 12 to under 18 years, compared to 12% in the placebo group. The mean ANC was 155 cells/μL (Xolremdi™) versus 281 cells/μL (placebo), while the mean absolute lymphocyte count (ALC) was 501 cells/μL (Xolremdi™) versus 563 cells/μL (placebo).

Xolremdi™ treatment significantly increased the time above the absolute neutrophil count (TATANC) threshold of 500 cells/μL compared to placebo. The least squares (LS) mean (SE) TATANC was 15.0 (1.89) hours for Xolremdi™ and 2.8 (1.52) hours for placebo,

with a statistically significant mean difference of 12.3 hours (95% CI: 7.2, 17.4; $p < 0.0001$). This effect was sustained over time. Similarly, the mean time above the absolute lymphocyte count (TATALC) threshold of 1,000 cells/μL was significantly greater in the Xolremdi™ group over the 52-week period compared to placebo.

The study also evaluated a composite endpoint combining total infection score and total wart change score using a Win-Ratio approach. The Win-Ratio for Xolremdi™ was 2.76 (95% CI: 1.60, 4.76), indicating that patients treated with Xolremdi™ were more likely to achieve favorable outcomes than those on placebo. Among patients who improved on the composite endpoint, most gains were due to reductions in total infection score rather than changes in wart burden. No significant difference was observed between groups in total wart change scores. Further analysis showed that Xolremdi™-treated patients experienced approximately 40% fewer total infections and a 60% reduction in annualized infection rate compared to placebo. The LS mean (SE) annualized infection rate was 1.5 (0.57) for Xolremdi™ versus 2.4 (0.72) for placebo.

Exclusivity and Patents

There are two listed exclusivities: New Chemical Entity (NCE), expiring April 26, 2029, and Orphan Drug Exclusivity (ODE), expiring April 26, 2031. The indication protected by the exclusivity is: to increase the number of circulating mature neutrophils and lymphocytes in patients 12 years of age and older with WHIM syndrome (warts, hypogammaglobulinemia, infections, and myelokathexis). The patents listed in the Orange Book are summarized in Table 25 (Appendix A).

Yorvipath®

Palopegteriparatide injection, for subcutaneous use

Fast Facts	
NDA Holder	Ascendis Pharma
Product Presentation	Solution for injection
Route of Administration	Subcutaneous
NDA Original Approval	August 9, 2024
NCE Exclusivity	August 9, 2029
ODE	Yes, exclusivity ending August 9, 2031
Mechanism of action	PTH(1-34) Release Mimicking Endogenous PTH to Regulate Calcium and Phosphate

Indication

Yorvipath is a parathyroid hormone analog (PTH[1-34]) indicated for the treatment of hypoparathyroidism in adults.

Dosage Form and Handling

Yorvipath is supplied as a clear, colorless injectable solution in a 14-dose, single-patient-use pen. Each pack contains two pens and 28 needles, providing a total of 28 doses. The formulation contains 3456 mcg/mL of palopegteriparatide, equivalent to 300 mcg/mL of teriparatide. It is available in three pen strengths: 168 mcg/0.56 mL (delivering 6, 9, or 12 mcg doses), 294 mcg/0.98 mL (for 15, 18, or 21 mcg doses), and 420 mcg/1.4 mL (for 24, 27, or 30 mcg doses). Prior to first use, Yorvipath must be refrigerated at 2°C to 8°C. After

opening, it can be stored at room temperature (up to 30°C) for up to 14 days. The product should remain in its original packaging to protect it from light and must not be frozen or exposed to heat.

Description

Yorvipath (palopegteriparatide injection) is a prodrug of teriparatide, designed as a parathyroid hormone analog containing the active PTH(1-34) fragment—the segment of the native 84–amino acid hormone responsible for its biological effects. This fragment is conjugated to an inert carrier molecule via proprietary TransCon technology. The carrier is a branched 40 kDa methoxypolyethylene glycol (mPEG), consisting of two 20 kDa arms, resulting in a combined average molecular weight of approximately 47.4 kDa for the entire molecule.

Dosing Regimen

Yorvipath treatment typically begins with an 18 mcg subcutaneous dose administered once daily. Dose adjustments are made in 3 mcg increments, with increases spaced at least 7 days apart and decreases allowed no more frequently than every 3 days. The approved dosing range is 6 to 30 mcg daily. Serum calcium levels should be monitored within 7 to 10 days after starting treatment or following any changes in Yorvipath dosage, calcium supplementation, or active vitamin D, to detect potential hypo- or hypercalcemia. The treatment goal is to adjust the dose to maintain calcium within the normal range, ideally without the need for active vitamin D or high-dose calcium supplements. Once a stable maintenance dose is reached, calcium levels should be reassessed every 4 to 6 weeks or as clinically indicated. If serum calcium remains low despite the maximum Yorvipath dose, resuming or adding calcium and/or active vitamin D supplementation may be necessary.

Mechanism of Action

Palopegteriparatide provides continuous release of PTH(1-34), mimicking endogenous parathyroid hormone to regulate calcium and phosphate homeostasis. It raises serum calcium levels and lowers serum phosphate by stimulating bone turnover, increasing renal calcium reabsorption and phosphate excretion, and enhancing active vitamin D synthesis to promote intestinal absorption of calcium and phosphate. These effects are mediated via the parathyroid hormone 1 receptor (PTH1R), which is primarily expressed on osteoblasts, osteocytes, and renal tubular cells.

Pharmacokinetics

Yorvipath is a prodrug that releases PTH(1-34) via autocleavage of the TransCon linker. Its pharmacokinetics (PK) demonstrate a dose-proportional increase in Cmax and AUC across a dose range of 12 to 24 mcg/day, with steady-state reached after 7 days of administration. At steady-state, Yorvipath provides continuous systemic exposure to released PTH(1-34) over the entire 24-hour dosing period. The mean steady-state PTH(1-34) profile, based on an average daily dose of 22.3 mcg (range: 12–33 mcg/day, n=7), includes both PTH(1-34) and its active metabolite, PTH(1-33).

Yorvipath absorption is characterized by a median Tmax of 4 hours (range: 4 to 8 hours). The apparent volume of distribution (Vd) of palopegteriparatide is 4.8 L (CV%: 50), exhibiting a distribution pattern similar to endogenous PTH. The elimination half-life of PTH released from palopegteriparatide is approximately 60 hours, with an estimated clearance (CL) of 0.58 L/day (CV%: 52). Both PTH(1-34) and its active metabolite, PTH(1-33), show comparable affinity for and activation of the parathyroid hormone 1 receptor (PTH1R).

There are no clinically significant differences in the pharmacokinetics of palopegteriparatide based on age, sex, or body weight. Although data on race and ethnicity are limited, no significant differences have been observed. In a renal impairment study, mild, moderate, and severe renal impairment did not significantly affect systemic PTH exposure following a single 50 mcg subcutaneous dose. However, no studies have been conducted in hypoparathyroidism patients with severe renal impairment. While no dedicated hepatic impairment study has been performed, mild to moderate hepatic impairment is not expected to influence palopegteriparatide pharmacokinetics.

The immunogenicity of Yorvipath depends on assay sensitivity and specificity, which limits comparisons with other studies. In clinical trials with a mean exposure of 850 days, 0.7% of patients developed low-titer, non-neutralizing antibodies to PTH, while 5% developed treatment-emergent PEG antibodies. Additionally, 2.2% had pre-existing PEG antibodies, causing transient effects on palopegteriparatide pharmacokinetics and serum calcium levels. Despite these immune responses, therapeutic effectiveness was maintained through dose adjustments.

Clinical Studies

The effectiveness and safety of Yorvipath in adults with hypoparathyroidism were evaluated in a 26-week, randomized, double-blind, placebo-controlled phase 3 study involving 82 participants. Subjects underwent a 4-week stabilization period to adjust calcium and vitamin D intake before randomization to either Yorvipath (n=61) or placebo (n=21), with treatment starting at 18 mcg/day alongside conventional therapy.

At Week 26, 68.9% (42/61) of participants in the Yorvipath group met the primary efficacy endpoint of maintaining normal albumin-corrected serum calcium levels (8.3 to 10.6

mg/dL) without increases in calcium or vitamin D doses, compared to 4.8% (1/21) in the placebo group—a treatment difference of 64.2% (95% CI: 49.5%, 78.8%). The Yorvipath group also demonstrated significantly higher response rates in individual components, including achieving normal serum calcium (80.3%), independence from active vitamin D (95.1%), and independence from therapeutic calcium doses (86.9%) compared to placebo. During the open-label extension, the efficacy endpoint was sustained by 39.3% (24/61) of participants at both Week 52 and Week 78. Additionally, 64% (39/61) maintained normal serum calcium levels with independence from active vitamin D and calcium at Week 52, increasing slightly to 66% (40/61) at Week 78.

Exclusivity and Patents

Yorvipath is protected by two exclusivities: New Chemical Entity (NCE) exclusivity, expiring August 9, 2029, and Orphan Drug Exclusivity (ODE), expiring August 9, 2031, for the treatment of hypoparathyroidism in adults. The patents listed in the Orange Book are summarized in Table 26 (Appendix A).

Zelsuvmi™

Berdazimer topical gel

Fast Facts	
NDA Holder	LNHC, Inc
Product Presentation	Gel
Route of Administration	Topical
NDA Original Approval	January 5, 2024
NCE Exclusivity	January 5, 2029
ODE	No
Mechanism of action	Nitric oxide releasing agent

Indication

Zelsuvmi™ is approved for the topical treatment of molluscum contagiosum in individuals aged one year and older.

Dosage Form and Handling

Zelsuvmi™ is packaged in a carton containing two tubes: Tube A, which holds berdazimer gel, and Tube B, which contains a hydrogel, along with a dosing guide. Prior to dispensing, the product should be stored refrigerated at 2°C to 8°C. The dispenser is required to write the "Discard after" date on the carton to monitor the usage period.

Once dispensed, Zelsuvmi™ should be stored at room temperature (20°C to 25°C) in a dry place. Because the formulation contains alcohol, it must be kept away from open flames.

Freezing is not permitted as it may compromise the stability of the formulation. The medication must be discarded 60 days after removal from refrigeration, even if unused.

Tube A (14 g) contains berdazimer sodium at 240 mg per gram, along with inactive ingredients including cyclomethicone, hexylene glycol, hydroxypropyl cellulose, and isopropyl alcohol. Tube B (17 g) contains a hydrogel comprising benzoic acid, carboxymethylcellulose sodium, cyclomethicone, ethanol (13% v/v), glycerin, potassium phosphate monobasic, and purified water.

Description

Berdazimer sodium is chemically identified as a partially hydrolyzed polysiloxane copolymer named poly[{[3-(methylamino)propyl]silasesquioxane}-co-{[3-(1-methyl-2-nitroso-2-oxidohydrazin-1-yl)propyl]silasesquioxane}-co-silicate (1:3:6 x)], with an approximate Si:OH ratio of 10:5.

Dosing Regimen

Equal amounts (0.5 mL) of gel from Tube A and Tube B should be dispensed onto the dosing guide, and the caps must be securely replaced on both tubes immediately. The gels should then be thoroughly mixed on the dosing guide.

Zelsuvmi™ should be applied immediately as a thin, even layer to each molluscum contagiosum (MC) lesion. Treatment is to be administered once daily for up to 12 weeks.

Mechanism of Action

Zelsuvmi™ is a nitric oxide–releasing agent; however, its mechanism of action in the treatment of molluscum contagiosum remains unknown.

Pharmacokinetics

In a study of 34 children (ages 2–12) with molluscum contagiosum (MC), Zelsuvmi™ was applied once daily for two weeks to a 484 cm² treatment area (mean: 34 lesions; 3 mL/day). Plasma levels of hydrolyzed MAP3 (hMAP3) were not quantifiable on Day 1, with only two subjects exhibiting detectable levels on Day 15. Plasma nitrate concentrations remained stable throughout the study, and no changes in methemoglobin levels were observed.

Clinical Studies

The efficacy of Zelsuvmi™ was evaluated in three multicenter, randomized, double-blind, vehicle-controlled trials involving subjects with molluscum contagiosum (MC). Trial 1 enrolled 891 subjects, Trial 2 enrolled 355, and Trial 3 enrolled 352. Subjects were randomized 1:1 in Trial 1 and 2:1 in Trials 2 and 3 to receive either Zelsuvmi™ or vehicle control, applied once daily for up to 12 weeks. The study population was predominantly pediatric, with 96% of participants aged 2 to 17 years, and included a demographically diverse cohort. Baseline MC lesion counts ranged from 3 to 70, with an average of 20.2 lesions per subject.

The primary efficacy endpoint was the proportion of subjects achieving complete clearance of MC lesions at Week 12, defined as a lesion count of zero. The secondary endpoint was clearance at Week 8. In Trial 1, complete clearance at Week 12 was achieved in 32.4% of subjects receiving Zelsuvmi™ versus 19.7% in the vehicle group (treatment difference: 12.8%; 95% CI: 7.1%, 18.6%). At Week 8, clearance was 19.6% versus 11.6%, respectively (treatment difference: 7.5%; 95% CI: 3.0%, 12.0%).

In Trial 2, Week 12 clearance was 30.0% for Zelsuvmi™ and 20.3% for vehicle (treatment difference: 9.2%; 95% CI: -0.04%, 18.4%), while Week 8 clearance was 13.9% vs. 5.9%

(treatment difference: 7.8%; 95% CI: 1.8%, 13.8%). In Trial 3, complete clearance at Week 12 was 26% for Zelsuvmi™ and 22% for vehicle, with a 95% confidence interval ranging from -5% to 14%.

Efficacy was demonstrated in Trials 1 and 2, while Trial 3 showed a smaller treatment difference. These findings support the potential of Zelsuvmi™ to promote MC lesion clearance when applied once daily for up to 12 weeks.

Exclusivity and Patents

One New Chemical Entity (NCE) exclusivity is listed in the Orange Book, with an expiration date of January 5, 2029. The patents listed in the Orange Book are summarized in Table 27 (Appendix A).

Zevtera

Ceftobiprole medocaril sodium for injection, for intravenous use

Fast Facts	
NDA Holder	Basilia Pharmaceutica International Ltd.
Product Presentation	Powder for solution
Route of Administration	Intravenous
NDA Original Approval	April 3, 2024
NCE Exclusivity	April 3, 2029
ODE	No
Mechanism of action	A cephalosporin antibacterial

Indication

Zevtera is an antibiotic approved for the treatment of various bacterial infections. It is indicated for Staphylococcus aureus bloodstream infection (bacteremia) (SAB), including right-sided infective endocarditis, caused by both methicillin-susceptible and methicillin-resistant strains.

Additionally, it is approved for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults, targeting Staphylococcus aureus (both methicillin-susceptible and resistant), Streptococcus pyogenes, and Klebsiella pneumoniae.

Zevtera is also indicated for community-acquired bacterial pneumonia (CABP) in adults and pediatric patients (aged 3 months to <18 years), covering Staphylococcus aureus

(methicillin-susceptible), Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, Escherichia coli, and Klebsiella pneumoniae.

Dosage Form and Handling

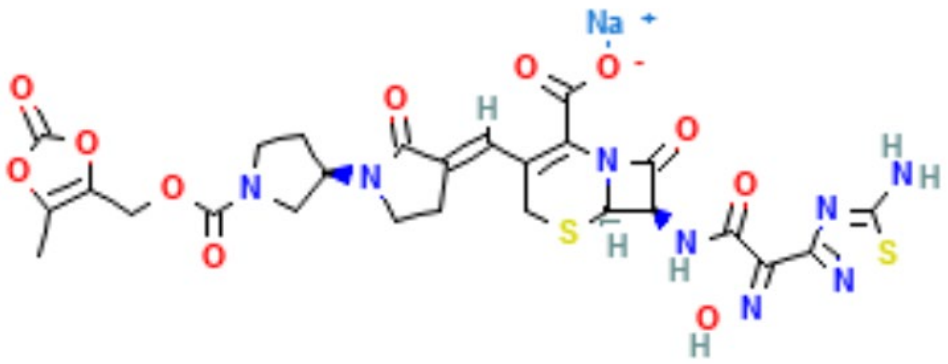
Zevtera is supplied as a sterile powder for reconstitution in single-dose glass vials, sealed with a rubber stopper and an aluminum seal with a flip-off cap. Each vial contains 667 mg of ceftobiprole medocaril sodium (equivalent to 500 mg of ceftobiprole) and is packaged in cartons containing 10 single-dose vials (NDCs pending).

Zevtera should be stored refrigerated at 2°C to 8°C, protected from light, and kept in its original carton until use. Before administration, it must be reconstituted and further diluted for intravenous infusion.

Each vial of Zevtera contains inactive ingredients, including 26.3 mg of citric acid monohydrate as a buffering agent and sodium hydroxide (q.s.) for pH adjustment. Each vial also contains approximately 32 mg of sodium. Once reconstituted, the solution has a pH range of 4.5 to 5.5.

Description

Zevtera (ceftobiprole medocaril sodium for injection) is a semisynthetic cephalosporin antibacterial agent presented as the sodium salt of ceftobiprole medocaril. It has a molecular weight of 690.6 g/mol. Its chemical structure is as follows:



Dosing Regimen

Adult patients: The recommended dosage regimen for Zevtera in adults varies by indication. For Staphylococcus aureus bloodstream infection (SAB), the recommended dose is 667 mg every 6 hours for the first 8 days, followed by 667 mg every 8 hours from day 9 onward. The total treatment duration may extend up to 42 days, depending on the severity of the infection and the patient's clinical response.

For acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP), the recommended dosage is 667 mg every 8 hours. Each dose should be administered by intravenous infusion over 2 hours. The typical treatment duration ranges from 5 to 14 days.

Pediatric patients with CABP: The dosing regimen for pediatric patients with community-acquired bacterial pneumonia (CABP) depends on age and weight, with treatment lasting between 7 and 14 days.

For children aged 12 to under 18 years, the recommended dose is 13.3 mg/kg (up to a maximum of 667 mg per dose) every 8 hours. Each dose should be administered by intravenous infusion over 2 hours at a concentration of 2.67 mg/mL. For children aged 3

months to less than 12 years, the recommended dose is 20 mg/kg (not exceeding 667 mg per dose) every 8 hours. These doses are also infused over 2 hours, but at a higher concentration of 5.33 mg/mL.

Mechanism of Action

Zevtera is a cephalosporin antibacterial agent. Ceftobiprole exerts bactericidal activity by inhibiting bacterial cell wall synthesis.

Pharmacokinetics

Zevtera (ceftobiprole medocaril sodium) is a prodrug of ceftobiprole that exhibits linear and time-independent pharmacokinetics, with no significant differences between single and multiple-dose administrations. The maximum plasma concentration Cmax) and area under the curve (AUC) increase proportionally over a dose range of 125 mg to 1000 mg (0.25 to 2 times the highest approved adult dose). In healthy adults with normal renal function, pharmacokinetic parameters were evaluated after multiple 2-hour intravenous infusions of Zevtera 667 mg (equivalent to 500 mg of ceftobiprole) every 8 hours, demonstrating consistent pharmacokinetics between single and multiple-dose administrations.

Ceftobiprole exhibits approximately 16% plasma protein binding, with 15–19% unbound in epithelial lining fluid (ELF). The volume of distribution at steady state (Vss) is 18 L, indicating moderate tissue penetration. Ceftobiprole undergoes minimal metabolism, has an elimination half-life ($t_{1/2}$) of 3.3 hours, and a clearance rate of 4.98 L/h. The drug is primarily excreted renally, with 83% eliminated unchanged in the urine, highlighting a strong dependence on renal clearance.

In specific populations, no significant pharmacokinetic differences were observed based on age, gender, or race/ethnicity. However, renal impairment notably affects ceftobiprole exposure, with the area under the curve (AUC) increasing 2.5-fold in moderate renal impairment and 3.3-fold in severe renal impairment. Patients with end-stage renal disease (ESRD; creatinine clearance [CLCr] <15 mL/min) showed no major pharmacokinetic differences, although ceftobiprole is removed by hemodialysis. Conversely, augmented renal clearance (CLCr >150 mL/min) is predicted to reduce ceftobiprole exposure; however, its impact in pediatric patients remains unknown.

In pediatric patients from birth to less than 18 years old with normal renal function, no clinically significant pharmacokinetic differences were observed following intravenous administration of Zevtera. However, Zevtera is not approved for use in infants younger than 3 months.

Regarding drug interactions, ceftobiprole neither inhibits nor induces cytochrome P450 (CYP450) enzymes, suggesting a low risk of metabolism-based interactions. Nonetheless, ceftobiprole inhibits the transporters OATP1B1, OATP1B3, MRP2, and BSEP, which may affect transport-mediated drug interactions. It does not inhibit P-glycoprotein, BCRP, OAT1, OAT3, OCT1, OCT2, or MATE1.

Clinical Studies

SAB: The efficacy of Zevtera in treating Staphylococcus aureus bloodstream infection (SAB), including right-sided infective endocarditis, was evaluated in a randomized, controlled, double-blind, multinational trial. Patients were assigned to receive either Zevtera 667 mg IV every 6 hours (Days 1–8), followed by every 8 hours thereafter, or daptomycin (6–10 mg/kg IV every 24 hours), with optional aztreonam for gram-negative

co-infections. Treatment duration ranged from 28 to 42 days, depending on the patient's clinical condition.

Eligible patients had a positive blood culture for S. aureus within 72 hours prior to randomization and presented with symptoms of bacteremia such as fever, tachycardia, or hypotension. In addition, patients were required to have at least one complication of SAB, including chronic dialysis, osteomyelitis, abscesses, or right-sided infective endocarditis (per Modified Duke's Criteria). Patients with uncomplicated SAB, left-sided endocarditis, or infections related to prosthetic heart valves were excluded. The study enrolled 390 patients (192 Zevtera, 198 daptomycin) from 60 centers across the USA, Europe, Latin America, and South Africa. The modified intent-to-treat (mITT) population comprised 387 patients (189 Zevtera, 198 daptomycin ± aztreonam) with a positive baseline blood culture for S. aureus.

At Day 70 (post-treatment evaluation visit), the primary efficacy endpoint—defined as survival, resolution of bacteremia, absence of complications, and no requirement for additional antibiotics—was achieved at similar rates in both treatment groups: 69.8% for Zevtera versus 68.7% for daptomycin. Among subgroups, success rates were also comparable, with Zevtera showing a 70.9% success rate in MSSA infections compared to 74.6% with daptomycin, 68.9% in MRSA infections versus 67.1% with daptomycin, and 66.7% success in definite right-sided infective endocarditis compared to 70.0% with daptomycin. Regionally, Ukraine exhibited higher success rates (84.1% Zevtera vs. 89.1% daptomycin), while other countries reported similar outcomes (50.4% vs. 50.9%).

Secondary outcomes also demonstrated comparable results between Zevtera and daptomycin. All-cause mortality rates were nearly identical (9.0% vs. 9.1%), and

microbiological eradication was slightly higher in the Zevtera group (82% vs. 77%). Complications from S. aureus bacteremia were marginally lower in the Zevtera group (6% vs. 7%), and bacteremia clearance times were modestly faster for MSSA infections (median of 3 days with Zevtera vs. 4 days with daptomycin), while MRSA clearance times were equal in both groups (5 days). Failure of S. aureus eradication occurred in 2 patients (1%) treated with Zevtera and 4 patients (2%) treated with daptomycin, with no resistance detected in ceftobiprole-treated patients.

Overall, the study demonstrated that Zevtera was non-inferior to daptomycin for the treatment of SAB, including both MRSA and MSSA infections, with comparable success rates, bacteremia clearance times, and mortality outcomes.

ABSSSI: The efficacy of Zevtera in treating acute bacterial skin and skin structure infections (ABSSSI) was evaluated in a randomized, controlled, double-blind, multinational trial. Patients received either Zevtera 667 mg IV every 8 hours or vancomycin plus aztreonam (vancomycin 1 g or 15 mg/kg IV every 12 hours, plus aztreonam 1 g IV every 12 hours). Treatment lasted 5 to 14 days, with metronidazole permitted for anaerobic infections; however, oral step-down therapy was not allowed. Eligible patients presented with ABSSSI—such as cellulitis/erysipelas, major cutaneous abscesses, or wound infections—with lesion sizes ≥75 cm² and systemic signs of infection. The study enrolled 679 patients (335 Zevtera, 344 vancomycin + aztreonam) across 32 centers in the USA and Europe, with the microbiological intent-to-treat (mITT) population including 506 patients who had a confirmed baseline pathogen.

The primary efficacy endpoint was early clinical response at 48–72 hours, defined as a ≥20% reduction in primary lesion size, survival at 14 days, and no need for additional

antibiotic therapy or complications. The secondary endpoint was investigator-assessed clinical success at the test-of-cure (TOC) visit (Day 15–22), occurring at least 5 days after treatment completion. Early clinical response rates were 91.3% with Zevtera versus 88.1% with vancomycin plus aztreonam, while clinical success at the test-of-cure (TOC) visit was 90.1% versus 89.0%, respectively, demonstrating the non-inferiority of Zevtera to standard therapy.

Among patients with a confirmed baseline pathogen, Zevtera showed similar or slightly better efficacy compared to vancomycin plus aztreonam. At the early clinical response assessment (48–72 hours), 93.4% of patients with gram-positive infections responded to Zevtera versus 91.3% with vancomycin plus aztreonam. For Staphylococcus aureus infections, Zevtera achieved a 94.5% response rate compared to 92.8% with vancomycin plus aztreonam. At the TOC visit, Zevtera reached a 97.6% success rate for S. aureus infections, compared to 96.4% with vancomycin plus aztreonam. Additionally, 100% of Klebsiella pneumoniae infections showed early clinical response, with both groups attaining a 97.8% success rate at TOC.

Overall, Zevtera was non-inferior to vancomycin plus aztreonam in treating ABSSSI, including MSSA, MRSA, and gram-negative infections. The comparable early clinical response and TOC success rates support Zevtera as an effective alternative for serious skin infections.

CABP: The efficacy of Zevtera in treating community-acquired bacterial pneumonia (CABP) was evaluated in a randomized, controlled, double-blind, multinational trial (NCT03862167). A total of 638 hospitalized adults requiring IV antibiotic therapy were randomized to receive either Zevtera 667 mg IV every 8 hours or levofloxacin 500 mg IV

every 24 hours (750 mg for fluoroquinolone-resistant pathogens). Patients were stratified according to the Pneumonia Outcomes Research Team (PORT) classification for severity, and oral step-down therapy was permitted. Eligible patients had radiographic evidence of pneumonia, clinical symptoms, and at least one risk factor (e.g., recent hospitalization, chronic illness, or immunosuppression). The microbiological intent-to-treat (mITT) population included 588 patients (314 Zevtera, 264 levofloxacin ± aztreonam).

The primary efficacy endpoint was clinical cure at the test-of-cure (TOC) visit (7–14 days after treatment completion), defined as resolution or improvement of symptoms without the need for additional antibacterial therapy. Zevtera demonstrated comparable efficacy to ceftriaxone plus linezolid, with clinical cure rates of 76.4% versus 79.3% in the ITT population and 81.6% versus 87.4% in the clinically evaluable (CE) population. Mortality rates were low and similar between groups (1.6% Zevtera vs. 2.5% ceftriaxone plus linezolid).

Early clinical success at Day 3 was also assessed post hoc, evaluating symptom resolution in patients with PORT Class III–V pneumonia. Zevtera achieved a 71.0% success rate compared to 71.1% for ceftriaxone plus linezolid, confirming consistent efficacy. Among patients with confirmed baseline pathogens, Zevtera showed similar or slightly lower success rates for S. pneumoniae (81.8% vs. 83.3%) and H. influenzae (78.6% vs. 84.6%), while response rates for MSSA (76.5%) and MRSA (71.4%) were comparable.

In pediatric patients aged 3 months to less than 18 years, a separate randomized, investigator-blind study evaluated Zevtera's safety and pharmacokinetics, although it was not powered to assess efficacy. A total of 138 pediatric patients were randomized (2:1) to receive Zevtera (13.3 or 26.7 mg/kg IV) or standard antibacterial therapy. Among them,

94% had community-acquired bacterial pneumonia (CABP), and 6% had hospital-acquired bacterial pneumonia (HABP). The median treatment duration was 6.0 days, and 88% of Zevtera-treated patients completed therapy without switching antibiotics. Clinical response rates at Day 4, end of treatment, and test-of-cure (TOC, 7–14 days post-treatment) were comparable between Zevtera and the comparator group, supporting its safety and potential efficacy in pediatric CABP patients.

In adults, Zevtera demonstrated non-inferior efficacy to ceftriaxone plus linezolid in treating CABP, with similar clinical cure rates, early response rates, and low mortality. In pediatric patients, Zevtera was well tolerated with high treatment completion rates. These findings support Zevtera as an effective alternative for CABP in both adult and pediatric populations aged 3 months and older.

Exclusivity and Patents

One New Chemical Entity (NCE) exclusivity is listed in the Orange Book, expiring on April 3, 2029. Additionally, NCE GAIN (Generating Antibiotic Incentives Now) exclusivity is also listed, expiring on April 3, 2034. No patents are currently listed.

Ziihera®

Zanidatamab-hrii for injection, for intravenous use

Fast Facts	
BLA Holder	Jazz Pharmaceuticals, Inc.
Dosage form	Powder for reconstitution
Route of Administration	Intravenous
BLA Approval	November 20, 2024 (New Biological Entity)* Accelerated Approval
ODE	Yes, November 20, 2031
Mechanism of action	A bispecific HER2-directed antibody that binds to two extracellular sites on HER2. Zanidatamab-hrii induces complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP), First-in-class

*BLA exclusivity is typically granted for 12 years from date of approval

Indication

Ziihera is approved for the treatment of adults with HER2-positive (IHC 3+) biliary tract cancer that is unresectable, metastatic, or previously treated, as determined by an FDA-approved diagnostic test.

Description

Zanidat.amab-hrii is a humanized, IgG-like bispecific antibody targeting HER2. It is produced in Chinese hamster ovary cells via recombinant DNA technology and has a molecular weight of 124.8 kDa.

Dosage Form and Handling

Ziihera (zanidatamab-hrii) for injection is supplied as a sterile lyophilized powder that must be reconstituted and diluted prior to intravenous administration. Each single-dose vial contains 300 mg of zanidatamab-hrii after reconstitution, along with the following inactive ingredients: polysorbate 20 (0.63 mg), sodium succinate (4.3 mg), succinic acid (4.3 mg), and sucrose (567 mg). When 5.7 mL of Sterile Water for Injection is added, the resulting solution has a concentration of 50 mg/mL, a deliverable volume of 6 mL, and a pH of 4.6. This solution is further diluted before infusion.

Ziihera should be stored refrigerated at 2°C to 8°C in its original carton to protect it from light. Do not freeze.

Dosing Regimen

The recommended dose of Ziihera is 20 mg/kg, administered by intravenous infusion every two weeks until disease progression or unacceptable toxicity occurs.

Mechanism of Action

Zanidatamab-hrii is a bispecific HER2-directed antibody that binds to two distinct extracellular sites on the HER2 receptor. This dual binding triggers receptor internalization, leading to decreased HER2 expression on the tumor cell surface. Zanidatamab-hrii induces complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP), collectively inhibiting tumor growth and promoting tumor cell death both in vitro and in vivo.

Pharmacokinetics

Zanidatamab-hrii exhibits dose-proportional pharmacokinetics, with Cmax increasing proportionally to dose. However, AUC accumulation exceeds dose proportionality,

showing a mean accumulation ratio of 2.4 over time. The volume of distribution is approximately 7.5 L, indicating limited tissue penetration.

The elimination half-life of zanidatamab-hrii is approximately 21 days, with a clearance rate of 0.012 L/h. It is primarily metabolized through catabolic pathways into small peptides. Pharmacokinetic studies have demonstrated no significant differences in drug exposure based on age, sex, or race. Mild to moderate renal and hepatic impairments do not significantly affect its pharmacokinetics; however, the impact of severe renal or hepatic impairment has not been studied.

Data on anti-drug antibody responses to zanidatamab-hrii remain limited, and the potential effects on pharmacokinetics, pharmacodynamics, safety, or efficacy are unknown. Additionally, no nonclinical studies have evaluated its carcinogenicity, mutagenicity, or effects on fertility.

Clinical Studies

The HERIZON-BTC-01 trial evaluated the efficacy of Ziihera (zanidatamab-hrii) in 62 patients with HER2-positive (IHC 3+) biliary tract cancer (BTC) who had unresectable or metastatic disease. All patients had received at least one prior gemcitabine-based systemic chemotherapy and had adequate cardiac function (LVEF ≥ 50%). Ziihera was administered intravenously at 20 mg/kg every two weeks until disease progression or unacceptable toxicity occurred. The primary efficacy endpoints were Objective Response Rate (ORR) and Duration of Response (DOR), assessed by independent central review (ICR) using RECIST v1.1.

The study population had a median age of 64 years, with 47% aged 65 or older and 55% female. The majority were Asian (61%), followed by White (31%) and other racial groups.

Regarding disease subtype, 53% had gallbladder cancer, 27% had intrahepatic cholangiocarcinoma, and 19% had extrahepatic cholangiocarcinoma. All patients had undergone at least one prior gemcitabine-based therapy, while 31% had two prior lines, and 10% had three or more. Most patients had an ECOG performance status of 1 (68%), indicating a relatively functional population.

Ziihera demonstrated an ORR of 52% (95% CI: 39–65%), with 3.2% achieving a complete response and 48% achieving a partial response. Among the 32 responders, the median duration of response (DOR) was 14.9 months (95% CI: 7.4, NE), with 59% maintaining response for at least six months and 44% for 12 months or longer. These results suggest that Ziihera provides a durable and meaningful clinical benefit for patients with HER2-positive BTC, a population with limited treatment options.

Exclusivity and Patents

The ODE database lists an exclusivity expiring on November 20, 2031, for the treatment of adults with previously treated, unresectable, or metastatic HER2-positive (IHC 3+) biliary tract cancer (BTC), as identified by an FDA-approved diagnostic test.

2025 Drug Monographs

Blujepa

Gepotidacin tablets, for oral use

Fast Facts	
NDA Holder	GlaxoSmithKline
Product Presentation	Tablet
Route of Administration	Oral
NDA Original Approval	March 25, 2025
NCE Exclusivity	March 25, 2030
	GAIN exclusivity until March 25, 2035
ODE	No
Mechanism of action	Novel antibiotic
	First-in-class

Typically, NCE exclusivity is granted for 5 years from approval

Indication

Blujepa is approved for use in female adults and pediatric patients aged 12 years and older weighing at least 40 kilograms (kg) to treat uncomplicated urinary tract infections (uUTIs) caused by susceptible bacteria, including Escherichia coli, Klebsiella pneumoniae, Citrobacter freundii complex, Staphylococcus saprophyticus, and Enterococcus faecalis.

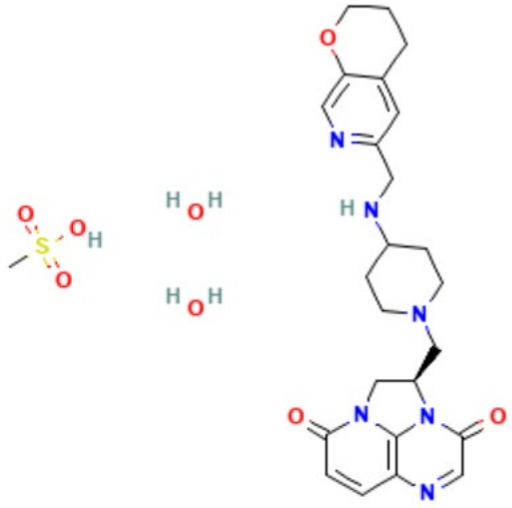
Dosage Form and Handling

Blujepa is supplied as film-coated tablets, each containing 750 mg of gepotidacin. The tablets are packaged in bottles of 20. Each tablet also contains the following inactive

ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, and yellow iron oxide. The product should be stored at controlled room temperature between 20°C and 25°C, with allowable excursions from 15°C to 30°C.

Description

Blujepa tablets contain gepotidacin mesylate dihydrate, which has a molecular weight of 580.66 g/mol. Its molecular structure is as follows:



Dosing Regimen

The recommended dose of Blujepa is 1,500 mg, administered as two 750 mg tablets taken orally twice daily, approximately 12 hours apart, after a meal to reduce gastrointestinal intolerance, for a treatment duration of 5 days.

Mechanism of Action

Blujepa is an antibacterial agent used to treat uncomplicated urinary tract infections caused by susceptible bacteria..

Pharmacokinetics

Gepotidacin exhibits approximately dose-proportional pharmacokinetics over the 1,500 mg to 3,000 mg range, with steady-state concentrations reached by Day 3 and around 40% accumulation. The absolute oral bioavailability is approximately 45%. The time to reach maximum plasma concentration (Tmax) is about two hours. Administration with a moderate-fat meal does not significantly affect the pharmacokinetics of gepotidacin.

The volume of distribution (Vd) is 172.9 liters, and plasma protein binding ranges from 25% to 41%. The terminal elimination half-life is 9.3 hours, and total clearance is 33.4 L/hour. Gepotidacin is primarily eliminated via oxidative metabolism mediated by CYP3A4, producing several metabolites. The major circulating metabolite, M4, accounts for up to approximately 11% of drug-related material. About 31% of the dose is recovered in urine (20% as unchanged drug), and 52% is recovered in feces (30% as unchanged drug). In subjects with moderate renal impairment, the area under the curve (AUC) increases by 1.2- to 1.5-fold and Cmax by 1.2- to 1.6-fold compared to healthy controls. In subjects with severe renal impairment (eGFR <30 mL/min), AUC and Cmax increased by 2.5-fold and 1.7-fold, respectively. Hemodialysis had limited impact on gepotidacin exposure. In subjects with moderate hepatic impairment, systemic exposure was similar to that in healthy subjects.

Effect of Other Drugs on the Pharmacokinetics of Gepotidacin

Coadministration of a strong CYP3A4 inhibitor, itraconazole (200 mg once daily for 3 days), with a single 1,500 mg dose of Blujepa resulted in an approximate 1.4-fold increase in gepotidacin Cmax and a 1.5-fold increase in AUC. Conversely, coadministration of the

strong CYP3A4 inducer rifampin (600 mg once daily for 7 days) with a single 1,500 mg dose of Blujepa led to a 52% decrease in gepotidacin AUC.

Effect of Gepotidacin on the Pharmacokinetics of Other Drugs

Coadministration of digoxin (0.5 mg dose) with two 3,000 mg doses of Blujepa administered 12 hours apart increased digoxin by 1.5-fold, AUC by 1.1-fold, and delayed Tmax. Similarly, coadministration of midazolam (2 mg single dose) with two 3,000 mg doses of Blujepa (12 hours apart) resulted in a 1.9-fold increase in midazolam AUC.

In vitro, gepotidacin is a substrate of uptake transporters OATP1B1 and OATP1B3, as well as efflux transporters P-gp and BCRP. Gepotidacin is not a significant inhibitor or inducer of CYP1A2, CYP2B6, or CYP3A4, nor is it a substrate of organic anion transporters OAT1, OAT2, or OAT3, organic cation transporters OCT2 or OCT3, or renal uptake transport proteins. However, in vitro, gepotidacin inhibited MATE1 and MATE2-K transporters.

Clinical Studies

Blujepa was evaluated in two randomized, double-blind, double-dummy, multicenter, non-inferiority trials (Trial 1: NCT04020341; Trial 2: NCT04187144) involving female patients with uncomplicated urinary tract infections (uUTIs). Both trials compared Blujepa 1,500 mg orally twice daily for 5 days with nitrofurantoin 100 mg orally twice daily for 5 days. The primary efficacy population was the microbiological intent-to-treat nitrofurantoin-susceptible (micro-ITTS) group, which included patients with a baseline qualifying uropathogen ($\geq 10^5$ CFU/mL) susceptible to nitrofurantoin.

Efficacy was assessed as a composite of clinical cure (resolution of uUTI symptoms without additional antimicrobial therapy) and microbiological response (reduction of

baseline uropathogens to <10^3 CFU/mL without additional antimicrobial therapy) at the Test-of-Cure visit (Day 10–13).

In Trial 1 (N = 634), the composite response was 51.8% for Blujepa and 47.0% for nitrofurantoin, with a treatment difference of 5.3% (95% CI: –2.4, 13.0). Clinical cure rates were 66.7% for Blujepa and 65.8% for nitrofurantoin [difference: 1.5% (95% CI: –5.8, 8.8)]. Microbiological response rates were 72.6% for Blujepa and 66.8% for nitrofurantoin [difference: 6.0% (95% CI: –1.2, 13.1)].

In Trial 2 (N = 567), the composite response was 58.9% for Blujepa and 44.0% for nitrofurantoin, with a treatment difference of 14.4% (95% CI: 6.4, 22.4). Clinical cure rates were 68.2% for Blujepa and 63.6% for nitrofurantoin [difference: 4.5% (95% CI: –3.2, 12.1)]. Microbiological response rates were 72.9% for Blujepa and 57.5% for nitrofurantoin [difference: 15.5% (95% CI: 7.9, 23.1)].

In both trials, Blujepa demonstrated numerically higher composite response rates at the Test-of-Cure visit compared to nitrofurantoin across all qualifying baseline uropathogens.

Exclusivity and Patents

As of April 2025, no exclusivities or patents are listed in the Orange Book.

Datroway®

Datopotamab deruxtecan-dlnk for injection, for intravenous use

Fast Facts	
BLA Holder	Daiichi Sankyo Inc.
Dosage form	Powder for reconstitution
Route of Administration	Intravenous
BLA Approval	January 17, 2025 (New Biological Entity)
ODE	No
Mechanism of action	A Trop2-directed antibody-drug conjugate (ADC) of the cytotoxic component, deruxtecan.

Indication

Datroway is approved for use in adults with unresectable or metastatic breast cancer that is hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative (IHC 0, 1+, or 2+/ISH-), who have previously undergone both endocrine-based therapy and chemotherapy for advanced disease.

Description

Datopotamab deruxtecan-dlnk is an antibody-drug conjugate (ADC) that targets Trop2 and delivers a topoisomerase I inhibitor. It consists of three main parts: a humanized IgG1 monoclonal antibody directed at Trop2, a cytotoxic agent (a topoisomerase I inhibitor called DXd), and a cleavable linker made of a tetrapeptide. The DXd payload, a derivative

of exatecan, is attached to the antibody via a maleimide-containing linker that can be cleaved by proteases.

The antibody is produced in CHO cells using recombinant DNA methods, while the linker and drug payload are chemically synthesized. On average, each antibody is conjugated with about four molecules of deruxtecan.

Dosage Form and Handling

Datroway (datopotamab deruxtecan-dlnk) for injection is a sterile, preservative-free lyophilized powder supplied in single-dose vials. Each vial contains 100 mg of datopotamab deruxtecan-dlnk, along with 3.88 mg of L-histidine, 5.25 mg of L-histidine hydrochloride monohydrate, 1.50 mg of polysorbate 80, and 450 mg of sucrose. After reconstitution with 5 mL of Sterile Water for Injection, USP, the resulting solution has a concentration of 20 mg/mL and a pH of 6.0. The solution should be administered via intravenous infusion after further dilution.

Store vials refrigerated at 2°C to 8°C in the original packaging to protect from light until reconstitution. Do not freeze. Avoid shaking the solution after reconstitution or dilution.

Dosing Regimen

The recommended dose of Datroway is 6 mg per kg of body weight, up to a maximum of 540 mg for patients weighing 90 kg or more. It is administered as an intravenous infusion every three weeks (a 21-day cycle) and continued until disease progression or the development of unacceptable toxicity.

Mechanism of Action

Datopotamab deruxtecan-dlnk is a Trop2-directed antibody-drug conjugate (ADC) composed of a humanized IgG1 monoclonal antibody targeting Trop2, linked to the topoisomerase I inhibitor DXd via a cleavable linker. Upon binding to Trop2-expressing

cells, including cancer cells, the ADC is internalized, and the linker is cleaved by lysosomal enzymes. This releases the membrane-permeable DXd, which induces DNA damage and triggers apoptotic cell death.

Pharmacokinetics

The pharmacokinetics of Datroway indicate that both the antibody-drug conjugate and its released payload, DXd, exhibit dose-proportional increases in exposure over the 4 to 10 mg/kg range. No clinically meaningful accumulation of datopotamab deruxtecan-dlnk was observed between Cycles 1 and 3.

The mean steady-state volume of distribution for the conjugate is approximately 3.5 L. DXd is highly protein-bound, with about 98% bound to plasma proteins.

Following administration, Datroway binds to Trop2-expressing cells and is internalized, where lysosomal enzymes cleave the linker to release DXd intracellularly. The median terminal half-life of the conjugate is approximately 4.8 days, and the apparent half-life of DXd is approximately 5.5 days. The estimated clearance of the conjugate is 0.6 L/day.

The antibody component is catabolized into peptides and amino acids through standard protein degradation pathways. DXd is primarily metabolized by CYP3A4 and does not undergo significant metabolism via UGT enzymes. It is a substrate of multiple transporters, including OATP1B1, OATP1B3, OCT1, OCT2, MATE2-K, P-gp, MRP1, and BCRP, but does not significantly inhibit major transporters such as P-gp or BCRP.

Pharmacokinetic parameters for both the conjugate and DXd increase with body weight. However, no clinically meaningful differences were observed based on age, sex, race, or the presence of mild to moderate renal or hepatic impairment. In patients with moderate

renal impairment, DXd AUC increased by approximately 2.4-fold compared to healthy subjects. The effects of severe renal or hepatic impairment remain unknown.

Data on the immunogenicity of datopotamab deruxtecan-dlnk are limited, and the clinical significance of anti-drug antibody formation has not been established.

Clinical Studies

The TROPION-Breast01 trial (NCT05104866) was a randomized, open-label, multicenter study evaluating Datroway (datopotamab deruxtecan-dlnk) in adult patients with unresectable or metastatic, hormone receptor (HR)-positive, HER2-negative (IHC 0, 1+, or 2+/ISH–) breast cancer. A total of 732 patients who had received prior endocrine-based therapy and one or two prior chemotherapy regimens in the unresectable or metastatic setting were randomized 1:1 to receive either Datroway (6 mg/kg intravenously every 3 weeks) or investigator's choice of chemotherapy (eribulin, capecitabine, vinorelbine, or gemcitabine). Randomization was stratified by number of prior chemotherapy regimens (one vs. two), prior CDK4/6 inhibitor use (yes vs. no), and geographic region.

The primary endpoint was progression-free survival (PFS), assessed by blinded independent central review (BICR) using RECIST v1.1. Median PFS was 6.9 months (95% CI: 5.7, 7.4) in the Datroway arm and 4.9 months (95% CI: 4.2, 5.5) in the chemotherapy arm, with a hazard ratio of 0.63 (95% CI: 0.52, 0.76; $p < 0.0001$).

Secondary endpoints included overall survival (OS), objective response rate (ORR), and duration of response (DoR). The confirmed ORR was 36% (95% CI: 31, 42) for Datroway and 23% (95% CI: 19, 28) for chemotherapy. Among responders in the Datroway arm, 0.5% achieved a complete response and 36% achieved a partial response. In the chemotherapy arm, no complete responses were observed, and 23% achieved partial

responses. The median DoR was 6.7 months (95% CI: 5.6, 9.8) for Datroway and 5.7 months (95% CI: 4.9, 6.8) for chemotherapy. Median OS was 18.6 months in the Datroway arm and 18.3 months in the chemotherapy arm; the difference was not statistically significant.

Exclusivity and Patents

None listed.

Gomekli™

Mirdametinib capsules, for oral use, tablets for oral suspension

Fast Facts	
NDA Holder	SpringWorks Therapeutics Inc.
Product Presentation	Capsule, Tablet for oral suspension
Route of Administration	Oral
NDA Original Approval	February 11, 2025
NCE Exclusivity	February 11, 2030
ODE	Yes, exclusivity ending February 11, 2032
Mechanism of action	A MEK 1/2 inhibitor which regulate cell proliferation and survival

Indication

Gomkeli™ is approved for use in adults and pediatric patients aged 2 years and older with neurofibromatosis type 1 (NF1) who have symptomatic plexiform neurofibromas (PN) that cannot be completely removed by surgery.

Dosage Form and Handling

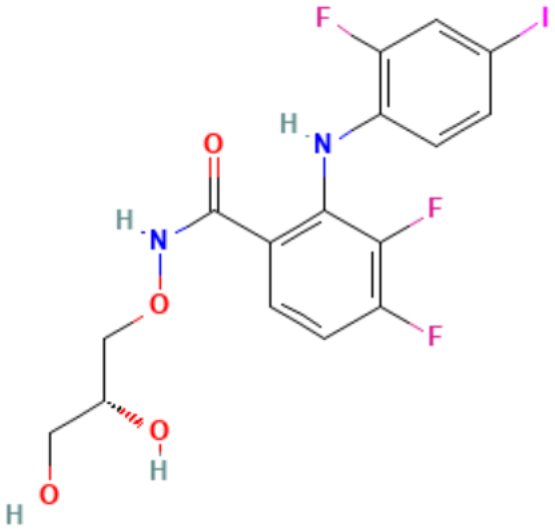
Gomkeli™ (mirdametinib) is available in two oral dosage forms: capsules and tablets for oral suspension. The capsules are available in 1 mg and 2 mg strengths and are designed to be swallowed whole. The tablets for oral suspension are available as 1 mg grape-flavored tablets, which can either be swallowed whole or dispersed in water and administered as a suspension. Gomkeli™ should be stored at controlled room temperature between 20°C and

25°C, with allowable temperature excursions between 15°C and 30°C. It must be protected from light.

The inactive ingredients in the capsules include croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The tablets for oral suspension contain similar excipients—croscarmellose sodium, magnesium stearate, and microcrystalline cellulose—along with grape flavoring and sucralose. The grape flavoring consists of corn syrup solids, modified corn starch, and triacetin to enhance palatability for pediatric patients.

Description

Gomkeli™ capsules and tablets for oral suspension contain mirdametinib, which has a molecular weight of 482.20 g/mol. The molecular structure of mirdametinib is as follows:



Dosing Regimen

The recommended dosage of Gomkeli™ (mirdametinib) is 2 mg/m², taken orally twice daily—approximately 12 hours apart—with or without food. Treatment is administered in 28-day cycles, with dosing on the first 21 days of each cycle.

Dosage is based on body surface area (BSA). Patients with a BSA between 0.40 and 0.69 m^2 should receive 1 mg twice daily. Those with a BSA from 0.70 to 1.04 m^2 should receive 2 mg twice daily, while patients with a BSA between 1.05 and 1.49 m^2 should receive 3 mg twice daily. For individuals with a BSA of 1.50 m^2 or greater, the recommended maximum dose is 4 mg twice daily. There is no established dosage recommendation for patients with a BSA below 0.40 m^2.

Mechanism of Action

Mirdametinib is an inhibitor of mitogen-activated protein kinases 1 and 2 (MEK1/2), which are key components of the MAPK/ERK signaling pathway that regulates cell proliferation and survival. In conditions such as neurofibromatosis type 1 (NF1), this pathway is often overactivated due to loss-of-function mutations in the NF1 gene, which normally acts as a negative regulator of Ras signaling. By inhibiting MEK1/2, mirdametinib reduces the downstream phosphorylation of ERK, thereby decreasing signaling through the MAPK pathway.

Pharmacokinetics

The pharmacokinetic profile of Gomkeli™ (mirdametinib) demonstrates oral absorption, with median peak plasma concentrations reached at approximately 0.8 hours for the tablet and 1.1 hours for the capsule. Steady-state levels are achieved in about six days, with an accumulation ratio ranging from 1.1 to 1.9. Administration with a high-fat, high-calorie meal leads to a 43% reduction in peak concentration (Cmax) and a 7% decrease in overall exposure (AUCinf) compared to the fasted state. The drug may be administered with or without food.

Mirdametinib is highly bound to plasma proteins (>99%) and has an apparent volume of distribution of 255 L (CV% 13). It is primarily metabolized via glucuronidation and oxidation, involving the enzymes UGT1A6, UGT2B7, and carboxylesterases (CES). The terminal elimination half-life is 28 hours (CV% 12), and the apparent systemic clearance is 6.3 L/h (CV% 13).

No clinically significant differences in pharmacokinetics were observed based on age (2 to 86 years), sex, or race. The pharmacokinetics of mirdametinib have not been evaluated in patients with moderate or severe hepatic impairment, severe renal impairment, or end-stage renal disease.

No clinical drug interaction studies have been performed for mirdametinib. In vitro data suggest it neither inhibits nor induces major CYP enzymes or key transporters. However, it is a substrate of BCRP and P-gp.

Clinical Studies

The efficacy of Gomkeli™ (mirdametinib) was evaluated in the ReNeu study (NCT03962543), a multicenter, single-arm trial involving 114 patients aged 2 years and older with symptomatic, inoperable neurofibromatosis type 1 (NF1)–associated plexiform neurofibromas (PN) causing significant morbidity. Patients received Gomkeli™ at a dose of 2 mg/m² orally twice daily for the first 21 days of each 28-day cycle, continuing until disease progression or unacceptable toxicity.

The primary efficacy outcome was the confirmed overall response rate (ORR), defined as the proportion of patients who achieved either a complete response (disappearance of the target PN) or a partial response (≥20% reduction in PN volume).

Among 58 enrolled adults (median age: 35 years; range: 18–69), 53% had progressing PN at baseline, 7% had prior MEK inhibitor treatment, and 69% had undergone surgery. The most common morbidities affecting over 25% of adult patients were pain (90%), disfigurement or major deformity (52%), and motor dysfunction (40%).

In the pediatric cohort of 56 patients (median age: 10 years; range: 2–17), 63% had progressing PN, 11% had received prior MEK inhibitor therapy, and 36% had undergone surgery. Morbidities reported in more than 25% of pediatric patients included pain (70%), disfigurement or major deformity (50%), and motor dysfunction (27%).

The median time to onset of response was 7.8 months (range: 4–19 months) in adults and was comparable in pediatric patients.

Based on blinded independent central review (BICR), the confirmed ORR was 41% (95% CI: 29%–55%) in adults and 52% (95% CI: 38%–65%) in pediatric patients. All responses were partial.

Regarding duration of response (DoR), 88% of adult responders maintained their response for at least 12 months, and 50% for at least 24 months. Among pediatric responders, 90% maintained a response for at least 12 months, and 48% for at least 24 months.

Exclusivity and Patents

The patents listed in the Orange Book are summarized in Table 28(Appendix A).

Grafapex

Treosulfan for injection, for intravenous use

Fast Facts	
NDA Holder	Medexus (medac GmbH)
Product Presentation	Powder for reconstitution
Route of Administration	Intravenous
NDA Original Approval	January 21, 2025
NCE Exclusivity	January 21, 2030
ODE	Yes, exclusivity date TBD
Mechanism of action	An alkylating cytotoxic agent

ODE typically lasts for 7 years from approval

Indication

Acute Myeloid Leukemia (AML):

Grafapex is approved for use in combination with fludarabine as part of a preparative regimen prior to allogeneic hematopoietic stem cell transplantation in adult and pediatric patients (aged 1 year and older) diagnosed with acute myeloid leukemia (AML).

Myelodysplastic Syndrome (MDS):

Grafapex is similarly approved for use in combination with fludarabine as part of a preparative regimen prior to allogeneic hematopoietic stem cell transplantation in adult and pediatric patients (aged 1 year and older) diagnosed with myelodysplastic syndrome (MDS).

Boxed Warning

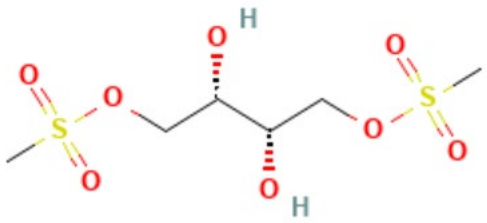
Grafapex may cause severe and prolonged suppression of bone marrow activity at the recommended dose. To prevent life-threatening complications arising from this extended myelosuppression, hematopoietic stem cell transplantation is required. Blood counts and other hematologic parameters should be carefully monitored.

Dosage Form and Handling

Grafapex is a sterile, lyophilized powder for injection supplied in single-dose vials of 1 gram or 5 grams. The 1-gram vial should be reconstituted with 20 mL, and the 5-gram vial with 100 mL of 0.45% Sodium Chloride Injection, 0.9% Sodium Chloride Injection, 5% Dextrose Injection, or Sterile Water for Injection. Reconstitution with Sterile Water for Injection alone is not recommended for children aged 12 years or younger due to the risk of hypo-osmolarity. Store the product between 20°C and 25°C, allowing temperature excursions between 15°C and 30°C.

Description

Grafapex for injection contains treosulfan, a bifunctional alkylating agent with a molecular weight of 278.3 g/mol. The chemical structure of treosulfan is as follows:



Dosing Regimen

The recommended dose of Grafapex is 10 g/m² per day, administered intravenously for three consecutive days starting on Day –4 before allogeneic hematopoietic stem cell

transplantation. It is combined with fludarabine, given at 30 mg/m² per day from Day –6 through Day –2. The transplantation occurs on Day 0. Antiemetic premedication should be administered before the first Grafapex dose and maintained on a fixed schedule throughout treosulfan treatment to control potential nausea and vomiting.

Mechanism of Action

Treosulfan is classified as an alkylating agent, with its cytotoxic effects primarily attributed to DNA alkylation. In mouse models of leukemia, treosulfan effectively depleted hematopoietic stem cells and demonstrated both immunosuppressive and antitumor activities.

Pharmacokinetics

Treosulfan is a prodrug that exhibits consistent pharmacokinetics at the approved dosage, with no evidence of accumulation in the body. After administration, it distributes widely with an average volume of distribution of approximately 41 liters and does not bind to plasma proteins.

Once in the body, treosulfan spontaneously converts into an active epoxide intermediate and is further metabolized into a diepoxybutane compound. These active metabolites are believed to drive the drug's cytotoxic effects. The elimination half-life of treosulfan is approximately 1.7 hours.

The pharmacokinetics of treosulfan are not significantly affected by sex, mild renal or hepatic impairment, or age under 65. However, the impact of moderate to severe organ impairment or use in elderly patients (≥65 years) remains unestablished. In pediatric patients, drug exposure is modestly higher than in adults—about 11% higher in those with

a body surface area (BSA) under 0.7 m² and 5% higher in those with a BSA between 0.7 and less than 1.1 m². Nonetheless, the terminal half-life remains similar across age groups. Treosulfan is metabolized primarily by CYP2D6, while its monoepoxide derivative is mainly metabolized via CYP2C8. It has been shown to inhibit CYP2C19 and CYP3A4 activity when midazolam is used as a probe substrate. However, it does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2D6, or CYP3A4 activities when testosterone serves as the reference substrate.

Treosulfan does not interfere with the function of several key transporters, including BCRP, BSEP, MATE1, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, and OCT2.

Clinical Studies

Grafapex (treosulfan) was evaluated in a randomized, active-controlled Phase 3 trial (MC-FludT.14/L) comparing it to busulfan, both combined with fludarabine, as conditioning regimens for allogeneic stem cell transplantation in adults aged 18 to 70 years with AML or MDS. Eligible patients had a Karnofsky performance status ≥60% and were either 50 years or older or had an HCT-CI score greater than 2. Key exclusions included significant organ dysfunction.

Patients received Grafapex at 10 g/m² on Days -4 to -2 or busulfan at 0.8 mg/kg every 6 hours on Days -4 and -3, alongside fludarabine 30 mg/m² on Days -6 to -2. Transplantation took place on Day 0. Antithymocyte globulin, cyclosporine, and methotrexate were administered for GVHD prophylaxis.

Among 570 patients (280 receiving Grafapex; 290 receiving busulfan), 365 had AML and 205 had MDS. The majority received peripheral blood stem cells. Grafapex demonstrated improved overall survival with a hazard ratio of 0.67 (95% CI: 0.51 to 0.90) compared to

busulfan. Subgroup analyses showed hazard ratios of 0.64 (95% CI: 0.51 to 0.90) for AML and 0.84 (95% CI: 0.51 to 1.06) for MDS. Kaplan–Meier analysis further supported better survival outcomes with Grafapex.

Exclusivity and Patents

Two exclusivities are listed in the Orange Book: one New Chemical Entity (NCE) exclusivity expiring on January 21, 2030, and an Orphan Drug Exclusivity (ODE) with the end date yet to be determined. The patents listed in the Orange Book are summarized in Table 29 (Appendix A).

Journavx

Suzetrigine tablets, for oral use

Fast Facts	
NDA Holder	Vertex Pharmaceuticals Inc.
Product Presentation	Tablet
Route of Administration	Oral
NDA Original Approval	January 30, 2025
NCE Exclusivity	January 30, 2030
ODE	None
Mechanism of action	A selective blocker of the NaV1.8 voltage-gated sodium channel

Indication

Journavx is prescribed for the management of short-term moderate to severe pain in adult patients.

Dosage Form and Handling

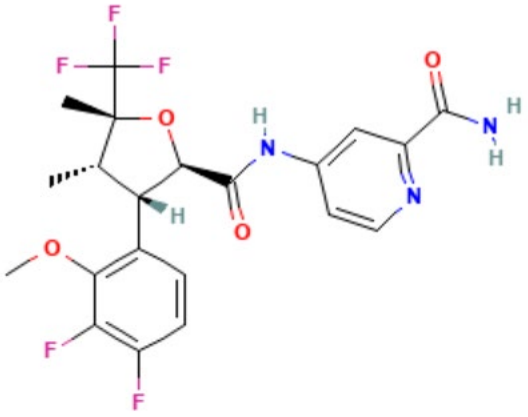
Journavx is formulated as a 50 mg oral tablet, packaged in plastic bottles. Each tablet contains the active ingredient suzetrigine, along with the inactive ingredients croscarmellose sodium, hypromellose acetate succinate, magnesium stearate, and microcrystalline cellulose. The film coating comprises FD&C Blue #2 aluminum lake, polyethylene glycol, partially hydrolyzed polyvinyl alcohol, talc, and titanium dioxide. The

tablets should be stored at room temperature between 20°C and 25°C, with allowable temperature excursions between 15°C and 30°C.

Description

The active ingredient in Journavx tablets is suzetrigine, which has a molecular weight of 473.39 g/mol. Its chemical structure is as follows:

The active ingredient in Journavx tablets is suzetrigine, which has a molecular weight of 473.39 g/mol. Its chemical structure is as follows:



Dosing Regimen

The initial recommended dose of Journavx is 100 mg taken by mouth. It should be taken on an empty stomach, either at least one hour before eating or two hours after, to prevent delayed absorption. Clear liquids such as water, apple juice, vegetable broth, tea, or black coffee may be consumed during this period. Beginning 12 hours after the first dose, continue with 50 mg of Journavx every 12 hours, which can be taken with or without food. The use of Journavx to treat moderate to severe acute pain has not been evaluated for durations longer than 14 days.

Mechanism of Action

Suzetrigine selectively blocks the NaV1.8 voltage-gated sodium channel, a critical mediator in the transmission of pain signals. This channel is predominantly found in peripheral sensory neurons, including those in the dorsal root ganglia. By inhibiting NaV1.8, suzetrigine diminishes the transmission of pain signals to the spinal cord and brain. Its primary active metabolite, M6-SUZ, also blocks NaV1.8, although it is roughly 3.7 times less potent than suzetrigine.

Pharmacokinetics

Suzetrigine, the active ingredient in Journavx, and its primary active metabolite, M6-SUZ, exhibit dose-dependent pharmacokinetics. Suzetrigine typically reaches 90% of steady-state levels within 3 days, while M6-SUZ attains steady state in 5 days. Their respective accumulation ratios are 3.4 and 4.5. The median time to peak concentration (Tmax) is approximately 3 hours for suzetrigine and 10 hours for M6-SUZ. Suzetrigine has a large volume of distribution (~495 L), is highly protein-bound (99%), and has an effective half-life of approximately 23.6 hours. M6-SUZ is also highly protein-bound (96%) and has a longer half-life of about 33 hours.

Suzetrigine is primarily metabolized via the CYP3A pathway and is eliminated through both feces (approximately 50%) and urine (around 44%), mostly as metabolites. Food intake delays absorption; high- and moderate-fat meals prolong the time to reach peak concentration, although overall exposure (AUC) and peak levels (Cmax) are not significantly affected. Therefore, the first dose should be taken on an empty stomach, but subsequent doses may be taken with or without food.

The pharmacokinetics of suzetrigine are consistent across adults regardless of age, sex, weight, or race. Mild hepatic or moderate renal impairment does not significantly affect

exposure, whereas moderate hepatic impairment increases suzetrigine and M6-SUZ levels. The effects of severe hepatic or advanced renal impairment (eGFR < 15 mL/min) have not been established.

Coadministration of Journavx with CYP3A inhibitors or inducers alters the pharmacokinetics of suzetrigine and M6-SUZ. With itraconazole (a strong CYP3A inhibitor), the geometric mean AUCinf of suzetrigine and M6-SUZ increased by 4.8-fold and 4.4-fold, respectively, while suzetrigine Cmax increased by 1.5-fold and M6-SUZ Cmax decreased by 32%.

Fluconazole (a moderate CYP3A inhibitor) increased AUCinf of suzetrigine and M6-SUZ by 1.5-fold and 1.2-fold, respectively, and Cmax by 1.4-fold and 1.1-fold. Rifampin (a strong CYP3A inducer) decreased AUCinf of suzetrigine and M6-SUZ by 93% and 85%, respectively; suzetrigine Cmax decreased by 80%, while M6-SUZ Cmax increased by 1.3-fold. Efavirenz (a moderate CYP3A inducer) decreased AUCinf of suzetrigine and M6-SUZ by 63% and 60%, respectively; suzetrigine Cmax decreased by 29%, and M6-SUZ Cmax increased by 1.3-fold.

Journavx administered at 50 mg every 12 hours decreased the geometric mean AUCinf and Cmax of midazolam (a sensitive CYP3A substrate) by 48% and 37%, respectively.

No clinically significant differences in suzetrigine or M6-SUZ pharmacokinetics were observed when Journavx was coadministered with omeprazole. Similarly, no clinically meaningful pharmacokinetic changes were noted when Journavx was used with digoxin (a P-gp substrate), ethinyl estradiol (a hormonal contraceptive), or levonorgestrel.

In vitro studies indicate that suzetrigine inhibits CYP2C8, CYP2C9, and CYP2C19, and induces CYP3A and, to a lesser extent, CYP2B6, CYP2C8, CYP2C9, and CYP2C19;

however, it is not expected to cause clinically significant drug interactions. It does not inhibit or induce CYP1A2, and neither suzetrigine nor M6-SUZ inhibits CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2D6, or CYP3A. Suzetrigine does not inhibit UGT1A1. In vitro data also show that suzetrigine and M6-SUZ are not substrates of BCRP, OATP1B1, or OATP1B3. Suzetrigine is not a P-gp substrate, while M6-SUZ is. Both inhibit OATP1B1, OATP1B3, and OAT3, but are unlikely to cause clinically significant interactions. Suzetrigine does not inhibit BCRP, OAT1, OCT2, MATE1, or MATE2-K. M6-SUZ also does not inhibit P-gp, BCRP, OCT2, MATE1, or MATE2-K.

Clinical Studies

The efficacy of Journavx for moderate to severe acute pain in adults was demonstrated in two randomized, double-blind, placebo- and active-controlled trials: one following full abdominoplasty (Trial 1, NCT05558410) and the other after bunionectomy (Trial 2, NCT05553366). Pain intensity was measured using an 11-point numeric pain rating scale (NPRS). Eligible patients reported moderate to severe pain (NPRS ≥4) within 4 hours post-abdominoplasty or during the 9-hour period after nerve block resolution in the bunionectomy study.

Participants were randomized to receive Journavx (100 mg loading dose, then 50 mg every 12 hours), placebo, or hydrocodone bitartrate/acetaminophen (HB/APAP; 5 mg/325 mg every 6 hours) for 48 hours. Rescue ibuprofen (400 mg every 6 hours) was allowed.

Trial 1: Among 1,118 adults randomized (Journavx n=447; placebo n=223; HB/APAP n=448), Journavx showed a significantly higher time-weighted sum of pain intensity difference over 48 hours (SPID48; LS mean 118.4) compared to placebo (70.1), with a mean difference of 48.4 (95% CI: 33.6, 63.1; $p < 0.0001$). Median time to meaningful pain

relief (≥2-point NPRS reduction) was 119 minutes with Journavx vs. 480 minutes with placebo; perceptible relief (≥1-point reduction) occurred at 34 minutes.

Trial 2: Among 1,073 adults randomized (Journavx n=426; placebo n=216; HB/APAP n=431), mostly female (85%) with a mean age of 48 years and baseline pain score of 6.8, Journavx demonstrated greater SPID48 (LS mean 99.9) than placebo (70.6), with a mean difference of 29.3 (95% CI: 14.0, 44.6; p = 0.0002). Median time to meaningful pain relief was 240 minutes with Journavx vs. 480 minutes with placebo; perceptible relief occurred at 60 minutes. Completion rates were 87% (Journavx), 82% (placebo), and 90% (HB/APAP), with discontinuations due to lack of efficacy at 12%, 16%, and 8%, respectively.

Exclusivity and Patents

Two exclusivities are listed in the Orange Book: one New Chemical Entity (NCE) expiring on January 21, 2030, and one Orphan Drug Exclusivity (ODE) with the exclusivity period to be determined (TBD). The patents listed in the Orange Book are summarized in Table 30 (Appendix A).

Qfitlia

Fitusiran injection, for subcutaneous use

Fast Facts	
NDA Holder	Genzyme Corporation
Product Presentation	Solution
Route of Administration	Subcutaneous
NDA Original Approval	March 28, 2025
NCE Exclusivity	Not listed yet*
ODE	Yes, exclusivity end date TBD*
Mechanism of action	A small interfering RNA (siRNA) that lowers plasma antithrombin (AT) levels by targeting and degrading AT messenger RNA (mRNA)

*NCE exclusivity typically granted for 5 years from approval. ODE typically granted for 7 years from approval

Indication

Qfitlia is indicated for the prophylactic treatment to reduce the frequency of bleeding episodes in patients aged 12 years and older with hemophilia A or B, regardless of the presence of inhibitors to factor VIII or IX.

Boxed Warning

Thrombotic Events: Serious blood clots have occurred in patients with risk factors such as low antithrombin (AT) activity (<15%), monthly 80 mg dosing, use of central lines, or

post-surgery when bleeding management protocols were not followed. Discontinue Qfitlia immediately if thrombosis develops.

Gallbladder Disease: Gallbladder complications, including those requiring surgery or causing secondary issues such as pancreatitis, have been reported. Monitor patients closely for symptoms, and consider discontinuing Qfitlia if gallbladder problems arise. Alternative therapies should be used in patients with a history of gallbladder disease.

Dosage Form and Handling

Qfitlia is provided as a solution for subcutaneous injection in two dosage forms: a 50 mg/0.5 mL single-dose prefilled pen and a 20 mg/0.2 mL single-dose vial, both at a concentration of 100 mg/mL. In addition to the active ingredient, fitusiran, each unit contains dibasic sodium phosphate, monobasic sodium phosphate, sodium chloride, and Water for Injection, USP. Phosphoric acid and sodium hydroxide are used to adjust the pH to 7.0.

Store the drug product in its original carton to protect it from light. The prefilled pen must be refrigerated at 2°C to 8°C, but it may be stored at room temperature (15°C to 30°C) for a single period of up to three months; once stored at room temperature, it should not be returned to refrigeration. The vial may be stored refrigerated or at room temperature, but once removed from refrigeration, it must not be returned.

Do not shake, freeze, heat, or expose Qfitlia to direct sunlight.

Description

Qfitlia contains fitusiran, a double-stranded small interfering RNA (siRNA) that targets antithrombin and is chemically conjugated to a triantennary N-acetylgalactosamine

(GalNAc) ligand to enhance liver-specific delivery. The molecular weight of fitusiran is 17,193 daltons.

Dosing Regimen

The recommended starting dose of Qfitlia is 50 mg, administered subcutaneously once every two months. Before initiating treatment, antithrombin (AT) activity should be assessed using an FDA-cleared test; treatment should not begin if AT levels are below 60%.

During therapy, the target AT activity range is 15% to 35%, balancing efficacy and safety. Dose adjustments are based on AT activity levels: if AT drops below 15%, a dose reduction is required. Conversely, if AT exceeds 35% after six months or if bleeding is inadequately controlled, a dose increase may be considered.

If AT activity remains persistently below 15%, the lowest available dose (10 mg every two months) should be discontinued. Once the patient is stabilized on a dose, AT levels should be monitored annually, with more frequent monitoring if bleeding persists.

Mechanism of Action

Qfitlia is a double-stranded small interfering RNA (siRNA) that reduces plasma antithrombin (AT) levels by targeting and degrading AT messenger RNA (mRNA) via the RNA interference (RNAi) pathway.

Pharmacokinetics

Following subcutaneous administration, Qfitlia is absorbed with a median time to maximum plasma concentration (Tmax) of approximately 2.9 to 3.8 hours. Plasma exposure, measured by Cmax and AUC, increases in a dose-proportional manner. The terminal elimination half-life (t½) ranges from approximately 5.6 to 8 hours, with no drug

accumulation observed after repeat dosing. Qfitlia demonstrates a high apparent volume of distribution and exhibits extensive plasma protein binding (~96.6%) at clinically relevant concentrations.

Fitusiran primarily distributes to the liver and is metabolized by endonuclease and exonuclease activity, generating progressively shorter oligonucleotide metabolites. It is not a substrate for cytochrome P450 (CYP) enzymes or drug transporters.

Population pharmacokinetic analyses indicate that race and mild to moderate renal impairment do not significantly impact drug exposure. However, Qfitlia has not been studied in patients with hepatic impairment or in pediatric populations under 12 years of age.

No clinical studies have evaluated potential interactions between Qfitlia and other drugs that are substrates, inhibitors, or inducers of CYP enzymes or drug transporters. Therefore, its interaction profile with commonly co-administered medications remains uncharacterized in clinical settings.

In vitro studies evaluating the potential for drug–drug interactions indicate that co-administered medications are unlikely to affect Qfitlia exposure, and Qfitlia is unlikely to alter the exposure of other drugs through CYP enzyme- or transporter-mediated pathways at clinically relevant concentrations.

In four clinical trials involving adults with hemophilia treated with Qfitlia for up to 250 weeks, anti-drug antibodies (ADAs) were detected in 10 of 290 patients (3.4%). These antibodies were generally low in titer and transient. No clinically meaningful effects of ADAs were observed on Qfitlia’s pharmacokinetics, pharmacodynamics, safety, or efficacy.

Clinical Studies

The clinical efficacy and safety of Qfitlia were evaluated in three key studies involving adolescents and adults (aged 12 years and older) with hemophilia A or B, with or without inhibitors. The pivotal trials, ATLAS-INH and ATLAS-A/B, initially assessed a fixed monthly dose of 80 mg Qfitlia. However, due to safety concerns—including thrombotic and hepatotoxic events—this dose was discontinued. An individualized antithrombin-based dosing regimen (AT-DR), targeting antithrombin (AT) activity between 15% and 35%, was subsequently adopted and evaluated in the ATLAS-OLE extension study.

In ATLAS-INH, 57 patients with inhibitors were randomized to receive either Qfitlia 80 mg monthly or on-demand bypassing agents (BPAs). Similarly, ATLAS-A/B enrolled 120 patients without inhibitors and randomized them to Qfitlia 80 mg monthly or on-demand clotting factor concentrates (CFCs). Participants from both studies—as well as from the crossover study ATLAS-PPX—transitioned into the ATLAS-OLE extension, where they began the AT-DR regimen. Final dose adjustments in ATLAS-OLE aimed to maintain AT activity within the target range, resulting in most patients receiving 50 mg or 20 mg every one to two months.

Efficacy data from the ATLAS-OLE study showed substantial reductions in annualized bleeding rates (ABR) compared to historical on-demand treatment. In patients with inhibitors, Qfitlia reduced treated bleeds by 73% compared to bypassing agents (BPAs), with ABRs of 5.1 versus 19.1, respectively. In patients without inhibitors, Qfitlia reduced bleeds by 71% compared to clotting factor concentrates (CFCs), with ABRs of 9.0 versus 31.4.

Comparable reductions were observed in spontaneous and joint bleeds, with improvements ranging from 71% to 82%. The median ABR for patients receiving the antithrombin-based dosing regimen (AT-DR) was 3.7 overall—1.9 in patients with inhibitors and 3.8 in those without.

Exclusivity and Patents

Exclusivities or patents are not listed in the Orange Book at present.

Romvimza™

Vimseltinib capsules, for oral use

Fast Facts	
NDA Holder	Deciphera Pharmaceuticals Inc.
Product Presentation	Capsule
Route of Administration	Oral
NDA Original Approval	February 14, 2025
NCE Exclusivity	February 14, 2030
ODE	None
Mechanism of action	A CSF1R kinase inhibitor. Inhibits CSF1R autophosphorylation and downstream signaling suppressing cell proliferation

Indication

Romvimza™ is approved to treat adults with tenosynovial giant cell tumor (TGCT) when symptoms are present and surgery could lead to serious complications or loss of function.

Dosage Form and Handling

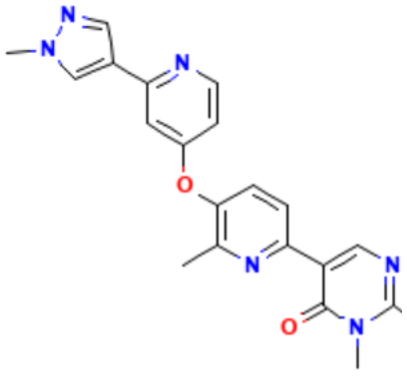
Romvimza™ is supplied as hard gelatin capsules available in three strengths: 14 mg, 20 mg, and 30 mg. Each strength is packaged in child-resistant blister packs containing 8 capsules, which provide a four-week supply when dosed twice weekly.

The capsule fill contains inactive ingredients including crospovidone, lactose monohydrate, and magnesium stearate. The capsule shells are composed of gelatin and titanium dioxide, with strength-specific colorants: Sunset Yellow FCF in the 14 mg and 20 mg capsules, tartrazine in the 20 mg capsules, and Brilliant Blue FCF with erythrosine in the 30 mg capsules. The imprint ink formulation includes black iron oxide, shellac, propylene glycol, potassium hydroxide, and strong ammonia solution.

Capsules should be stored at controlled room temperature between 20°C and 25°C, with permissible excursions from 15°C to 30°C, and must remain in their original blister packaging until use.

Description

The active ingredient, vimseltinib dihydrate, is a crystalline weak base with a molecular with of 467.52 g/mol. The chemical structure is:



$.2H_2O$

Dosing Regimen

The recommended dose of Romvimza™ is 30 mg administered orally twice weekly, with a minimum interval of 72 hours between doses, according to the healthcare professional's prescribed schedule. Romvimza™ may be taken with or without food. Capsules must be swallowed whole and should not be opened, broken, or chewed. If vomiting occurs within

30 minutes of dosing, the dose should be repeated; otherwise, patients should proceed with the next scheduled dose.

Mechanism of Action

Vimseltinib, the active ingredient in Romvimza™, acts as a kinase inhibitor that selectively targets the colony-stimulating factor 1 receptor (CSF1R). The proliferation of CSF1R-expressing cells is suppressed by vimseltinib through inhibition of CSF1R autophosphorylation and downstream signaling, which is normally induced by CSF1 ligand binding.

Pharmacokinetics

Pharmacokinetic profiles of vimseltinib were evaluated following a single 30 mg oral dose and repeated dosing at 30 mg twice weekly. Vimseltinib exhibits dose-proportional pharmacokinetics, with a median time to peak concentration (Tmax) of approximately 1 hour (range: 0.5 to 4 hours). Administration with a high-fat meal does not significantly impact its pharmacokinetic parameters.

The drug demonstrates a moderate volume of distribution (~90 L) and is highly bound to plasma proteins (~96.5%). It has a prolonged elimination half-life of about 6 days and a clearance rate of 0.5 L/h. Vimseltinib is primarily metabolized via oxidative pathways including N-demethylation and N-dealkylation, with minimal cytochrome P450 involvement.

Population pharmacokinetic analyses revealed no clinically meaningful effects of age, sex, race, body weight, tumor type (TGCT or other solid tumors), or mild to moderate renal impairment on vimseltinib exposure. The impact of severe renal impairment or moderate to severe hepatic impairment remains unstudied.

In terms of drug interactions, coadministration with P-glycoprotein (P-gp) substrates such as dabigatran may increase their systemic exposure, particularly when taken concurrently. To mitigate this effect, vimseltinib should be administered at least 4 hours prior to these substrates.

Co-administration with other agents, including itraconazole (a P-gp inhibitor) or rabeprazole (a proton pump inhibitor), does not significantly alter vimseltinib exposure. In vitro studies indicate that vimseltinib is neither a substrate, inhibitor, nor inducer of most major cytochrome P450 (CYP) enzymes but does interact with several drug transporters. Specifically, it inhibits P-gp, BCRP, OATP1B1/1B3, OCT2, MATE1, and MATE2-K, which may affect serum creatinine levels by altering renal transporter activity—without representing true renal impairment.

Clinical Studies

The efficacy of Romvimza™ was demonstrated in a Phase 3, randomized, double-blind, placebo-controlled trial (MOTION; NCT05059262) involving 123 adult patients with symptomatic tenosynovial giant cell tumor (TGCT) in whom surgery was expected to result in functional impairment or severe morbidity.

Patients were randomized in a 2:1 ratio to receive Romvimza™ 30 mg orally twice weekly (n = 83) or placebo (n = 40) for 24 weeks. Randomization was stratified by tumor location (lower limb vs. other) and geographic region (U.S. vs. non-U.S.).

At Week 25, the overall response rate (ORR) per RECIST v1.1—assessed by blinded independent radiologic review—was 40% (95% CI: 29%, 51%) in the Romvimza™ group versus 0% (95% CI: 0%, 9%) in the placebo group ($p < 0.0001$).

Among Romvimza™-treated patients, 5% achieved a complete response and 35% a partial response. The median duration of response was not reached; however, 85% of responders maintained their response for ≥6 months, and 58% for ≥9 months.

Key secondary outcomes also favored Romvimza™.

At Week 25, the least squares mean improvement in active range of motion from baseline was 14.6 (95% CI: 4.0, 25.3; p = 0.0077).

The mean change in PROMIS-PF (15-item physical function score) was 4.6 points in the Romvimza™ group versus 1.3 points in the placebo group, yielding a least squares mean difference of 3.3 (95% CI: 1.4, 5.2; p = 0.0007).

A BPI-30 pain response—defined as a ≥30% improvement in worst pain score without increased narcotic use—was achieved in 48.2% of Romvimza™ patients compared to 22.5% of placebo patients (difference: 26.2%; 95% CI: 9.5, 42.8; p = 0.0056).

Tumor response based on tumor volume score (TVS) was observed in 67% (95% CI: 56%, 77%) of Romvimza™ patients versus 0% in the placebo group (p < 0.0001).

Individual patient-level analyses also showed greater improvements in active range of motion in the Romvimza™ group compared with placebo at Week 25.

Exclusivity and Patents

One New Chemical Entity (NCE) exclusivity is listed in the Orange Book, expiring on February 14, 2030.

Orange Book-listed patents are summarized in Table 31 (Appendix A).

APPENDIX – A: Orange Book Patents

Appendix A offers a concise summary of the Orange Book-listed patents associated with the compounds covered in the monographs. Each table includes the applicable patent numbers, the type of patent (drug substance, drug product, or method of use), and a summary of the key claims. The data reflect the most recent version of the Orange Book available at the time of this book's latest update and may be revised in the future.

Although broader patent portfolios may extend beyond those listed in the Orange Book, this summary provides a foundational overview of key areas of patent protection. It serves as a practical starting point for more detailed research, where appropriate. This overview complements the other datasets included in each monograph and supports the overarching goal of the Drug Monograph Digest—to serve as a comprehensive, self-contained reference.

By consolidating essential patent data into a single, accessible format, this overview minimizes the need to consult multiple external sources—such as the Orange Book, USPTO databases, or complex patent filings—to gain an initial understanding of the patent landscape.

This summary is intended for informational purposes only and does not replace the need for thorough patent due diligence.

Table 1: Orange Book patents for Attruby

US Patent/Exp. Date Patent Type	Key Disclosures
8877795/ May 5, 2031 Drug Product	The claims describe pharmaceutical compositions comprising compounds that stabilize transthyretin (TTR) tetramers and reduce aggregation. These compositions include specific molecular structures with defined linkers and functional groups and may optionally contain pharmaceutically acceptable excipients or adjuvants, while explicitly excluding certain solvents.
9169214/ May 5, 2031 Drug Product U-4046*	The claims in this patent are similar in scope to those in the previous one but involve distinct compounds, structural variations, and applications.
9642838/ May 5, 2031 Drug Substance Drug Product	The claims describe a specific compound, Formula VIIc, and its pharmaceutically acceptable salts. They also encompass pharmaceutical compositions containing the compound or its salts in combination with pharmaceutically acceptable excipients.
9913826/ May 5, 2031 U-4046	The claims describe methods for treating transthyretin (TTR) amyloid diseases by administering a therapeutically effective amount of specific compounds or their pharmaceutically acceptable salts. They further detail the pharmaceutical use of

US Patent/Exp. Date Patent Type	Key Disclosures
	these compounds in the treatment of various amyloid-related and neurodegenerative diseases.
10398681/ May 5, 2031 Drug Product	The claims describe a kit comprising a unit dose of specific compounds, or their pharmaceutically acceptable salts, intended to stabilize proteins prone to misfolding and aggregation. The claims further outline variations of the included compounds and specify the inclusion of a package insert detailing their intended use.
10513497/ February 16, 2038 Drug Substance	The claims describe Crystalline Form Type A of acoramidis (AG-10) as its hydrochloride (HCl) salt, characterized by specific X-ray powder diffraction (XRPD) patterns, thermal analysis, and other analytical methods. This crystalline form is further defined as being substantially free of other crystalline or amorphous forms and demonstrating distinct stability and physicochemical properties under controlled conditions.
10842777/ May 5, 2031 U-4046	The claims describe methods for stabilizing transthyretin (TTR) and reducing amyloid fibril formation in tissues or biological fluids through the administration of specific compounds or their pharmaceutically acceptable salts. Additionally, the claims encompass methods for detecting and quantifying TTR levels in

US Patent/Exp. Date Patent Type	Key Disclosures
	biological samples using labeled derivatives of these compounds.
11058668/ March 22, 2039 U-4046	The claims describe methods for treating transthyretin (TTR) amyloidosis through the oral administration of a defined dose of acoramidis (AG-10) hydrochloride, administered twice daily. They further outline its therapeutic applications across various forms of ATTR.
11260047/ February 16, 2038 Drug Product	The patent describes high-load tablet formulations of acoramidis (AG-10) or its pharmaceutically acceptable salt, comprising at least 40% AG-10 by weight. The formulations include various pharmaceutical excipients, and the claims also encompass the tablet's rapid dissolution properties.
11919865/ August 16, 2039 U-4046	The patent describes a method for treating transthyretin (TTR) amyloid diseases using Crystalline Form Type A of Acoramidis hydrochloride. This form is characterized by defined X-ray powder diffraction (XRPD) patterns, thermal analysis, and other analytical techniques. It is further disclosed that the crystalline form is substantially free of other polymorphic or amorphous forms.

US Patent/Exp. Date Patent Type	Key Disclosures
12005043/ August 16, 2039 Drug Product U-4046	This patent is similar in scope to U.S. Patent No. 11,260,047, but differs in specific formulation parameters, including filler composition, excipient ranges, and additional specifications.
12070449/ March 22, 2039 U-4046	The patent describes a method for treating or slowing ATTR cardiomyopathy by administering 1,600 mg of acoramidis hydrochloride (or another pharmaceutically acceptable form) orally twice daily. The claims also cover various treatment outcomes.

*U-4046 - Treatment of the cardiomyopathy of wild-type or variant transthyretin-mediated amyloidosis (ATTR-CM).

Table 2: Orange Book patents for Cobenfy

US Patent/Exp. Date Patent Type	Key Disclosures
10238643/ July 21, 2030 Drug Product	The claims describe an oral medicament containing xanomeline and trospium chloride, formulated as immediate-release, controlled-release, or a combination thereof. Some claims specify single-capsule formulations with defined xanomeline and trospium chloride ratios.
10265311/ July 21, 2030 U-3513*	The claims describe a method for treating central nervous system disorders—including schizophrenia, Alzheimer's disease, Huntington's disease, Parkinson's disease, and Lewy body dementia—by orally administering xanomeline and trospium chloride. The claims specify dosage ranges, administration frequencies, and formulation variations, including single or separate dosage forms..
10369143/ July 21, 2030 U-3513	The claims describe a method for treating central nervous system disorders by orally administering an initial dose of xanomeline and trospium chloride, followed by a dose escalation after tolerance is established (dose titration). The claims specify dosage ranges, administration frequencies, and formulation variations, including single or separate dosage forms. Some claims also detail an intermediate dosing phase

US Patent/Exp. Date Patent Type	Key Disclosures
	between the initial and increased doses. xanomeline may be provided as its tartaric acid salt.
10369144/ July 21, 2030 Drug Product U-3513	The claims describe a single-capsule oral formulation containing xanomeline (or its salt) and trospium chloride, where xanomeline is present at doses that may cause certain side effects, and trospium chloride is included to mitigate these effects. The formulation is claimed in immediate-release, controlled-release, or combination-release forms. The claims specify dosage ranges, twice-daily administration for treating schizophrenia, and use in other central nervous system disorders.
10695339/ July 21, 2030 U-3513	The claims describe a method for treating central nervous system disorders through oral administration of xanomeline salt and trospium chloride within a 24-hour period. The claims specify dosage ranges, administration frequencies, and formulation variations—including single or separate dosage forms—are specified. Certain claims also describe xanomeline salt in its tartaric acid salt form.
10925832/ September 27, 2039	The claims describe an oral pharmaceutical composition comprising xanomeline beads and trospium beads,

US Patent/Exp. Date Patent Type	Key Disclosures
Drug Product	characterized by defined bead sizes, weight proportions, and dissolution rates. The formulation is presented in capsule form, with specified dosage strengths of xanomeline free base and trospium chloride. Certain claims also specify rapid dissolution rates and impurity limits for the xanomeline beads.
10933020/ September 27, 2039 Drug Product	The claims describe an oral pharmaceutical composition comprising xanomeline beads and trospium beads, characterized by defined bead sizes, weight proportions, and dissolution rates. The formulation is presented in capsule form, with specified dosage strengths of xanomeline free base and trospium chloride. Additional claims cover pharmacokinetic properties, treatment of muscarinic receptor-related disorders, impurity limits, and methods for preparing the composition.
11452692/ September 27, 2039 U-3513	The claims describe a method for treating muscarinic receptor-related disorders—including schizophrenia, neurodegenerative diseases, movement disorders, depression, pain, drug addiction, tauopathy, and synucleinopathy—by orally administering xanomeline (or its salt) and trospium salt twice daily in a capsule formulation containing xanomeline and trospium beads. The claims specify dosing regimens, treatment duration, bead

US Patent/Exp. Date Patent Type	Key Disclosures
	sizes, and the use of xanomeline tartrate and trospium chloride as the active ingredients.
11471413/ September 27, 2039 U-3513	The claims describe a method of administering a dosage form containing xanomeline and trospium salt, with both compounds released at comparable rates to achieve a defined in vivo plasma profile—featuring a median Tmax of 2 hours for xanomeline and 1 hour for trospium. The claims specify pharmacokinetic parameters, oral administration, twice-daily dosing for a minimum of 7 days, and the use of xanomeline tartrate and trospium chloride. Some claims additionally specify rapid dissolution properties.
11890378/ September 27, 2039Drug Product	The claims describe an oral pharmaceutical composition comprising xanomeline and trospium chloride beads, with defined dosage strengths, dissolution characteristics, and impurity thresholds. They specify an in vivo plasma profile, the inclusion of antioxidants, and the use of xanomeline tartrate. The claims also encompass a method for treating schizophrenia, including dose escalation across multiple treatment periods, while excluding patients at high risk for urinary retention, gastric retention, or narrow-angle glaucoma.

*U-3513 – Treatment of schizophrenia in adults

Table 3: Orange Book patents for Crenessity

US Patent/Exp. Date Patent Type	Key Disclosures
10905690/January 21, 2035 U-4049*	The patent describes a method for treating Congenital Adrenal Hyperplasia (CAH) using a CRF1 receptor antagonist—specifically SSR-125543 or a pharmaceutically acceptable salt thereof. The claims outline various dosing strategies, including bedtime administration and timing aligned with the circadian rhythm of ACTH release.
11311544/January 21, 2035 U-4049	The patent describes a method for treating congenital adrenal hyperplasia (CAH) in glucocorticoid-treated patients using a CRF1 receptor antagonist—specifically SSR-125543 or a pharmaceutically acceptable salt thereof—allowing for glucocorticoid dose reductions of 10–50%. The method includes the use of specific glucocorticoids (hydrocortisone, prednisone, prednisolone, or dexamethasone), with optional co-administration of fludrocortisone, and applies to patients with classical CAH caused by CYP21A2 mutations. The CRF1 antagonist is administered at bedtime and formulated in various dosage forms suitable for both adults and children.
11730739/January 21, 2035 U-4049	This patent builds upon the previous one by incorporating biomarker-based treatment monitoring, identifying 17-hydroxyprogesterone (17-OHP), ACTH, and androstenedione

US Patent/Exp. Date Patent Type	Key Disclosures
	levels as key indicators of therapeutic response. It also includes monitoring for adverse events such as iatrogenic Cushing's syndrome, Addisonian syndrome, hypertension, and signs of adrenal insufficiency. Additionally, the patent refines the patient population by introducing genetic criteria—specifically excluding individuals with CYP11B1 mutations—and outlines a more detailed dosing regimen, including administration at bedtime, at or before the circadian release of ACTH, or 3–4 hours prior to that release.

*U-4049 – Adjustive treatment of classical congenital adrenal hyperplasia

Table 4: Orange Book patents for Duvyzat

US Patent/Exp. Date Patent Type	Key Disclosures
7329689/January 15, 2026 Drug Substance Drug Product	The claims cover the crystalline monohydrate hydrochloride salt of the (6-diethylaminomethyl-naphthalen-2-yl) methyl ester of (4-hydroxycarbamoylphenyl) carbamic acid, as well as its pharmaceutical compositions.
9421184/February 3, 2032 U-3885	This invention relates to a method for treating muscular dystrophy, particularly Duchenne muscular dystrophy (DMD), using a compound with a defined structural formula, or its pharmaceutically acceptable salts or solvates. The claims specify dose ranges and dosing regimens. The compound may be formulated as a solid or liquid and administered via various routes. It may also exist in monohydrate or crystalline form.
9867799/ February 3, 2032 U-3885	This invention relates to a method for treating muscular dystrophy, particularly Duchenne muscular dystrophy (DMD), using a combination of diethyl-[6-(4-hydroxycarbamoyl-phenylcarbamoyloxymethyl)-naphthalen-2-yl-methyl]-ammonium chloride (or its pharmaceutically acceptable salts or solvates) and an anti-inflammatory agent, specifically steroids such as prednisolone, prednisone, or deflazacort. The claims

US Patent/Exp. Date Patent Type	Key Disclosures
	encompass dosage ranges, treatment regimens, and various pharmaceutical forms, including monohydrate and crystalline forms.
10688047/October 28, 2036 Drug Product U-3885	This invention discloses physically and chemically stable oral liquid formulations of Givinostat, specifically aqueous suspensions containing Givinostat (or its pharmaceutically acceptable salts) in combination with wetting agents, density-modifying agents, buffering agents, and suspending agents. The claims specify particular excipients, concentration ranges, and methods of preparation. Additionally, the claims cover a method of treating diseases responsive to histone deacetylase inhibitors (HDACi).

*U-3885 - A method for the treatment of Duchenne Muscular Dystrophy (DMD) using givinostat

Table 5: Orange Book patents for Exblifep

US Patent/Exp. Date Patent Type	Key Disclosures
7687488/ December 3, 2027 Drug Substance Drug Product U-3851*	The patent describes 2-substituted methyl penam derivatives, including their stereoisomers, tautomers, polymorphs, and pharmaceutically acceptable salts, along with pharmaceutical compositions containing these compounds. It also covers formulations incorporating the derivatives—either alone or in combination with other antibiotics such as penicillins, cephalosporins, or aminoglycosides—for treating bacterial infections in mammals.
11124526/ November 7, 2034 U-3852*	The patent describes a crystalline β-lactamase inhibitor defined by characteristic XRPD peaks, thermal properties (TGA, DSC), and specific preparation methods. It covers multiple crystalline forms and includes a crystallization process derived from the amorphous form. The compound is intended for treating bacterial infections, either alone or in combination with antibiotics.

*U-3851 - The use of specified polymorphs of EXBLIFEP (cefepime and enmetazobactam) for treating complicated urinary tract infections (cUTI), including pyelonephritis, caused by designated susceptible microorganisms.

*U-3852 - The use of EXBLIFEP (cefepime and enmetazobactam) for treating complicated urinary tract infections (cUTI), including pyelonephritis, caused by designated susceptible microorganisms.

Table 6: Orange Book patents for Flyrcado

US Patent/Exp. Date Patent Type	Key Disclosures
7344702/ May 26, 2026 Drug Substance	The disclosed patent relates to compounds and methods for imaging myocardial perfusion. It describes the use of contrast agents containing a compound that binds to MC-1, coupled with an imaging moiety. The method involves administering the contrast agent to a patient, followed by diagnostic imaging to assess myocardial perfusion. The claims cover contrast agents selected from a defined group of disclosed structures.
8226929/ June 21, 2028 U-4011	The claims describe methods for detecting, imaging, or monitoring myocardial perfusion through the administration of a sterile formulation or contrast agent containing fluorine-18, followed by diagnostic imaging. The claims specify variations in the chemical structure of the contrast agents, each tailored for myocardial perfusion imaging.
8936777/ June 30, 2031 U-4011	The claims describe methods for synthesizing imaging agents, including ^18F-labeled compounds, by detailing manufacturing processes, precursor chemistry, and reaction conditions. They also cover a method of imaging a subject, specifying dosage levels and imaging procedures, as well as a cassette-based system for preparing imaging agents.

US Patent/Exp. Date Patent Type	Key Disclosures
9161997/ February 4, 2026 Drug Substance Drug Product U-4011	The claims describe a contrast agent for myocardial perfusion imaging, comprising a compound that binds MC-1 and a radioisotope suitable for nuclear medicine imaging. Various radioisotopes are specified, including ^18F and 99mTc. The claims also cover diagnostic kits for preparing imaging agents, which may contain additional stabilizers or processing components. Furthermore, sterile formulations and methods for imaging, detecting, and monitoring myocardial perfusion through contrast agent administration followed by diagnostic imaging are included.
9603951/ May 2, 2031 U-4011	This patent builds upon 9161997 by refining the contrast agent composition, specifically focusing on Fluorine-18 (^18F) and Technetium-99m (^99mTc) to enhance imaging precision. It also expands the diagnostic kit formulation to include additional stabilizing agents, ligands, and buffers.
9687571/ November 1, 2032 Drug Product U-4011	The claims describe a radiopharmaceutical composition for medical imaging that includes a radiopharmaceutical compound, ascorbic acid as a stabilizer, and a controlled pH range. They specify variations in ascorbic acid concentration and pH, along with a method for preparing the composition. Additionally, the claims cover a method for myocardial imaging

US Patent/Exp. Date Patent Type	Key Disclosures
	involving administration of the composition followed by diagnostic imaging.

U-4011 - Method of positron emission tomography (PET) for cardiac imaging.

Table 7: Orange Book patents for Iqirvo

US Patent/Exp. Date Patent Type	Key Disclosures
11185519/ March 30, 2037 U-3955.	The patent covers the use of elafibranor (GFT505) for treating Primary Biliary Cholangitis (PBC) in patients with an inadequate response to ursodeoxycholic acid (UDCA). The method involves administering a therapeutically effective amount of elafibranor, primarily via oral dosing at 80 mg or 120 mg once daily, with a broader dose range of 70 mg to 130 mg per administration. The composition can be formulated in various dosage forms, with an emphasis on oral formulations.
11331292/ March 30, 2037 U-1854	The patent describes a method for treating Primary Biliary Cholangitis (PBC) using elafibranor (GFT505), an active compound administered orally as detailed in the prior patent. The method also permits co-administration with UDCA or other anti-cholestatic agents to enhance therapeutic efficacy.
11850223/ March 30, 2037 U-1854	The patent relates to the use of Elafibranor (GFT505) for treating pruritus associated with primary biliary cholangitis (PBC). It claims a method for managing PBC-related pruritus by orally administering Elafibranor in various doses and formulations, either alone or in combination with ursodeoxycholic acid (UDCA) or other anti-cholestatic agents.

US Patent/Exp. Date Patent Type	Key Disclosures
11857523/ March 30, 2037 U-3955	The patent relates to the use of Elafibranor (GFT505) for treating pruritus in primary biliary cholangitis (PBC) patients who exhibit an inadequate response to ursodeoxycholic acid (UDCA). The claims include a method for administering Elafibranor in various doses and formulations, either alone or in combination with UDCA or other anti-cholestatic agents.

U-3955 - Treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults who have had an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA.

U-1854 - Treatment of primary biliary cholangitis (PBC).

Table 8: Orange Book patents for Itovebi

US Patent/Exp. Date Patent Type	Key Disclosures
8242104/ September 27, 2030 Drug Substance Drug Product	The patent covers benzoxazepine compounds with diverse structural variations, designed as lipid kinase inhibitors—particularly targeting PI3K isoforms such as p110α—for the treatment of cancer and related disorders. The invention also encompasses multiple stereoisomers, tautomers, and pharmaceutically acceptable salts, underscoring their potential therapeutic applications.
8343955/ September 27, 2030 U-4024	The patent builds upon the previous one by additionally claiming a method of treatment involving the administration of benzoxazepine compounds in a therapeutically effective amount for the treatment of specific cancers.
9650393/ July 1, 2036 Drug Substance Drug Product	This patent describes benzoxazepin-oxazolidinone compounds as PI3K modulators for treating cancers associated with PI3K dysregulation, particularly breast cancer and non-small cell lung cancer (NSCLC). The core claims encompass specific derivatives with defined substitutions, stereoisomers, tautomers, and pharmaceutically acceptable salts. Additionally, the patent covers pharmaceutical compositions containing these

US Patent/Exp. Date Patent Type	Key Disclosures
	compounds, treatment methods—including combination therapies—and a therapeutic kit for breast cancer treatment.
10851091/ July 1, 2036 Drug Substance Drug Product	This patent describes Inavolisib (GDC-0077) and its pharmaceutically acceptable salts, as well as pharmaceutical compositions comprising the compound. The core claims cover the specific chemical structure and formulations that include various pharmaceutically acceptable excipients.
11028100/ April 26, 2038 Drug Substance Drug Product	This patent describes crystalline polymorphs of Inavolisib (GDC-0077), specifically including anhydrate and hydrate forms. The core claims cover Form A, Form D, and Form B, each defined by distinct solid-state and thermal properties. The patent also claims pharmaceutical compositions containing these polymorphs, formulated with pharmaceutically acceptable excipients in tablet form across specified dosage ranges. Additionally, milled forms of these polymorphs are included to enhance formulation characteristics.
11760753/ July 1, 2036 U-4024	The patent describes benzoxazepin oxazolidinone compounds as PI3K modulators for the treatment of cancers driven by PI3K dysregulation, with particular emphasis on breast cancer and non-small cell lung cancer (NSCLC). The core claims define the

US Patent/Exp. Date Patent Type	Key Disclosures
	structural scope of these compounds, including derivatives, stereoisomers, and pharmaceutically acceptable salts. The patent also covers pharmaceutical compositions, therapeutic methods, combination therapies, and a treatment kit, specifically highlighting applications in PIK3CA- or PTEN-mutant, HER2-positive, and triple-negative breast cancers.

*U-4024 - Combination with palbociclib and fulvestrant for treatment of adults with endocrine-resistant PIK3CA-mutated HR-positive HER2-negative locally advanced or metastatic breast cancer following recurrence on or after completing adjuvant endocrine therapy.

Table 9: Orange Book patents for Lazcluze

US Patent/Exp. Date Patent Type	Key Disclosures
9593098/October 13, 2035 Drug Substance Drug Product U-3985	The invention discloses aminopyrimidine-based protein kinase inhibitors and their pharmaceutically acceptable salts for the treatment of cancers and immune-related disorders. It encompasses structurally defined compounds (Formulas I–IV), methods of synthesis, pharmaceutical compositions, and their use in selectively inhibiting mutant EGFR variants (e.g., Del E746-A750, L858R, T790M) over wild-type EGFR. Therapeutic applications include non-small cell lung cancer (NSCLC) and other solid tumors, autoimmune and inflammatory diseases, neurodegenerative conditions, and transplant rejection.
11453656/April 18, 2038 Drug Substance Drug Product	This patent describes the mesylate salt of a specific aminopyridine derivative, detailing its crystalline structure, thermal characteristics, and pharmaceutical applications. It also covers pharmaceutical formulations incorporating the salt for the treatment of protein kinase-mediated disorders.
11850248/August 01, 0241	This patent discloses a method for treating cancer in humans using lazertinib, a third-generation EGFR tyrosine kinase inhibitor (TKI). It specifically targets EGFR mutation-positive

US Patent/Exp. Date Patent Type	Key Disclosures
U-3985	non-small cell lung cancer (NSCLC), including cases with T790M mutations and brain metastases. The patent outlines dosage regimens and treatment durations for drug administration.
11879013/May 21, 2040 U-3995	This patent discloses a combination therapy for treating cancers expressing EGFR or c-Met, including non-small cell lung cancer (NSCLC). The therapy involves a bispecific antibody that targets both EGFR and c-Met, administered in combination with a third-generation EGFR tyrosine kinase inhibitor (TKI), such as lazertinib. The patent details the antibody's structure, the synergistic mechanism of action against cancer-associated mutations, and the dosage regimens for achieving therapeutic efficacy.
11981659/April 18, 2038 U-3995	This patent relates to the mesylate salt form of a specific aminopyridine derivative, characterized by its crystalline structure, thermal behavior, and water content. The invention covers pharmaceutical compositions containing the compound and its use in treating protein kinase-mediated disorders, particularly non-small cell lung cancer (NSCLC), including cases involving EGFR mutations.

*U-3985 - First-line treatment of adults with locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR exon 19 deletions or exon 21 L858R substitution mutations, in combination with amivantamab.

Table 10: Orange Book patents for Leqselvi

US Patent/Exp. Date Patent Type	Key Disclosures
11919907/May 21, 2041 Drug Product U-3976	This invention relates to a deuterated JAK1/JAK2 inhibitor with ≥90% deuterium incorporation at specified positions, including specific compounds such as Compound 10 and their pharmaceutically acceptable salts (e.g., phosphate). The compound may be administered alone or in combination with other JAK inhibitors (e.g., CTP-543) in pharmaceutical compositions, such as tablets or capsules, for the treatment of JAK-mediated diseases, particularly alopecia areata. The described methods encompass cellular JAK inhibition, monotherapy or combination therapy, and defined dosing regimens (e.g., 16 or 24 mg/day).
10561659/May 4, 2037 U-3976	This patent claims methods for treating hair loss disorders, including alopecia areata, by administering a deuterated JAK inhibitor (Compound I) or its pharmaceutically acceptable salt. It covers deuterated compounds with a specified level of deuterium incorporation, as well as pharmaceutical compositions comprising the compound and a pharmaceutically acceptable carrier or diluent. The patent also includes formulations in tablet

US Patent/Exp. Date Patent Type	Key Disclosures
	form or as phosphate salts. The claimed treatment is intended for oral administration and is applicable to human subjects.
12076323/May 4, 2037 U-3976	The invention discloses deuterated JAK1/JAK2 inhibitors, including specific compounds such as Compound 10, featuring high deuterium incorporation to enhance pharmacokinetics and stability. These compounds, or their phosphate salts, may be formulated into tablets or capsules and administered alone or in combination with other JAK inhibitors (e.g., CTP-543) for the treatment of JAK-related diseases, particularly hair loss disorders such as alopecia areata. The claims encompass pharmaceutical compositions, methods of treatment, cellular JAK inhibition, and defined combination dosing regimens, including 16 or 24 mg/day.

U3796 Treatment of adults with alopecia areata

Table 11: Orange Book patents for Livdelzi

US Patent/Exp. Date Patent Type	Key Disclosures
7301050/ August 2, 2025 Drug Substance Drug Product	The invention relates to 4-((phenoxyalkyl)thio)-phenoxyacetic acid derivatives that function as PPARδ modulators for the treatment of dyslipidemia and related cardiometabolic disorders. It encompasses structurally diverse compounds, including specific enantiomers and pharmaceutical compositions, optimized for potency and receptor selectivity.
7709682/ September 19, 2026 Drug Substance	The invention relates to crystalline L-lysine salts of (R)-{4-[2-ethoxy-3-(4-trifluoromethyl-phenoxy)-propylsulfanyl]-2-methyl-phenoxy}-acetic acid, a compound known to modulate peroxisome proliferator-activated receptor delta (PPARδ). These salts are chaThe invention relates to crystalline L-lysine salts of (R)-{4-[2-ethoxy-3-(4-trifluoromethylphenoxy)propylsulfanyl]-2-methylphenoxy}acetic acid, a compound known to modulate peroxisome proliferator-activated receptor delta (PPARδ). These salts are defined by distinct polymorphic forms, characterized by their unique X-ray diffraction peak profiles

US Patent/Exp. Date Patent Type	Key Disclosures
9486428/March 19. 2035 U-1854	This patent discloses a method for treating intrahepatic cholestatic diseases, particularly primary biliary cholangitis (PBC), by administering seladelpar or its pharmaceutically acceptable salts. The claims encompass oral administration, pharmaceutical compositions, defined dosing regimens, and the optional use of combination therapy with ursodeoxycholic acid.
10272058/ March 19. 2035 U-1854	This patent discloses a method for treating primary biliary cholangitis (PBC) by administering seladelpar or its pharmaceutically acceptable salts. The claims specify a once-daily dosing regimen for both seladelpar and its L-lysine dihydrate salt form.
11406611/ March 19. 2035 U-1854	This patent discloses a method for treating intrahepatic cholestatic diseases by administering seladelpar or its L-lysine dihydrate salt. The claims specify oral administration, a once-daily dosing regimen, and defined dosage ranges for both the free acid and its salt form.

US Patent/Exp. Date Patent Type	Key Disclosures
11596614/ March 19. 2035 U-1854	This patent discloses a method for treating intrahepatic cholestatic diseases by administering seladelpar or its pharmaceutically acceptable salts. The claims encompass oral administration, a once-daily dosing regimen, and specify dosage amounts of 5 mg or 10 mg of seladelpar or its L-lysine salt, administered orally once daily.

U-1854 – Treatment of primary biliary cholangitis

Table 12: Orange Book patents for Lumisight

US Patent/Exp. Date Patent Type	Key Disclosures
9032965/December 8, 2031 U-3980	The patent claims an in vivo method for treating tumors by administering a molecular imaging probe that preferentially clears from healthy tissue while labeling tumor-associated inflammatory cells. The probe comprises a fluorescent label within the 350–670 nm range and a pharmacokinetic modifier—such as PEG or dextran—with a molecular weight between 20,000 and 40,000 g/mol. Following initial tumor resection, the resection bed is exposed to light and imaged using a single-cell resolution imaging system to detect residual labeled cells, enabling further resection if necessary. The method includes features such as systemic or topical probe administration, imaging 12 to 36 hours post-administration, use in human subjects, and the ability to label both tumor cells and tumor-associated inflammatory cells.
9155471/October 12, 2031 U-3980	The patent discloses a method for detecting diseased cells by administering a molecular imaging probe with optical properties in the visible spectrum (350–670 nm). The probe includes PEG or methoxyPEG biomodifiers that enable selective retention in diseased cells while allowing clearance from healthy tissue. The

US Patent/Exp. Date Patent Type	Key Disclosures
	method supports the detection of cancer, as well as diseased central nervous, cardiac, bone, tendon, and muscle cells. The imaging system captures in situ images with detection depths ranging from 1 cm to 1 mm. The claims specify both systemic and topical in vivo administration of the imaging probe.
9532835/December 08, 2031 U-3980	The patent discloses a method for tumor treatment using a molecular imaging probe containing a fluorescent label that selectively targets tumor cells. The claims cover the administration route (systemic or topical), imaging timeframe, composition and molecular weight of the pharmacokinetic modifier, types of fluorescent labels, tumor cell detection range, applicability to human subjects, and components of the imaging system—including a light source, optical receptor, and image processor capable of single-cell resolution. The method enables selective tumor detection and image-guided resection while minimizing interference from deep tissue signals.
9763577/September 14, 2034 Drug Substance Drug Product U-3980	The patent discloses compounds with defined structural formulas, including their pharmaceutically acceptable salts. The claims outline structural variations, such as the integer range for n (400–500 and 40–400) and an mPEG portion with a molecular weight of approximately 20,000 g/mol. The patent also includes

US Patent/Exp. Date Patent Type	Key Disclosures
	claims for methods of imaging diseased cells, specifying an optimal imaging timeframe of 12–24 hours post-administration and the applicable routes of administration.
10285759/December 08, 2031 U-3980	The patent discloses a method for treating tumors using a molecular imaging probe that selectively labels tumor and tumor-associated cells while clearing from healthy tissue. The claims include light excitation within the 100–2500 nm range, single-cell resolution imaging, and detection of labeled cells within 1 cm of the resection bed. The imaging system comprises a light source, an optical receptor (e.g., CCD, APD, or CMOS), and an image processor that detects tumor cells, maps fluorescence intensity, and compares fluorescence levels to identify residual tumor presence.
11592396/September 01, 0230 Drug Substance U-3980	This patent discloses compositions and methods for enhancing the imaging of tumor resections. The claims focus on molecular imaging probes, pharmacokinetic modifiers, enzyme-activated fluorescence, and specific variations of PEG and amino acid linkers.

U-3980- A method comprising administering pegulicianine to a human and obtaining an image of a tumor bed after tumor resection to distinguish in situ cancer cells from healthy cells.

Table 13: Orange Book patents for Miplyffa

US Patent	Key Disclosures
9289472/August 11, 2029 U-4021	The invention discloses a method for treating lysosomal storage diseases (LSDs) by administering a hydroxylamine derivative that increases intracellular Hsp70 levels through the upregulation of Hsp70 gene expression. The method applies to disorders such as Niemann-Pick disease (types A–D). Preferred hydroxylamine derivatives include arimoclomol. Treatment may be administered as monotherapy or in combination with other therapeutic modalities.
9884058/June 26, 2029 U-4021	Similar to the above patent, this invention differs in disease scope and treatment modalities.
11045460/August 19, 2029 U-4021	This patent discloses a method for treating Niemann-Pick disease Type C (NPC) in humans through the oral administration of arimoclomol or its pharmaceutically acceptable salts. The method specifies a dosage range of 1 μg to 100 mg per kg of body weight and permits combination therapy with miglustat or enzyme replacement therapy (ERT), including imiglucerase, agalsidase beta, or agalsidase alpha.

U4021 - Use of arimoclomol, in combination with miglustat, for treatment of neurological manifestations of Niemann-Pick disease type C (NPC).

Table 14: Orange Book patents for Ohtuvayre

US Patent/Exp. Date Patent Type	Key Disclosures
10945950/September 15, 2035 Drug Product	This patent discloses a liquid inhalation formulation of RPL554, a PDE3/4 inhibitor for the treatment of asthma and COPD. Key claims include a suspension with controlled particle size (0.2–5 μm) and concentration (0.1–6 mg/mL), optionally containing phosphate buffers, as well as a nebulizer comprising the composition.
9062047/August 21, 2031 Drug Substance U-3962	This patent discloses a crystalline polymorph of RPL554. The claims describe the composition and characterization of a stable polymorph with improved purity, storage stability, and dissolution properties. The patent includes solid pharmaceutical formulations incorporating the polymorph, with or without additional therapeutic agents. It also outlines manufacturing processes for producing the crystalline form and claims its medical use in treating chronic obstructive pulmonary disease (COPD), including administration to mammals.
9956171/September 15, 2035 Drug Substance	This patent discloses a liquid pharmaceutical composition of RPL554 for inhalation, intended for the treatment of respiratory diseases such as COPD and asthma. The claims describe a

US Patent/Exp. Date Patent Type	Key Disclosures
U-3962	suspension with controlled particle size (Dv50 of 0.2–5 µm), a pH range of 4–8, and a drug concentration of 0.01–40 mg/mL. The formulation may include optional surfactants, buffers, and tonicity adjusters. The patent also covers water-based formulations suitable for nebulization, as well as therapeutic applications in respiratory and inflammatory conditions.

U-3962 - Method of use for the maintenance treatment of chronic obstructive pulmonary disease (COPD) in adult patients.

Table 15: Orange Book patents for Ojemda

US Patent/Exp. Date Patent Type	Key Disclosures
8293752/ August 4, 2031 Drug Substance Drug Product	This patent discloses a class of chemical compounds designed to inhibit RAF protein kinase activity. The claims define the structural features of these compounds, including various substitutions. The patent also covers pharmaceutical compositions containing the compounds in combination with pharmaceutically acceptable carriers, adjuvants, or vehicles. Additionally, it claims the use of these compounds in combination with other therapeutic agents, such as chemotherapeutics, anti-inflammatory drugs, and immunomodulatory agents.
10426782/ June 23, 2035 Drug Product	This patent discloses a pharmaceutical composition formulated to enhance the stability and bioavailability of a pan-RAF kinase inhibitor. The composition comprises a solid dispersion extrudate containing the active drug, a solubility-enhancing polymer (copovidone), and pharmaceutically acceptable excipients. The patent also claims a method for preparing this formulation.

Table 16: Orange Book patents for Revuforj

US Patent/Exp. Date Patent Type	Key Disclosures
10683302/ June 8, 2037 Drug Substance Drug Product	This patent discloses a class of small-molecule inhibitors that block the interaction between menin and MLL/MLL fusion proteins, which are critical in MLL-rearranged leukemias and other cancers. The invention encompasses a broad chemical scaffold (Formula I) with various structural modifications, as well as specific potent compounds, pharmaceutically acceptable salts, crystalline forms, and pharmaceutical compositions. These compounds are intended for use in treating cancers driven by dysregulated menin–MLL signaling.
11479557/ June 8, 2037 Drug Product U-4045	This patent discloses novel small-molecule inhibitors that target the menin–MLL interaction for the treatment of leukemia. It encompasses a broad range of structural variants, detailing molecular frameworks, substitutions, and functional groups within compounds of Formula I. The claims include methods for treating various leukemia subtypes, including mixed lineage leukemia (MLL), MLL-rearranged (MLL-r) leukemia, acute myeloid leukemia (AML), and nucleophosmin (NPM1)-mutated

US Patent/Exp. Date Patent Type	Key Disclosures
	AML, through administration of these compounds. The patent also covers pharmaceutical compositions containing these inhibitors for therapeutic use.

U-4045 - Treatment of relapsed or refractory acute leukemia with a lysine methyltransferase 2A gene (KMT2A) translocation in adult and pediatric patients 1 year and older

Table 17: Orange Book patents for Rezdiffra

US Patent/Exp. Date Patent Type	Key Disclosures
7452882/ September 12, 2026 Drug Substance Drug Product	This patent discloses a class of thyroid hormone analogs featuring a core heterocyclic structure designed to function as thyroid hormone receptor ligands. These compounds include various substituents that modulate receptor activity and are claimed in multiple embodiments, including their pharmaceutically acceptable salts. The patent also describes pharmaceutical compositions containing these compounds for therapeutic use, particularly in the treatment of metabolic disorders such as obesity, hyperlipidemia, diabetes, and thyroid-related conditions.
9266861/ September 17, 2033 Drug Substance Drug Product	This patent discloses specific crystalline forms of Compound A, characterized by distinct X-ray powder diffraction patterns that ensure improved purity and stability. The core claims include pharmaceutical compositions incorporating these polymorphic forms, as well as synthetic and crystallization methods for their preparation.
10376517/ September 17, 2033	This patent discloses pharmaceutical compositions containing polymorphic forms and methods for treating resistance to thyroid

US Patent/Exp. Date Patent Type	Key Disclosures
U-3861	hormone (RTH) in patients with TRβ mutations, as well as metabolic and cardiovascular disorders, including hypercholesterolemia, fatty liver disease, atherosclerosis, and nonalcoholic steatohepatitis (NASH). The patent also specifies purity thresholds (≥95%) for the polymorphic forms and provides detailed X-ray diffraction data to define their crystalline structure.
11564926/ September 17, 2033 Drug Substance Drug Product U-3861	This patent discloses treatments for nonalcoholic steatohepatitis (NASH), hypercholesterolemia, and resistance to thyroid hormone (RTH) syndrome in patients with TRβ mutations. It also describes assays for detecting TRβ mutations, specifies genetic substitutions, and outlines methods of administration. The polymorphic forms, with high purity (>95%), are optimized for oral delivery, supporting pharmaceutical applications in metabolic and thyroid-related conditions.
11986481/ September 17, 2033 U-3861	This patent discloses specific dosage ranges (approximately 10 mg to 200 mg per day) and various administration methods, including oral tablets, single-dose regimens, and formulations containing pharmaceutical excipients. It also describes pharmaceutical compositions suitable for oral delivery, with

US Patent/Exp. Date Patent Type	Key Disclosures
	defined purity thresholds (≥95% or ≥98%). The invention supports daily administration for the long-term treatment of metabolic disorders.

U-3861 - Method of use for treatment of adults with noncirrhotic nonalcoholic steatohepatitis (nash) with moderate to advanced liver fibrosis (consistent with stages f2 to f3 fibrosis.

Table 18: Orange Book patents for Rytelo

US Patent/Exp. Date Patent Type	Key Disclosures
7494982/ December 27, 2025 Drug Substance Drug Product	This patent discloses compounds comprising an oligonucleotide moiety covalently linked to a lipid moiety, specifically designed to inhibit human telomerase by hybridizing with its RNA component. The core claim focuses on a compound containing a thiophosphoramidate linkage between nucleosides. The patent also claims pharmaceutical compositions incorporating these compounds.
9375485/ March 15, 2033 U-3956	This patent discloses a method for treating myelofibrosis (MF) and myelodysplastic syndromes (MDS) by administering a telomerase inhibitor composed of oligonucleotides complementary to the RNA component of telomerase. The inhibitor includes at least one N3'→P5' thiophosphoramidate internucleoside linkage. The claims also cover pharmaceutical compositions incorporating a lipid moiety, such as palmitoyl (C16), to enhance delivery. Additionally, the patent specifies multiple administration routes, including oral, intravenous, subcutaneous, and intramuscular, along with formulations

US Patent/Exp. Date Patent Type	Key Disclosures
	containing pharmaceutically acceptable excipients to improve therapeutic efficacy.
9388415/ September 09, 2025	This patent claims methods for inhibiting telomerase activity using oligonucleotide compounds containing a thiophosphoramidate linkage. The methods involve contacting the enzyme, a cell (particularly cancer cells), or a patient with these compounds to suppress telomerase function. The compounds may be administered as part of a pharmaceutical composition. Specific claims cover the treatment of a broad range of cancers, including breast, lung, and hematologic malignancies such as leukemia and lymphoma. The approach leverages the telomerase-inhibiting properties of the compounds for potential use in cancer therapy.
9388416/ September 09, 2025	This patent claims methods for inhibiting cancer cell proliferation and treating cancer using oligonucleotide compounds containing a thiophosphoramidate linkage. These methods involve contacting cancer cells or administering the compounds to patients as part of a pharmaceutical composition. The claims encompass a broad spectrum of cancers, including solid tumors (e.g., lung and breast cancer) and hematologic

US Patent/Exp. Date Patent Type	Key Disclosures
	malignancies (e.g., leukemia, lymphoma, and myeloma). Several claims are directed toward specific cancer types, underscoring the therapeutic potential across diverse oncologic indications.
12171778/June 16, 2039	This patent discloses a method for treating myelodysplastic syndrome (MDS) by administering a telomerase inhibitor, specifically imetelstat or its sodium salt. The method involves classifying patients as naïve to treatment with a hypomethylating agent (HMA) or lenalidomide, selecting them for telomerase inhibitor therapy, and administering an effective dose to manage the condition. The claims cover the treatment of relapsed or refractory MDS, particularly in patients with low or intermediate-1 IPSS risk scores who are also transfusion-dependent. The patent further details intravenous administration protocols, specifying dosages of 7–10 mg/kg at varying intervals, including weekly, every three weeks, or every four weeks.

U-3986 - Method of use for treatment of patients with myelodysplastic syndromes (MDS) who have transfusion-dependent anemia.

Table 19: Orange Book patents for Sofdra

US Patent/Exp. Date Patent Type	Key Disclosures
8147809/ March 26, 2027 Drug Substance Drug Product	This patent discloses a class of chemical compounds characterized by a core structure featuring a pyrrolidinium bromide moiety with various stereoisomeric configurations and substituents. It also describes pharmaceutical compositions incorporating these compounds. The core claims focus on the novel chemical structures and their use in pharmaceutical formulations for anticholinergic effects.
8628759/ November 13, 2026 U-2398	This patent discloses methods and compositions for eliciting an anticholinergic response using specific chemical compounds. The claims cover a range of medical applications, including the treatment of chronic obstructive pulmonary disease (COPD) and asthma, induction of mydriasis (pupil dilation), and reduction of excessive sweating through an antiperspirant effect. The patent also describes various administration routes, such as direct application to the eyes or skin. Additionally, it outlines multiple stereochemical variants of the core compounds to enhance therapeutic efficacy.

US Patent/Exp. Date Patent Type	Key Disclosures
9220707/ March 14, 2034 U-2398	This patent discloses a method for treating hyperhidrosis (excessive sweating) through the topical application of a pharmaceutical composition containing specific soft anticholinergic compounds. The claims focus on the formulation and administration method, detailing a cream, gel, powder, or emulsion with varying concentrations of the active compound, applied to the skin before bedtime to effectively reduce sweat production. Additional claims refine the concentration range of the active ingredient, duration of effectiveness (lasting between 8 to 24 hours), and the option for a second application in the morning to enhance results. The patent also outlines stereoisomeric variations of the active compounds, optimizing their chemical composition, safety, and efficacy for improved hyperhidrosis treatment.
9492429/ March 14, 2034 Drug Product U-2398	This patent discloses a method for treating hyperhidrosis (excessive sweating) through the topical application of a pharmaceutical composition containing specific soft anticholinergic compounds. The claims focus on the formulation and method of administration, specifying a cream, gel, powder, lotion, or emulsion containing 1.0% to 25% of the active

US Patent/Exp. Date Patent Type	Key Disclosures
	compound, applied to the skin before bedtime to reduce sweat production by at least 25% for a duration of 8 to 24 hours. Additional claims further define the concentration range of the active ingredient (2% to 10%), alternative stereoisomeric forms, and the option of a second morning application to extend effectiveness. The patent also describes chemical variants of the active compounds, optimizing their composition, safety, and therapeutic efficacy for managing hyperhidrosis.
9895350/ March 14, 2034 U-2398	This patent introduces further refinements to the chemical composition and stereochemistry of the active compound.
10383846/ March 14, 2034 U-2398	This patent introduces further refinements to the chemical composition and stereochemistry of the active compounds.
10947192/ May 22, 2034 U-2398	The patent further refines the chemical composition, stereoisomeric variations, concentration ranges, and packaging options, including both single-use and multi-dose containers.

US Patent/Exp. Date Patent Type	Key Disclosures
10952990/ May 22, 2034 U-2398	This patent introduces additional chemical refinements, more precise dosing parameters, and preservative-free formulation options.
10959983/ May 22, 2034 U-2398	This patent introduces improvements in sweat reduction efficacy, specifying that sweat production can be reduced by 30% to 75% in some cases, and by as much as 70% to 99% in others.
10961191/ May 22, 2034 U-2398	This patent further refines the chemical composition, defines the role of ethanol as a co-solvent, elaborates on its stability advantages, and introduces additional potential improvements.
11026919/ May 22, 2034 U-2398	This patent introduces more precisely targeted application areas, including the palms, plantar surfaces of the feet, groin, axilla (underarm), and facial regions. It also discloses refined chemical compositions, explicit ethanol requirements, higher active ingredient concentration specifications, and additional stability-enhancing agents.
11034652/ May 22, 2034	This patent introduces greater specificity regarding viscosity agents, along with other refinements in its claims.

US Patent/Exp. Date Patent Type	Key Disclosures
U-2398	
11052067/ May 22, 2034 U-2398	This patent claims a topical treatment for hyperhidrosis using a stable, anhydrous gel formulation of a soft glycopyrrolate derivative, applied before sleep to reduce sweating by at least 25% for six hours or more. The formulation includes high concentrations of anhydrous ethanol (≥70%), select excipients, and defined stereoisomeric forms of the active agent, offering improved safety and stability over traditional aqueous glycopyrrolate treatments.
11084788/ May 22, 2034 U-2398	This patent discloses claims similar to those in earlier filings but with more focused and refined claim language.
11123325/ July 20, 2037 U-2398	This patent discloses claims similar to previous filings but expands the methods of use to include both bedtime and general application.
11566000/ May 22, 2040 Drug Substance	This patent claims a stable, non-hygroscopic cocrystal form (Form CO) of sofpironium bromide, composed of the 1′ R and 1′ S diastereomers in a 1:3 ratio, characterized by defined

US Patent/Exp. Date Patent Type	Key Disclosures
Drug Product	purity, thermal behavior, and diffraction patterns. It also covers topical formulations containing this cocrystal and a solvent-based manufacturing method that produces a high-purity active ingredient suitable for pharmaceutical applications.
11584715/ May 22, 2040 Drug Substance Drug Product	This patent claims a stable, non-hygroscopic crystalline mixture (Form B) of sofpironium bromide, composed of Form CO (a cocrystal) and Form MN (the single 1′ R diastereomer), characterized by distinct PXRD peaks and specified purity and impurity thresholds. It also covers a topical composition containing Form B and a manufacturing method that employs defined solvent conditions to produce the crystal form suitable for pharmaceutical use.

U-2398 - Topical treatment of primary axillary hyperhidrosis in adults and pediatric patients 9 years of age and older.

Table 20: Orange Book patents for Tryngolza

US Patent/Exp. Date Patent Type	Key Disclosures
9127276/May 01, 2034 Drug Substance	This patent discloses compounds containing groups such as a nucleoside, nucleotide, monomeric subunit, reactive ester, linker, cleavable moiety, or oligomeric compound. The linker may include an amine, amide, ester, ether, pyrrolidine, PEG, polyamide, or disulfide bond. The claims specify the precise chemical structures of the linkers and other substituents.
9157082/April 27, 2032 U-4050	This patent discloses a method for increasing HDL levels by administering a modified antisense oligonucleotide targeting ApoCIII. The oligonucleotide is single-stranded, 12 to 30 nucleobases in length, and incorporates structural modifications, including phosphorothioate internucleoside linkages and chemically modified sugars and nucleobases. It follows a gapmer design comprising a 5' wing, central gap, and 3' wing. The compound is administered parenterally, such as by subcutaneous injection, and may be co-administered with lipid-lowering or anti-inflammatory agents.

US Patent/Exp. Date Patent Type	Key Disclosures
9163239/ May 01, 2034 Drug Substance	This patent discloses a modified oligonucleotide composition designed to modulate gene expression. The oligonucleotide is 12 to 30 nucleobases in length and includes at least one modified internucleoside linkage, such as a phosphorothioate modification. Additional structural features are described. The compound is administered parenterally, including via subcutaneous injection, and may be co-administered with lipid-lowering agents, antibodies, or siRNA therapeutics. Further claims specify variations in the chemical backbone and the precise chemical structures of the modified oligonucleotide.
9181549/ May 01, 2034 Drug Substance U-4050	This patent discloses a modified oligonucleotide composition, similar to previous patents, but featuring broader chemical modifications and more specific structural variations.
9593333/February 14, 2034 U-4050	This patent discloses a method for treating lipoprotein lipase (LPL) deficiency by administering a modified antisense oligonucleotide targeting ApoCIII. The method lowers circulating triglyceride levels and is applicable to conditions such as familial chylomicronemia syndrome (FCS) and other LPL deficiency-related disorders. Structural features and

US Patent/Exp. Date Patent Type	Key Disclosures
	variations of the antisense oligonucleotide are detailed. The compound is administered parenterally, including via subcutaneous injection, and may be co-administered with lipid-lowering agents, LPL activators, or anti-inflammatory drugs. The method is intended for use in both humans and animals.

U-4050 - Use in reducing triglycerides in adults with familial chylomicronemia syndrome (FCS)

Table 21: Orange Book patents for Tryvio

US Patent/Exp. Date Patent Type	Key Disclosures
8324232/ September 21, 2029 Drug Substance Drug Product U-3878	This patent discloses a compound and its pharmaceutically acceptable salts for the treatment of hypertension and pulmonary arterial hypertension. It also covers pharmaceutical compositions containing these compounds and a synthesis process involving specific chemical reactions with strong bases and halogenating agents such as BCl_3 or BBr_3.
10919881/ February 26, 2038 Drug Substance Drug Product	This patent discloses a crystalline form of a compound, defined by specific X-ray powder diffraction (XRPD) patterns. It describes distinct polymorphic forms along with their stability, purity, pharmaceutical applications, and methods for preparation and formulation in solid pharmaceutical compositions.
11174247/ November 6, 2037 U-3879	This patent discloses a pharmaceutical composition comprising aprocitentan (or a pharmaceutically acceptable salt thereof) in combination with valsartan (or another angiotensin receptor blocker), and optionally a calcium channel blocker or a diuretic such as hydrochlorothiazide. The patent also covers a crystalline form of aprocitentan, along with its methods of preparation, dosage forms, and medical applications.

11680058/ July 26, 2038 U-3878	This patent discloses a method for treating cardiovascular, renal, and neurological disorders—including hypertension, heart failure, chronic kidney disease (CKD), and diabetes-related conditions—by administering a specific crystalline form of a pharmaceutical compound. It also covers methods for preparing the crystalline form and formulating it into pharmaceutical dosage forms.
11787782/ March 2, 2038 U-3877	U.S. Patent No. 11,787,782 discloses a pharmaceutical composition containing aprocitentan in crystalline Form A, combined with an angiotensin-converting enzyme (ACE) inhibitor such as enalapril. The patent also describes oral dosage forms and methods for treating hypertension—including resistant hypertension—chronic kidney disease (CKD), and heart failure.

U-3877: Treatment of hypertension in adult patients inadequately controlled on other antihypertensive drugs, using combination therapy that includes an angiotensin-converting enzyme (ACE) inhibitor.

U-3878: Treatment of hypertension in adult patients not adequately managed with other antihypertensive drugs, through combination therapy.

U-3879: Treatment of hypertension in adult patients inadequately controlled on other antihypertensive drugs, using combination therapy that includes an angiotensin receptor blocker (ARB).

Table 22: Orange Book patents for Vafseo

US Patent/Exp. Date Patent Type	Key Disclosures
7811595/ March 13, 2028 Drug Substance Drug Product	This patent discloses a class of compounds that inhibit HIF-1α prolyl hydroxylase, a key enzyme involved in oxygen sensing and erythropoietin regulation. The invention claims a core chemical scaffold with extensive variability at multiple positions. These compounds are intended for the treatment of conditions such as peripheral vascular disease (PVD), coronary artery disease (CAD), heart failure, ischemia, and anemia. The claims cover both broad and specific chemical structures, including a comprehensive range of heteroaryl and phenyl derivatives, along with their pharmaceutically acceptable salts. Pharmaceutical compositions incorporating these compounds are also disclosed.
8323671/ April 03, 2028 U-3876	The disclosed invention relates to HIF-1α prolyl hydroxylase inhibitors and their pharmaceutical compositions, intended for the treatment of anemia, peripheral vascular disease (PVD), coronary artery disease (CAD), heart failure, ischemia, and for promoting wound healing. The claims detail specific chemical structures, substituents, and linking groups, along with their pharmaceutically acceptable salts. The patent also identifies

US Patent/Exp. Date Patent Type	Key Disclosures
	particular compounds specifically applicable to the treatment of anemia and wound healing.
8343952/ August 14, 2027 Drug Substance Drug Product	This patent describes a class of HIF-1α prolyl hydroxylase inhibitors developed for the treatment of peripheral vascular disease (PVD), coronary artery disease (CAD), heart failure, ischemia, and anemia. The claimed compounds feature a core molecular scaffold with substituent variations such as fluorophenyl, chlorophenyl, trifluoromethylphenyl, methoxyphenyl, and heterocyclic rings including pyridine and dioxin derivatives. The patent also covers pharmaceutically acceptable salts, pharmaceutical formulations, and compositions specifically intended for the treatment of anemia and wound healing.
8598210/ June 26, 2027 Drug Substance Drug Product	The patent claims a class of HIF-1α prolyl hydroxylase inhibitors, including specific compounds, structurally related derivatives, and pharmaceutical compositions. The core claims focus on distinct molecular structures, formulations containing these inhibitors, and preferred derivative compounds.
8940773/ June 26, 2027 U-3876	The patent claims a class of HIF-1α prolyl hydroxylase inhibitors, including specific compounds, structurally related derivatives, and pharmaceutical compositions. The core claims

US Patent/Exp. Date Patent Type	Key Disclosures
	focus on distinct molecular structures, formulations containing these inhibitors, and preferred derivative compounds.
9701636/ November 14, 2034 Drug Substance Drug Product	This patent covers crystalline forms of vadadustat, along with their pharmaceutical compositions and methods of use. It includes claims for compositions containing crystalline vadadustat with varying drug loads and purity specifications. Additionally, the patent claims oral dosage forms formulated with pharmaceutically acceptable carriers incorporating these compositions.
9987262/ November 14, 2034 U-3876	This patent covers methods for treating anemia—particularly that associated with chronic kidney disease (CKD)—using a crystalline form of Compound (I). It defines key parameters such as X-ray powder diffraction (XRPD) patterns, purity thresholds, and composition requirements, including limitations on other crystalline or amorphous forms and impurity levels. The claims encompass both the direct administration of crystalline Compound (I) and its inclusion in pharmaceutical compositions.
10149842/ November 14, 2034 Drug Substance	This patent covers crystalline forms of vadadustat, characterized by defined X-ray powder diffraction (XRPD) patterns, a specific melting point, and established purity

US Patent/Exp. Date Patent Type	Key Disclosures
Drug Product	requirements. It restricts the presence of other crystalline forms and amorphous content and includes pharmaceutical compositions, oral dosage forms, and a crystallization method using acetone.
11065237/ November 14, 2034 Drug Substance Drug Product U-3876	This patent covers crystalline forms of vadadustat, their pharmaceutical compositions, and methods for treating anemia, including anemia associated with chronic kidney disease (CKD). It defines X-ray powder diffraction (XRPD) patterns, solid-state properties, purity thresholds, and impurity limits. The claims restrict the presence of other crystalline or amorphous forms, limit impurities, and establish high-purity standards. Additionally, the patent covers pharmaceutical compositions, oral dosage forms, and therapeutic methods for anemia treatment.
11324734/ March 31, 2036 Drug Product	This patent covers tablet formulations of vadadustat, detailing intra-granular, extra-granular, and film-coating components. The claims specify ingredient compositions, excipients, and drug loads across various dosage strengths. It further defines tablet weight, excipient ratios, and formulation characteristics to ensure consistent dosage and manufacturing quality.

US Patent/Exp. Date Patent Type	Key Disclosures
11844756/ March 31, 2036 U-3876	This patent covers methods for treating anemia using vadadustat tablet formulations, particularly in chronic kidney disease (CKD) patients, including both dialysis-dependent and non-dialysis-dependent individuals. It defines tablet composition, dosage regimens, patient selection criteria, and dose adjustment protocols. The claims also specify administration timing, baseline hemoglobin assessment, and limitations on dose modifications.
11857543/ June 09, 2034 U-3876	This patent covers methods for treating anemia in chronic kidney disease (CKD) patients by orally administering vadadustat at specified daily doses. It defines dosage regimens, patient eligibility criteria, hemoglobin monitoring protocols, dose adjustment guidelines, and co-administration with iron supplements for both pre-dialysis and dialysis-dependent patients.
RE47437/ June 26, 2027 Drug Substance Drug Product	This patent covers specific HIF prolyl hydroxylase inhibitor compounds, their pharmaceutical compositions, and formulations. It details structural variations, excipient components, and dosage forms intended for treating anemia and related disorders.

U-3876 - Treatment of anemia due to chronic kidney disease in adults who have been receiving dialysis for at least three months.

Table 23: Orange Book patents for Voranigo

US Patent/Exp. Date Patent Type	Key Disclosures
9579324/ July 11, 2034 Drug Substance	The patent covers various compounds featuring heterocyclic core structures—such as pyridinyl, phenyl, and pyrazolyl rings—with diverse functional group modifications and their pharmaceutically acceptable salts.
10172864/ November 11, 2034 Drug Substance Drug Product	The patent claims novel compounds and methods for treating cancer, specifically targeting tumors with IDH1 or IDH2 mutations. The core claims focus on small-molecule inhibitors featuring a defined heterocyclic ring system, which may be substituted with various functional groups such as halogens, alkyl, hydroxy, amino, cyano, carbonyl, and sulfonyl groups. The claims further specify preferred structural variations and molecular constraints designed to optimize therapeutic efficacy. Additionally, the patent covers pharmaceutically acceptable salts and hydrates of these compounds, along with formulations combining the active ingredient with pharmaceutically acceptable carriers.
11345677/ January 16, 2039 Drug Substance	This patent claims cocrystal solid forms of a cancer-treating compound combined with citric acid, characterized by distinct X-ray diffraction patterns and thermal properties. It covers

US Patent/Exp. Date Patent Type	Key Disclosures
Drug Product U-3978	pharmaceutical compositions containing these cocrystals and their use in treating cancers with IDH1 or IDH2 mutations, including gliomas, leukemia, and other malignancies. The claims specify mutation types, treatment strategies for newly diagnosed, relapsed, or refractory cancers, and corresponding dosage regimens.
11844758/ December 4, 2035 U-3977	The patent claims a method for treating anemia by administering a compound of a specified formula, including variations in its structural components. It also claims a method for promoting wound healing using the same class of compounds.

U-3977 - A method of treating a glioma characterized by an IDH1 mutation following surgery, wherein the glioma is Grade 2 astrocytoma or oligodendroglioma.

U-3978 - A method of treating a cancer characterized by an IDH1 or IDH2 mutation or a combination thereof following surgery, wherein the cancer is grade 2 astrocytoma or oligodendroglioma.

Table 24: Orange Book patents for Voydeya

US Patent/Exp. Date Patent Type	Key Disclosures
9796741/ February 25, 2035 Drug Substance U- 3933	This patent discloses a broad class of complement Factor D inhibitors, covering both their chemical compositions and methods of use for treating complement-mediated diseases. The invention supports wide chemical diversity through flexible ring structures and substituent configurations. Therapeutic claims focus on indications such as paroxysmal nocturnal hemoglobinuria (PNH), age-related macular degeneration (AMD), and autoimmune or inflammatory disorders.
12076319/ August 2, 2038 U-3933	This patent covers methods for treating paroxysmal nocturnal hemoglobinuria (PNH) by combining a C5 inhibitor—such as eculizumab or ALXN1210—with an orally administered complement factor D (CFD) inhibitor compound or its pharmaceutically acceptable salt. The claims specify various treatment protocols based on patients' hemoglobin and lactate dehydrogenase (LDH) levels, transfusion history, and prior C5 inhibitor therapy.

U-3933 - Treatment of extravascular hemolysis (EVH) in adults with paroxysmal nocturnal hemoglobinuria (PNH) as add-on therapy to ravulizumab or eculizumab.

Table 25: Orange Book patents for Xolremdi

US Patent/Exp. Date Patent Type	Key Disclosures
10548889/ December 11, 2038 Drug Product	This patent covers X4P-001, a pharmaceutical composition for treating CXCR4-associated diseases. It comprises a core active compound combined with one or more specified additives in defined weight percentages. The claims allow various additive combinations but explicitly exclude a particular compound from the formulation.
10610527/ December 22, 2036 U-3932	This patent covers methods of treating WHIM syndrome using X4P-001 or its pharmaceutically acceptable derivatives. The invention defines dosing regimens, routes of administration (once or twice daily oral), and diagnostic or therapeutic criteria including improvements in ANC, ALC, and immune function. It applies to patients with CXCR4 mutations or overexpression, and includes claims for biomarker monitoring. Key therapeutic endpoints include sustained increases in immune cell counts and improved vaccine responsiveness, supporting a disease-modifying role for X4P-001.
10953003/ December 14, 2036 Drug Product	This patent covers pharmaceutical compositions of X4P-001 in unit doses ranging from 10 mg to 1200 mg. The formulations specify defined proportions of excipients, including microcrystalline cellulose, dibasic calcium phosphate

US Patent/Exp. Date Patent Type	Key Disclosures
	dihydrate, and croscarmellose sodium, with several compositional variations. The claims also describe unit dosage forms—particularly capsules—engineered to ensure precise and consistent oral dosing.
11045461/ December 11, 2038 Drug Product	This patent covers X4P-001 compositions with defined concentrations of active and additive compounds, strict impurity thresholds, and enantiomeric purity specifications. The claims also describe formulations with controlled levels of additional compounds, which may be developed as pharmaceutical products using carriers or adjuvants.
11219621/ December 22, 2036 U-3932	This patent covers a method for treating WHIM syndrome using X4P-001 at daily doses between 200 mg and 600 mg, administered once or twice daily. The treatment targets patients with warts, CXCR4 mutations, or elevated CXCR4 expression, and involves biomarker monitoring through blood samples. The method is designed to increase absolute neutrophil and lymphocyte counts (ANC and ALC), improve protective antibody responses, reduce respiratory infections, and elevate circulating white blood cell levels.
12115156/ December 11, 2038	This patent covers compositions of X4P-001 with defined concentrations of active and additive compounds, strict

US Patent/Exp. Date Patent Type	Key Disclosures
Drug Product	impurity limits, and enantiomeric purity specifications. The claims detail controlled levels of specific compounds, thresholds for total and organic impurities, and enantiomeric excess. The composition can be formulated into pharmaceutical products using an adjuvant, carrier, or vehicle, and includes unit dosage forms such as 100 mg capsules.

U-3932 - Treatment of patients 12 years and older with warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome.

Table 26: Orange Book patents for Yorvipath

US Patent/Exp. Date Patent Type	Key Disclosures
8906847/ April 30, 2031 Drug Substance Drug Product U-3982	This patent discloses a prodrug comprising a drug-linker conjugate (D–L), where the biologically active moiety (D) is nitrogen-containing and the linker (L) is non-biologically active and cleavable after administration to release D–H. The linker structure (L1) is chemically defined and may be substituted with one to four groups (L2–Z), where L2 is a bond or spacer and Z is a carrier. The claims cover a wide range of chemical structures and functional groups for the linker components. The prodrug may incorporate small molecule drugs, peptides, proteins, or other biopolymers, including parathyroid hormone and PEG-based carriers. The patent also includes claims on precursors, pharmaceutical compositions, and methods of administration.
11590207/ September 28, 2037 U-3982	This patent discloses methods for treating hypoparathyroidism using a pharmaceutical composition comprising a controlled-release parathyroid hormone (PTH) compound. The method involves once-daily subcutaneous administration of a reduced molar equivalent dose (20–40%) of PTH(1-84), sufficient to maintain serum calcium levels above 8.5 mg/dL. The PTH compound is structurally defined by conjugation to SEQ ID

US Patent/Exp. Date Patent Type	Key Disclosures
	NO:51 via a linker, with additional specifications regarding pH, dosage range, and administration frequency. The claims apply to mammalian subjects, including humans.
11759504/ September 28, 2037 Drug Product	The patent discloses a pharmaceutical composition comprising a controlled-release parathyroid hormone (PTH) compound with a defined pharmacokinetic profile. Following subcutaneous administration, the composition achieves a peak-to-trough ratio of free PTH in plasma of less than 4 at steady state, with some claims specifying a ratio below 3. The compound includes a PTH moiety (SEQ ID NO:51) conjugated via a defined linker to a 40 kDa polyethylene glycol (PEG) carrier (Z), with a release half-life of at least 12 hours. The claims encompass delivery via injection or pen device, a range of pH values, and administration in both human and non-human primates.
11857603/ September 28, 2037 U-3982	This patent discloses methods for treating hypoparathyroidism in human patients using a controlled-release parathyroid hormone (PTH) compound with defined pharmacokinetic properties. The compound comprises a PTH moiety (SEQ ID NO:51) linked to a carrier via a specified linker (L2–L1), forming a composition that achieves a peak-to-trough plasma concentration ratio of less

US Patent/Exp. Date Patent Type	Key Disclosures
	than 4 at steady state, or less than 3 in certain claims. The PTH release half-life is at least 12 hours. The method involves administration at intervals of 24 hours or longer, delivered via subcutaneous injection or a pen device. The composition's pH is defined between 3 and 8, with narrower claims specifying a range of pH 4 to 5. Additional structural details are provided for the linker and the PEG-based carrier (Z).
11890326/ September 28, 2037 Drug Product	This patent further expands on the previously listed claims. It also covers both solid and liquid pharmaceutical compositions containing the conjugate, optionally formulated with water and having a pH between 4 and 6.
11918628 Drug Product	The patent also covers pharmaceutical compositions—both solid and liquid—containing the conjugate, with certain claims specifying a pH range of 4 to 6 and the use of water as the solvent in liquid formulations.

U-3982 – Treatment of hypoparathyroidism in adults.

Table 27: Orange Book patents for Zelsuvmi

US Patent/Exp. Date Patent Type	Key Disclosures
8282967/ May 30, 2026 Drug Substance	The patent discloses nitric oxide-releasing particles composed of a co-condensed silica network incorporating a pre-formed nitric oxide donor. The silica network is formed from methylaminopropyl trimethoxysilane (MAP3) and tetraethyl orthosilicate (TEOS). The claims cover the synthesis process, specific silane mixtures, particle size ranges, and MAP3 concentrations across various mol% ranges.
8956658/ May 30, 2026 Drug Substance	The patent discloses nitric oxide-releasing particles composed of a co-condensed silica network incorporating a pre-formed nitric oxide donor. The silica network is formed from methylaminopropyl trimethoxysilane (MAP3) and tetraethyl orthosilicate (TEOS). The claims cover the synthesis process, specific silane mixtures, particle size ranges, and MAP3 concentrations across various mol% ranges.
9289442/ July 3, 2032 Drug Product	The patent discloses an anhydrous topical pharmaceutical composition for treating dermatological conditions, including acne. The composition includes hydroxypropyl cellulose, ethyl

US Patent/Exp. Date Patent Type	Key Disclosures
U-3803	or isopropyl alcohol, hexylene glycol, cyclomethicone, and diazeniumdiolated co-condensed silica particles. The claims cover particle size, shelf life, and storage conditions.
9526738/ September 3, 2031 Drug Product	The patent discloses topical compositions comprising nitric oxide-releasing polysiloxane macromolecules formulated in either hydrophobic or hydrophilic gel bases. Hydrophobic bases include mineral oil, petrolatum, or silicone gel, while hydrophilic bases contain alcohols (e.g., isopropyl alcohol) and hydroxypropyl cellulose. The claims cover compositions with varying nitric oxide storage capacities, particle sizes, and stability profiles. These formulations may also include additional active agents and are intended for applications such as wound healing, burn treatment, and acne therapy.
9737561/ August 20, 2030 U-3802	The patent discloses a method for treating skin conditions by topically administering a composition containing nitric oxide-releasing polysiloxane macromolecules formulated in either a hydrophobic (mineral oil-based) or hydrophilic (alcohol-based) gel base. The method is used to reduce inflammation, modulate

US Patent/Exp. Date Patent Type	Key Disclosures
	cytokine activity, and treat inflammatory skin disorders such as impetigo, psoriasis, tinea pedis, and onychomycosis. The compositions also exhibit antimicrobial effects, including biofilm dispersion, inhibition of biofilm formation, and eradication of bacteria within established biofilms.
9855211/ February 27, 2034 Drug Product U-3800 U-3801	The patent discloses a dual-phase topical composition consisting of an aqueous buffered hydrogel and an anhydrous alcohol gel, combined in a defined ratio. The aqueous phase includes viscosity-enhancing agents, polyhydric alcohols, buffering agents, and water, while the anhydrous phase contains alcohols, humectants, and diazeniumdiolate-modified polysiloxane macromolecules. The claims specify acceptable pH ranges and controlled nitric oxide release rates. The patent also covers a kit with the two phases stored separately and a method of enhancing nitric oxide release by mixing and applying the phases to the skin.
10258564/ November 22, 2034 U-3797	The patent discloses a dual-phase topical composition for treating both inflammatory and noninflammatory skin lesions. The first phase is an aqueous hydrogel comprising viscosity-

US Patent/Exp. Date Patent Type	Key Disclosures
U-3798 U-3799	enhancing agents, polyhydric alcohols, buffering agents, and water. The second phase is an anhydrous formulation containing organic solvents, humectants, water-repellent agents, and a nitric oxide-releasing compound bearing a diazeniumdiolate functional group. The two compositions are stored separately and mixed prior to or during application. The claims define nitric oxide release parameters, therapeutic efficacy, pH ranges, ingredient concentrations, and nitric oxide content.
10265334/ July 3, 2032 Drug Product	The patent discloses an anhydrous topical composition consisting essentially of hydroxypropyl cellulose, ethanol or isopropyl alcohol, hexylene glycol, cyclomethicone, and a nitric oxide-releasing compound. The nitric oxide-releasing agent comprises diazeniumdiolated co-condensed silica particles and is present in concentrations ranging from 0.01% to 40% by weight. The claims specify defined concentration ranges for both the nitric oxide-releasing compound and hydroxypropyl cellulose, with variations in formulation depending on the use of ethanol or isopropyl alcohol as the solvent.
10322081/ July 10, 2035	The patent discloses a topical composition for the treatment and prevention of viral skin infections through the administration of

US Patent/Exp. Date Patent Type	Key Disclosures
U-3793 U-3794 U-3795 U-3796	a nitric oxide (NO)-releasing formulation. The composition includes NO-releasing co-condensed silica particles functionalized with diazeniumdiolate groups and is designed to maintain defined nitric oxide release kinetics over time. The claims specify compositional parameters such as pH and active ingredient concentration, and permit formulations in which components are combined either prior to or during application to the skin.
10376538/ August 20, 2030 Drug Product	The patent discloses nitric oxide-releasing topical compositions formulated in either hydrophobic (mineral oil-based) or hydrophilic (alcohol-based) gel bases. The claims encompass formulation parameters related to nitric oxide retention stability, particle size, and solvent characteristics. The compositions may include additional active agents such as anti-acne compounds, antimicrobials, benzoyl peroxide, and corticosteroids. Intended therapeutic applications include wound healing, burn treatment, and acne therapy.
10736839/ July 10, 2035 Drug Product	The patent discloses a topical composition for treating and preventing viral skin infections and reducing lesion size through the administration of a nitric oxide (NO)-releasing formulation.

US Patent/Exp. Date Patent Type	Key Disclosures
U-3790 U-3791 U-3792	The composition includes a NO-releasing active pharmaceutical ingredient selected from diazeniumdiolates, nitrosothiols, nitrosamines, hydroxyl nitrosamines, hydroxylamines, or hydroxyurea. The claims define nitric oxide release kinetics, specifying both continuous and cumulative NO release parameters.
11040006/ July 10, 2035 Drug Product U-3789	The patent discloses a delivery system for treating and preventing viral infections through a nitric oxide-releasing composition. The composition includes diazeniumdiolated co-condensed silica particles dispersed in water, with the nitric oxide-releasing active ingredient present within a defined weight range. The system is suitable for administration to mucosal surfaces or body cavities, enabling controlled and localized nitric oxide delivery with potential antiviral efficacy. The system is designed for delivery to mucous membranes or body cavities, including the nostrils, mouth, tongue, and pharynx. The patent defines NO-release kinetics and compositional variations, including co-condensed silica networks.
11285098/ February 28, 2034	The patent discloses a hydrogel composition with a defined pH range, specifically formulated without an active pharmaceutical

US Patent/Exp. Date Patent Type	Key Disclosures
Drug Product	ingredient (API). The hydrogel primarily comprises water, polyhydric alcohols (e.g., glycerin), viscosity-increasing agents (e.g., hydroxypropyl cellulose), and buffering agents to maintain pH stability. The composition may optionally include neutralizing agents and preservatives. The claims encompass both minimal formulations containing only essential components and more complex variants incorporating additional stabilizers to enhance shelf life and structural integrity.
11723858/ July 10, 2035 Drug Product U-3788	The patent discloses a delivery system for treating and preventing viral infections using a nitric oxide-releasing composition. The formulation comprises diazeniumdiolated co-condensed silica particles suspended in water, with defined parameters for nitric oxide release (Cmax) and pH. The active ingredient is present within a specified weight percentage range. The delivery system is designed for application to mucosal surfaces and body cavities, including the nostrils, mouth, tongue, and pharynx, enabling targeted and localized treatment.

U-3788: Method of administering a nitric oxide releasing active pharmaceutical ingredient to treat and/or prevent viral infection.

U-3789: Method of treating and/or preventing viral infection using a nitric oxide releasing active ingredient.

U-3790: Method of treating and/or preventing molluscum contagiosum with a nitric oxide releasing topical composition.

U-3791: Method of treating, preventing, or reducing lesions caused by molluscum contagiosum.

U-3792: Method of treating and/or preventing viral infection with a topical nitric oxide releasing component.

U-3793: Method of administering a nitric oxide releasing API in a combination topical composition.

U-3794: Method of treating and/or preventing viral infection with a topical composition including a nitric oxide releasing API.

U-3795: Method of treating and/or preventing molluscum contagiosum with a topical composition including a nitric oxide releasing API.

U-3796: Method of preventing and/or reducing appearance and/or size of malignant lesion with a topical composition including a nitric oxide releasing API.

U-3797: Method of topically reducing lesions with two separately stored components.

U-3798: Method of topically reducing lesions with two separately stored components where one component includes a nitric oxide releasing compound.

U-3799: Method of topically reducing lesions with two separately stored components where one component includes water.

U-3800: Method of applying released nitric oxide to skin from combination including anhydrous alcohol gel.

U-3801: Method of increasing release of nitric oxide from anhydrous alcohol gel.

U-3802: Method of treating skin ailment with nitric oxide releasing macromolecules and hydrophilic gel.

U-3803: Method of application of topical pharmaceutical composition to treat dermatological condition.

Table 28: Orange Book patents for Gomkeli

US Patent/Exp. Date Patent Type	Key Disclosures
11066358/ February 17, 2041 Drug Substance	This patent discloses a crystalline composition of essentially pure Form IV of N—((R)-2,3-dihydroxypropoxy)-3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-benzamide, characterized by its stability under standard storage conditions and a low level of a specific dimeric impurity (PF-00191189). The patent also claims pharmaceutical compositions containing this crystalline form, particularly for oral administration as tablets or capsules, and describes its therapeutic use in the treatment of tumors, cancers, and Rasopathy disorders.
11084780/ February 17, 2041 Drug Substance	This patent discloses multiple polymorphic crystalline forms and an amorphous form of N—((R)-2,3-dihydroxypropoxy)-3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-benzamide (mirdametinib), each distinguished by unique XRPD fingerprint peaks. It further describes specific synthetic methods for preparing the compound, as well as pharmaceutical compositions comprising the disclosed solid forms. The therapeutic use of these forms in treating tumors, cancers, and Rasopathy disorders is also included.

US Patent/Exp. Date Patent Type	Key Disclosures
11453641/ February 17, 2041 U-4130	This patent discloses methods of treating Neurofibromatosis using low-dose oral formulations (1–4 mg) of Form IV mirdametinib, identified by specific or representative XRPD patterns.
11806321/ February 17, 2041 U-4130	This patent discloses methods for treating tumors and NF1-associated plexiform neurofibromas using body surface area (BSA)-adjusted oral dosing of mirdametinib in both pediatric and adult patients. The claims include dosing strategies, clinical response criteria, diagnostic requirements, management of adverse events, and therapeutic selection based on objective response rates.
11806322/ March 16, 2043 U-4130	This patent discloses methods for treating NF1-associated inoperable plexiform neurofibromas using oral mirdametinib administered to achieve a targeted pharmacokinetic exposure ($AUC_{0–tau}$ < 300 ng·h/mL). The claims cover BSA-adjusted dosing, clinical and genetic diagnostic criteria, treatment response endpoints, adverse event management, and therapeutic selection based on objective response rates.
11819487/ February 17, 2041	This patent discloses methods for treating pediatric patients (ages 2–15) with NF1-associated inoperable

US Patent/Exp. Date Patent Type	Key Disclosures
U-4130	plexiform neurofibromas using body surface area–adjusted dosing of oral mirdametinib. The claims cover treatment schedules, diagnostic criteria, dose modifications in response to adverse events, response-based patient selection, and therapeutic outcomes such as tumor shrinkage and pain reduction.
11839595/ March 16, 2043 U-4130	This patent discloses methods of treating NF1-associated inoperable plexiform neurofibromas by administering oral mirdametinib, with a focus on limiting early pharmacokinetic exposure (Cmax ≤ 40 ng/mL). The claims include BSA-adjusted dosing, diagnostic criteria, adverse event management, and patient selection based on objective tumor response.
11883375/ March 16, 2043 U-4130	This patent discloses methods of treating NF1-associated inoperable plexiform neurofibromas in patients aged ≥2 years using oral mirdametinib, with an emphasis on achieving controlled pharmacokinetic exposure (AUC_{0}–tau < 300 or 400 ng·h/mL) on Day 1 and body surface area–adjusted dosing. The claims cover patient stratification, response-based outcomes, adverse event management, and lesion-specific clinical contexts.

US Patent/Exp. Date Patent Type	Key Disclosures
12011424/ February 17, 2041 U-4130	This patent discloses a method for treating NF1-associated inoperable plexiform neurofibromas in pediatric patients aged 2–10 years using 1 mg of mirdametinib administered twice daily. The claims emphasize specific clinical scenarios (e.g., symptomatic, progressive, or morbidity-associated PN), define relevant lesion types, and specify a cyclic dosing regimen.
12029711/ March 15, 2044 U-4130	This patent discloses oral dosage forms of mirdametinib with controlled particle size and defined pharmacokinetic parameters, including AUC and Cmax targets. The formulations—available as capsules, tablets, or dispersible tablets—are intended for treating NF1-associated plexiform neurofibromas and other tumors. The patent also includes body surface area–adjusted dosing regimens for pediatric and adult patients, detailing dosing bands, dosage forms, and treatment selection criteria based on objective response rates.
12037306/ February 17, 2041 U-4130	This patent discloses methods for treating neurofibromatosis type 1 (NF1) using orally administered crystalline Form IV mirdametinib at defined low doses (0.5–4 mg). The claims cover pharmaceutical

US Patent/Exp. Date Patent Type	Key Disclosures
	compositions, including capsules and tablets, with an emphasis on stringent impurity control—particularly targeting the dimeric impurity PF-0091189.
12220390/ March 16, 2043 U-4130	This patent discloses methods for treating NF1-associated inoperable plexiform neurofibromas in both pediatric and adult patients using oral mirdametinib. The claims emphasize pharmacokinetic targets ($AUC_{0–12h}$ < 300–400 ng·h/mL), relevant clinical and diagnostic criteria, and lesion characteristics. The treatment regimen features a 3-week-on, 1-week-off dosing cycle, permits dose reductions for adverse events, and supports treatment selection based on objective tumor response rates.
12257215/ March 16, 2043 U-4130	This patent discloses methods for treating NF1-associated inoperable plexiform neurofibromas using body surface area–adjusted oral mirdametinib dosing (2–3 mg BID). The claims address patients aged 2–15 and those ≥12 years, include clinical and genetic diagnostic criteria, and specify lesion types and treatment outcomes such as tumor shrinkage and pain reduction. The regimen follows a 3-week-on, 1-week-off cycle, allows dose adjustments for

US Patent/Exp. Date Patent Type	Key Disclosures
	adverse events, and supports therapeutic selection based on objective response rates.
12263146/ February 17, 2041 U-4130	This patent discloses methods for treating NF1-associated inoperable plexiform neurofibromas using body surface area (BSA)–adjusted dosing of oral mirdametinib (1–4 mg BID) in patients aged 2 years and older. The claims specify distinct BSA bands with corresponding doses and outline a framework for therapeutic selection based on objective response rates.

U-4130 - Treatment of adult and pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic plexiform neurofibromas (PN) not amenable to complete resection.

Table 29: Orange Book patents for Grafapex

US Patent/Exp. Date Patent Type	Key Disclosures
US 7199162/ October 12, 2025 U-4142	This patent discloses the use of treosulfan as a conditioning agent prior to allogeneic stem cell or bone marrow transplantation. It claims total doses ranging from 20 to 60 g/m² administered over 2 to 7 days, either by continuous infusion or daily doses. Treosulfan may be used alone or combined with agents such as fludarabine, cyclophosphamide, or immunosuppressive antibodies, and may also be administered alongside whole-body irradiation. The core claims focus on dosing ranges, administration methods, and combination therapies.

U-4142 - Administering treosulfan as a preparative regimen for allogeneic stem cell transplantation**.**

Table 30: Orange Book patents for Journavx

US Patent/Exp. Date Patent Type	Key Disclosures
11834441/December 04, 2040 Drug Substance Drug Product U-4125	This patent discloses a class of compounds featuring a substituted tetrahydrofuran-pyridine carboxamide scaffold, designed as sodium channel inhibitors with particular specificity for NaV1.8. The claims include a broad Markush formula encompassing structural diversity, specific stereoisomers, and numerous individual compounds bearing varied aryl substitutions such as difluoromethoxy, trifluoromethyl, methoxy, and chloro groups. The patent further protects pharmaceutically acceptable salts of these compounds, supporting their potential use in treating pain and related neurological disorders.

U-4125 – Treatment of moderate to severe acute pain in adults using suzetrigene.

Table 31: Orange Book patents for Romvimza

US Patent/Exp. Date Patent Type	Key Disclosures
9181223/March 14, 2034 Drug Substance Drug Product U-4145	This patent discloses a class of kinase inhibitor compounds that selectively target c-FMS (CSF-1R), c-KIT, and PDGFR, intended for treating cancer, autoimmune disorders, and metabolic bone diseases. The core claims define the structural framework and derivatives of these compounds, including specific examples. Additional claims cover pharmaceutical compositions, formulation additives, and therapeutic methods for a broad range of indications, with administration routes including oral, parenteral, inhalation, and subcutaneous delivery.
11103507/February 03, 2040 U-4145	This patent discloses methods for treating tenosynovial giant cell tumor (TGCT), including diffuse-type TGCT (DTGCT), and various solid and hematologic cancers using vimseltinib or a pharmaceutically acceptable salt thereof. The core claims focus on the oral administration of vimseltinib at therapeutically effective doses, specifying fixed-dose ranges and regimens that include defined loading and maintenance phases. Additional claims cover clinical outcomes such as improved tumor response, enhanced range of motion, and modulation of tumor-associated

US Patent/Exp. Date Patent Type	Key Disclosures
	macrophages, as well as treatment of tumors expressing CSF1R, CSF1, or IL-34. Some claims also include co-administration of vimseltinib with immunomodulatory or chemotherapeutic agents.
11679110/ February 03, 2040 U-4145	This patent discloses methods for treating tenosynovial giant cell tumor (TGCT), including diffuse-type TGCT (DTGCT) and other tumors associated with tumor-associated macrophages (TAMs), using vimseltinib or a pharmaceutically acceptable salt thereof. The core claims cover oral administration twice weekly at doses ranging from 2 mg to 60 mg, with specific emphasis on clinically relevant doses such as 14 mg, 20 mg, and 30 mg. Additional claims address treatment durations (e.g., 6 months or 1 year) and the use of vimseltinib to target tumors expressing CSF1R, CSF1, or IL-34, either within the tumor or its microenvironment.

U-4145 – Treatment of tenosynovial giant cell tumor

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About this book

Drug Monograph Digest offers curated insights into FDA- approved drugs from 2024–2025, sourced from authoritative public domains. Designed as a practical reference, it highlights key drug product attributes—such as dosage forms, dosing regimens, mechanisms of action, and regulatory designations.

With succinct summaries of drug product characteristics, pharmacokinetic data, clinical trial results, and patent and exclusivity summaries from the FDA's Orange Book, the digest delivers both scientific depth and business perspective. This time-saving guide is invaluable for pharmaceutical professionals, academicians, investors, and legal experts seeking a concise yet comprehensive overview of newly approved therapies.

About the author

Madhu Pudipeddi, PhD, is a pharmaceutical professional with over 25 years of industry experience. Specializing in drug development and Chemistry, Manufacturing, and Controls (CMC), he has authored numerous research articles and book chapters in the fields of formulation science and pharmaceutical development. He is currently Senior Vice President, Prelude Therapeutics, Wilmington, DE.

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