

RESEARCH MONOGRAPH . COMPOUND PROFILE

Danuglipron

An orally bioavailable benzimidazole-carboxylic acid developed at Pfizer as the first clinical-stage small-molecule full agonist of the human GLP-1 receptor, distinguished from peptidic GLP-1 receptor agonists by oral bioavailability without absorption enhancers and from other non-peptide candidates by a unique extracellular domain binding mode requiring the primate-specific tryptophan 33 residue.

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ABSTRACT

Danuglipron (PF-06882961) is an orally bioavailable, non-peptide, small-molecule full agonist of the human glucagon-like peptide-1 receptor (GLP-1R) discovered at Pfizer through a sensitized high-throughput screen of 2.8 million compounds and advanced through Phase 2b clinical development for type 2 diabetes mellitus and obesity before discontinuation in April 2025 following a single case of potential drug-induced liver injury in a dose-optimization study. The compound is a benzimidazole-6-carboxylic acid bearing a piperidine-linked pyridine with a 4-cyano-2-fluorobenzyloxy substituent and an (S)-oxetanylmethyl group (molecular formula C₃₁H₃₀FN₅O₄; molecular weight 555.61; CAS 2230198-02-2). Danuglipron activates the GLP-1R with nanomolar potency at cAMP accumulation and insulin secretion endpoints in cells expressing human or primate receptor, but is inactive at rodent GLP-1R owing to a species-specific binding pocket that requires tryptophan at position 33 of the receptor extracellular domain (Trp33ECD), a residue that is serine in mouse, rat, and rabbit. A cryogenic electron microscopy structure at 2.5 angstrom resolution (PDB 7S15) revealed that danuglipron binds at the orthosteric peptide-binding site but engages the extracellular domain in a distinct conformation in which the ECD rotates and Trp33 moves approximately 14 angstroms to close the top of the small-molecule binding pocket, a conformational rearrangement not observed with peptide agonists. The compound signals through canonical Gs-coupled cAMP production, beta-arrestin recruitment, and receptor internalization pathways in a manner broadly similar to the endogenous peptide GLP-1(7-36)amide, and is therefore classified

as an approximately unbiased full agonist at the receptor level, in contrast to the partial-agonist, Gs-biased profile of the competing small-molecule candidate orforglipron. Pharmacokinetics in humans are characterized by rapid oral absorption with minimal food effect, a terminal elimination half-life of approximately 5 to 6 hours supporting twice-daily dosing for the immediate-release formulation, hepatic clearance predominantly through CYP3A4-mediated oxidative metabolism, hepatic uptake via organic anion-transporting polypeptide transporters OATP1B1, OATP1B3, and OATP2B1, and negligible renal excretion of unchanged drug. In the Phase 1 multiple ascending-dose trial in 98 patients with type 2 diabetes (Saxena et al. 2021, Nature Medicine), danuglipron produced dose-dependent reductions in fasting and postprandial glucose with tolerability limited principally by gastrointestinal adverse events (nausea, vomiting, dyspepsia). In the Phase 2 randomized trial in 411 patients with type 2 diabetes (Saxena et al. 2023, JAMA Network Open), the 120 mg twice-daily dose produced a placebo-adjusted HbA1c reduction of 1.16 percentage points, a fasting plasma glucose reduction of 33.24 mg/dL, and clinically meaningful body weight reduction over 16 weeks. In the Phase 2b obesity trial (Buckeridge et al. 2025, Diabetes, Obesity and Metabolism), placebo-adjusted body weight reductions ranged from 5.0 to 12.9 percent at 26 to 32 weeks, with discontinuation rates exceeding 50 percent across all dose groups principally due to gastrointestinal adverse events. Pfizer discontinued twice-daily danuglipron development in December 2023 due to tolerability concerns and advanced a once-daily modified-release formulation that met pharmacokinetic objectives in dose-optimization studies; however, in April 2025, a single asymptomatic case of potential drug-induced liver injury in a dose-optimization study, combined with a comprehensive

portfolio review and regulatory input, led Pfizer to discontinue all danuglipron development. The compound is not approved in any jurisdiction. It is available as a research-grade preparation from multiple chemical suppliers and serves as a critical reference compound for the emerging class of non-peptide oral GLP-1R agonists.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Danuglipron (recommended; not yet formally adopted by the World Health Organization at the time of program discontinuation).

Development code: PF-06882961 (Pfizer). The development code is the canonical identifier in the medicinal chemistry and early clinical literature, including the seminal Griffith et al. (2022) Journal of Medicinal Chemistry disclosure and the Saxena et al. (2021) Phase 1 report in Nature Medicine [1, 2].

Chemical Abstracts Service registry number: 2230198-02-2 (free acid). The tris(hydroxymethyl)aminomethane (Tris) salt form has been used in some clinical formulations; the free acid is the reference form for research applications.

PubChem CID: 134611040.

ChEMBL identifier: ChEMBL4518483.

International Union of Pure and Applied Chemistry name: (S)-2-((4-(6-((4-cyano-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-1-(oxetan-2-ylmethyl)-1H-benzo[d]imidazole-6-carboxylic acid.

Protein Data Bank entry: 7S15 (GLP-1 receptor bound with danuglipron in complex with Gs heterotrimer, solved by cryogenic electron microscopy at 2.5 angstrom resolution) [1].

1.2 Structural class and chemistry

Danuglipron is a non-peptide, small-molecule agonist of the GLP-1 receptor. The structural class is best described as a benzimidazole-carboxylic acid bearing multiple heterocyclic and aryl substituents. The compound occupies a distinct chemical space from the peptidic GLP-1R agonists (semaglutide, liraglutide, tirzepatide, exenatide) and from the other clinical-stage small-molecule GLP-1R agonists (orforglipron, lotiglipron), which are based on different core scaffolds [3, 4].

Molecular formula: C₃₁H₃₀FN₅O₄ (free acid).

Exact mass: 555.2282 g/mol (monoisotopic).

Molecular weight: 555.61 g/mol (free acid).

Physical properties: The free acid is a white to off-white solid. Soluble in dimethyl sulfoxide; moderately soluble in methanol; sparingly soluble in water at neutral pH. The carboxylic acid moiety confers pH-dependent aqueous solubility with improved dissolution under basic conditions. The Tris salt form provides improved aqueous solubility for clinical formulations.

Stereochemistry: Danuglipron contains a single defined stereocenter at position 2 of the oxetane ring, specified as the (S)-configuration. The oxetanylmethyl group is attached to the N-1 nitrogen of the benzimidazole ring and was introduced during the medicinal chemistry optimization to reduce metabolic clearance while maintaining GLP-1R potency. Investigators acquiring research-grade danuglipron should confirm the correct (S)-enantiomer by chiral high-performance liquid chromatography or by optical rotation against a reference standard.

Key structural features: The molecule comprises five principal pharmacophoric elements: (a) a benzimidazole-6-carboxylic acid core that anchors hydrogen bonds within the GLP-1R transmembrane domain; (b) a piperidine linker connecting the core to the receptor extracellular domain-engaging substructure; (c) a pyridine ring at the 4-position of the piperidine; (d) a 4-cyano-2-fluorobenzyloxy group on the pyridine that extends into a hydrophobic cleft between the receptor ECD and extracellular loop 2; and (e) the (S)-oxetanylmethyl group on the benzimidazole nitrogen that modulates metabolic stability and physicochemical properties [1].

1.3 Synthesis

The published medicinal chemistry route to danuglipron proceeds through convergent synthesis of the benzimidazole, piperidine, and pyridine fragments followed by late-stage coupling [1]. The benzimidazole-6-carboxylic acid core is constructed from an appropriately substituted diaminobenzoic acid derivative by condensation with a suitable aldehyde or carbonyl equivalent. The piperidine ring is introduced by reductive amination or N-alkylation at the 2-position of the benzimidazole via a methylene linker. The pyridine fragment bearing the 4-cyano-2-fluorobenzyloxy substituent is prepared by nucleophilic aromatic substitution of a 2,6-dihalopyridine with the corresponding 4-cyano-2-fluorobenzyl alcohol, followed by Suzuki or other cross-coupling to introduce the piperidine. The (S)-oxetanylmethyl group is

installed by alkylation of the benzimidazole N-1 nitrogen with an enantiomerically pure oxetane-2-ylmethyl electrophile (mesylate or halide), with the (S)-stereochemistry established from a chiral pool precursor or by asymmetric synthesis.

The carboxylic acid moiety was a critical late-stage addition to the medicinal chemistry program: incorporation of the carboxylic acid provided substantial GLP-1R potency gains (approximately 100-fold) with improved off-target pharmacology and reduced metabolic clearance relative to earlier analogs lacking this group [1]. Industrial-scale synthesis has not been disclosed in published form. Research-grade material is supplied by multiple vendors at greater than 98 percent purity by HPLC.

2. Abstract

Danuglipron (PF-06882961) is an orally bioavailable, non-peptide, small-molecule full agonist of the human glucagon-like peptide-1 receptor (GLP-1R), discovered at Pfizer through a sensitized high-throughput screen and optimized through structure-guided medicinal chemistry to achieve nanomolar agonist potency at the human receptor with oral bioavailability in the absence of absorption enhancers [1, 2].

The compound represents a conceptual advance in GLP-1R pharmacology: the peptidic GLP-1R agonists (semaglutide, liraglutide, tirzepatide, exenatide, dulaglutide) have transformed the treatment of type 2 diabetes mellitus and obesity but require subcutaneous injection or, in the case of oral semaglutide (Rybelsus), co-formulation with the absorption enhancer sodium N-[8-(2-hydroxybenzoyl)aminocaprylate] (SNAC) and administration under strict fasting conditions. Danuglipron was designed to circumvent these limitations through a fully synthetic, orally bioavailable small molecule that activates the GLP-1R without injection or absorption enhancer.

The clinical development program produced dose-dependent glycemic efficacy (HbA1c reduction of up to 1.16 percentage points placebo-adjusted at 120 mg twice daily over 16 weeks in type 2 diabetes) and clinically meaningful weight loss (up to 12.9 percent placebo-adjusted at 32 weeks in obesity), but was limited by high rates of gastrointestinal adverse events (nausea in up to 73 percent, vomiting in up to 47 percent of treated participants) and by high discontinuation rates exceeding 50 percent across active dose groups [5, 6, 7]. Pfizer discontinued the twice-daily immediate-release formulation in December 2023 and advanced a once-daily modified-release formulation; however, a single case of potential drug-induced liver injury in a dose-optimization study, combined with a comprehensive portfolio review, led to full program discontinuation in April 2025 [8, 9].

The compound is not approved in any jurisdiction and is not in active commercial development. It is available as a research-grade preparation from multiple chemical suppliers and serves as a critical tool compound for GLP-1R structural biology, for understanding small-molecule agonism at class B1 G protein-coupled re-

ceptors, and as a benchmark for the emerging class of non-peptide oral GLP-1R agonists including orforglipron (Eli Lilly), which remains in active Phase 3 development [10, 11].

3. Discovery and Development History

3.1 Origin and high-throughput screening

Danuglipron was discovered at Pfizer Worldwide Research, Development and Medical in Cambridge, Massachusetts, and Groton, Connecticut, as part of a program to identify orally bioavailable, non-peptide agonists of the GLP-1 receptor. The GLP-1R is a class B1 (secretin family) G protein-coupled receptor with a large extracellular domain that normally binds the 30-amino-acid peptide GLP-1(7-36)amide. The identification of small-molecule agonists for class B1 GPCRs is a recognized challenge in medicinal chemistry owing to the large, shallow, peptide-binding cleft that is poorly suited to conventional drug-like small molecules [1].

The Pfizer team employed a sensitized high-throughput screen in which the positive allosteric modulator 4-(3-benzyloxyphenyl)-2-ethylsulfinyl-6-(trifluoromethyl)pyrimidine (BETP) was used to amplify the signal from weak agonists in a cAMP accumulation assay, thereby lowering the detection threshold for low-potency hits. From a library of approximately 2.8 million compounds, the screen identified hits at a rate of 0.013 percent, yielding a series of 5-fluoropyrimidine-based GLP-1R agonists with weak (micromolar) potency [1].

3.2 Medicinal chemistry optimization

Iterative structure-activity relationship optimization of the initial hit series proceeded through several stages. The replacement of the pyrimidine core with a benzimidazole scaffold provided improved potency and metabolic stability. Optimization of the substituent on the benzimidazole nitrogen (ultimately the (S)-oxetanylmethyl group) improved metabolic clearance without detriment to receptor potency. The critical breakthrough was the incorporation of a carboxylic acid at the 6-position of the benzimidazole, which provided approximately 100-fold gains in GLP-1R agonist potency with improved off-target selectivity and reduced CYP inhibition [1].

The final compound, designated PF-06882961 (danuglipron), achieved nanomolar potency in cAMP accumulation assays at the human GLP-1R (EC₅₀ approximately 1 to 10 nM depending on cell line and assay configuration), full agonist intrinsic ac-

tivity relative to GLP-1(7-36)amide, oral bioavailability in nonhuman primates, and an adequate safety margin in repeat-dose rat and cynomolgus monkey toxicology studies to support advancement to human clinical testing [1].

3.3 Structural biology

A cryogenic electron microscopy (cryo-EM) structure of danuglipron bound to the GLP-1R in complex with the heterotrimeric Gs protein was solved at 2.5 angstrom resolution and deposited as PDB entry 7S15 [1]. The structure revealed that danuglipron binds at the orthosteric site occupied by the N-terminal residues of GLP-1 peptide agonists but induces a distinct conformational rearrangement in which the receptor ECD rotates relative to the peptide-bound state and the Trp33 residue of the ECD side chain moves approximately 14 angstroms to cap the top of the small-molecule binding pocket. This conformational closure creates a hydrophobic lid over the binding site that is stabilized by pi-stacking interactions between Trp33 and the fluoropyridine and benzimidazole aromatic systems of danuglipron. In rodent GLP-1R, position 33 is serine rather than tryptophan, which cannot form the required pi-stacking interactions and cannot close the binding pocket, explaining the complete absence of danuglipron activity at rodent receptor [1].

3.4 Clinical development timeline

Phase 1 (2018 to 2020): A randomized, placebo-controlled, multiple ascending-dose trial (NCT03538743) enrolled 98 patients with type 2 diabetes and evaluated danuglipron at doses of 0.5 to 300 mg twice daily for 28 days. Results were published by Saxena et al. in *Nature Medicine* in June 2021 [2].

Phase 2 (2020 to 2022): A 16-week, randomized, double-blind, placebo-controlled trial (NCT04707313) in 411 patients with type 2 diabetes evaluated target doses of 2.5, 10, 40, 80, and 120 mg twice daily. Results were published by Saxena et al. in *JAMA Network Open* in May 2023 [5].

Phase 2 dose-escalation (2021 to 2022): A parallel 12-week Phase 2 study compared different dose-escalation schemes (starting dose 5 vs. 10 mg twice daily; escalation steps of 1 vs. 2 weeks) targeting 80, 120, and 200 mg twice daily. Results were published by Saxena et al. in *Diabetes, Obesity and Metabolism* in 2023 [6].

Phase 1 Japan (2021 to 2022): A Phase 1 study in Japanese adults with type 2 diabetes was published by Ono et al. in *Diabetes, Obesity and Metabolism* in 2023, confirming comparable pharmacokinetics and pharmacodynamics in the Japanese population [12].

Phase 2b obesity (2022 to 2023): A randomized, placebo-controlled, dose-ranging Phase 2b study in adults with obesity (without diabetes) evaluated multiple danuglipron doses twice daily for 26 or 32 weeks. Pfizer announced topline results in December 2023; full results were published by Buckeridge et al. in *Diabetes, Obesity and Metabolism* in 2025 [7].

December 2023: Pfizer discontinued the twice-daily immediate-release formulation based on high discontinuation rates (exceeding 50 percent) in the Phase 2b obesity trial and pivoted to a once-daily modified-release formulation [8].

July 2024: Pfizer reported that dose-optimization studies of the once-daily modified-release formulation met key pharmacokinetic objectives and confirmed a formulation with the potential to deliver a competitive efficacy and tolerability profile [8].

April 2025: Pfizer announced discontinuation of all danuglipron development following a single case of potential drug-induced liver injury in a dose-optimization study, after review of the totality of clinical data and regulatory input [9].

4. Mechanism of Action

Danuglipron is a full agonist of the human glucagon-like peptide-1 receptor. Its molecular mechanism is characterized by orthosteric binding at the peptide-binding site of the GLP-1R with engagement of the receptor extracellular domain, canonical Gs-coupled signaling, and species-selective activity restricted to primate GLP-1R.

4.1 GLP-1 receptor pharmacology

The GLP-1 receptor is a class B1 (secretin family) G protein-coupled receptor expressed on pancreatic beta cells, pancreatic alpha cells, the gastrointestinal tract (enteroendocrine L cells, gastric parietal cells, enteric neurons), the central nervous system (hypothalamic arcuate and paraventricular nuclei, nucleus tractus solitarius, area postrema, mesolimbic dopamine circuits), the heart, and the kidney. The receptor is the physiological target of the incretin hormone GLP-1(7-36)amide, which is secreted by intestinal L cells in response to nutrient ingestion and mediates glucose-dependent insulin secretion, glucagon suppression, gastric emptying delay, and central satiety signaling [13, 14].

The receptor comprises a large N-terminal extracellular domain (ECD) of approximately 120 amino acids that makes initial contact with the C-terminal alpha-helix of GLP-1 peptide, and a seven-transmembrane domain (TMD) bundle that engages the N-terminal residues of the peptide and transduces the activation signal to the intracellular Gs heterotrimer. This two-step "trap and trigger" binding mechanism, in which the ECD captures the peptide and the TMD activates signaling, has been a barrier to small-molecule agonist discovery because the peptide-binding cleft spans both domains and covers a large surface area [13].

4.2 Danuglipron binding mode

Danuglipron binds at the orthosteric site in the TMD but also makes critical contacts with the ECD, specifically through the Trp33 residue [1]. The cryo-EM structure (PDB 7S15) shows that the benzimidazole-carboxylic acid core of danuglipron is positioned within the TMD cavity at a site overlapping the binding position of the N-terminal residues (His7 to Glu15) of GLP-1 peptide. The carboxylic acid forms hy-

drogen bonds with residues in transmembrane helices 1, 2, and 7 and with extracellular loop 2. The piperidine linker projects upward from the TMD cavity into the junction between the TMD and ECD. The pyridine and 4-cyano-2-fluorobenzyloxy groups extend into a hydrophobic cleft between the ECD and extracellular loop 2, where they are capped by the indole side chain of Trp33, which has moved approximately 14 angstroms from its position in the peptide-bound structure to close the top of the small-molecule binding pocket [1].

This conformational rearrangement is unique to the small-molecule binding mode. In the peptide-bound GLP-1R structures, Trp33 is oriented away from the binding cleft and does not participate in ligand engagement. In the danuglipron-bound structure, the ECD has rotated slightly relative to the peptide-bound conformation, and Trp33 has swung into the binding site to form pi-stacking interactions with the aromatic systems of danuglipron. The requirement for this tryptophan residue explains the species selectivity: position 33 is tryptophan in human and nonhuman primate GLP-1R but serine in mouse, rat, rabbit, and dog GLP-1R. Serine cannot provide the pi-stacking interaction, and accordingly danuglipron shows no agonist activity at rodent GLP-1R in cAMP or insulin secretion assays [1].

4.3 Signal transduction

Danuglipron activates the canonical Gs-cAMP-protein kinase A signaling cascade with full agonist efficacy relative to GLP-1(7-36)amide. In addition, danuglipron promotes beta-arrestin 1 and beta-arrestin 2 recruitment to the GLP-1R and receptor internalization, consistent with the profile of an approximately unbiased agonist at the receptor level [1]. This signaling profile contrasts with the competing small-molecule agonist orforglipron (LY3502970), which is a partial agonist with strong Gs bias (high cAMP potency relative to minimal beta-arrestin recruitment), a pharmacological distinction that has implications for receptor desensitization, tachyphylaxis, and the gastrointestinal adverse-event profile [10, 11].

The downstream consequences of GLP-1R activation in pancreatic beta cells include glucose-dependent insulin secretion (through cAMP-mediated closure of ATP-sensitive potassium channels, calcium influx, and insulin granule exocytosis), beta-cell survival and proliferation (through CREB, IRS-2, and PI3K-Akt signaling), and suppression of glucagon secretion from alpha cells. In the central nervous system, GLP-1R activation in the arcuate nucleus and nucleus tractus solitarius produces anorexia and reduced food intake, which underlies the weight loss effect. In

the gastrointestinal tract, GLP-1R activation delays gastric emptying, which contributes to both the postprandial glucose-lowering effect and the nausea and vomiting adverse events [13, 14].

4.4 Composite pharmacology and selectivity

Danuglipron is highly selective for the GLP-1R over the related class B1 GPCRs: the glucagon receptor (GCGR), the glucose-dependent insulinotropic polypeptide receptor (GIPR), and the GLP-2 receptor. No agonist activity has been reported at these receptors at concentrations up to 10 micromolar. The compound was profiled against a broad panel of off-target receptors, ion channels, and enzymes during the medicinal chemistry optimization; the carboxylic acid moiety substantially improved the off-target selectivity profile relative to earlier analogs in the series, including reduced hERG channel inhibition [1].

The selectivity for primate over rodent GLP-1R is absolute at pharmacologically relevant concentrations, a property that distinguishes danuglipron from both the peptidic GLP-1R agonists (which are active across mammalian species) and from orforglipron (which also shows species selectivity but through a different binding pocket that does not involve Trp33) [1, 10].

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Danuglipron is absorbed from the gastrointestinal tract after oral administration without requirement for absorption enhancers or fasting conditions. Food intake has minimal impact on absorption, resulting in comparable area under the curve (AUC) and peak concentration (C_{max}) values in fed versus fasted states [2, 12]. This is a significant practical advantage over oral semaglutide (Rybelsus), which requires administration 30 minutes before the first food, beverage, or other oral medication of the day with no more than 4 ounces of plain water.

Time to peak plasma concentration (T_{max}) after oral administration of the immediate-release formulation is approximately 1.5 to 3 hours. Oral bioavailability has not been reported as an absolute value in published human studies but is sufficient to achieve pharmacologically active plasma concentrations at the studied oral doses (2.5 to 300 mg twice daily) [2].

5.2 Distribution

Distribution characteristics have been determined in preclinical species and in human clinical studies. The compound shows adequate distribution to target tissues including pancreas and central nervous system. Plasma protein binding has not been reported in a published human study; preclinical data in rat and monkey suggest moderate protein binding. The relatively short half-life (5 to 6 hours) suggests moderate tissue distribution without extensive accumulation.

5.3 Metabolism

Danuglipron is metabolized predominantly in the liver through cytochrome P450-mediated oxidative pathways. The principal CYP isoform responsible for the primary oxidative metabolism is CYP3A4, with contributions from CYP3A5 and other minor CYP isoforms [15]. Non-CYP-mediated metabolism and conjugation path-

ways (glucuronidation) contribute to total clearance. Key biotransformations include hydroxylation, O-dealkylation, oxetane ring hydrolysis followed by acetylation and methylation [15].

The in vitro half-life in human liver microsomes is 208 plus or minus 31 minutes, and in rat liver microsomes 81 plus or minus 16 minutes, indicating moderate hepatic extraction across species [1].

Hepatic uptake of danuglipron is mediated by organic anion-transporting polypeptide (OATP) transporters, specifically OATP1B1, OATP1B3, and OATP2B1 [15]. This transporter-mediated hepatic uptake contributes to the first-pass extraction and has implications for drug-drug interactions with OATP inhibitors (cyclosporine, rifampin single-dose, gemfibrozil).

5.4 Elimination

The terminal elimination half-life of danuglipron is approximately 5 to 6 hours at steady state for the immediate-release formulation, supporting twice-daily dosing to maintain therapeutic plasma concentrations throughout the dosing interval [2, 12]. Renal excretion is negligible, with less than 0.1 percent of unchanged drug recovered in urine [16]. Elimination is therefore predominantly metabolic (hepatic biotransformation) rather than renal clearance.

A renal impairment study published by Fediuk et al. (2024) confirmed that renal impairment does not meaningfully alter danuglipron pharmacokinetics, consistent with the predominantly hepatic elimination [16].

5.5 Routes of administration

The only route studied in humans is oral administration. Two formulation strategies were pursued:

Immediate-release (IR) formulation: Administered twice daily without food restriction. This was the formulation used in all Phase 1 and Phase 2 clinical trials. The short half-life of approximately 5 to 6 hours necessitated twice-daily dosing, which contributed to the gastrointestinal adverse-event burden through high peak-to-trough concentration fluctuation.

Modified-release (MR) formulation: A once-daily modified-release formulation was developed to reduce peak-to-trough plasma concentration fluctuation, extend the dosing interval to once daily, and potentially improve gastrointestinal tolerability by reducing C_{max}-driven nausea and vomiting. Pfizer reported in July 2024 that the MR formulation met key pharmacokinetic objectives in dose-optimization studies, confirming a profile supportive of once-daily dosing [8].

5.6 Special populations

Japanese population: The Ono et al. (2023) Phase 1 study in Japanese adults with type 2 diabetes confirmed comparable pharmacokinetics and pharmacodynamics to the global Phase 1 population, with no clinically meaningful differences in exposure or tolerability [12].

Renal impairment: Danuglipron pharmacokinetics are not meaningfully altered in participants with mild, moderate, or severe renal impairment, consistent with negligible renal clearance of unchanged drug [16].

Hepatic impairment: No published study of danuglipron pharmacokinetics in hepatic impairment is available. Given the predominantly hepatic metabolism, reduced clearance in severe hepatic impairment would be expected, and the single case of potential drug-induced liver injury in clinical development underscores the importance of hepatic monitoring in any future research application.

6. Preclinical Pharmacology

6.1 Species selectivity and the Trp33 requirement

The defining preclinical characteristic of danuglipron is its absolute species selectivity for primate GLP-1R. In cAMP accumulation assays using cells expressing human, cynomolgus monkey, mouse, rat, and rabbit GLP-1R, danuglipron activated human and cynomolgus monkey receptors with nanomolar potency but showed no agonist activity at mouse, rat, or rabbit receptors at concentrations up to 10 micromolar [1].

Site-directed mutagenesis of the human GLP-1R confirmed that the Trp33Ser mutation (converting the human residue to the rodent residue) abolished danuglipron activity, while the reciprocal Ser33Trp mutation in the mouse GLP-1R conferred danuglipron sensitivity. This unambiguously identified Trp33 as the molecular determinant of species selectivity [1].

The species selectivity has profound implications for preclinical pharmacology: standard rodent models of type 2 diabetes and obesity (db/db mouse, ob/ob mouse, Zucker diabetic fatty rat, diet-induced obese mouse) cannot be used to evaluate danuglipron efficacy. Preclinical efficacy studies required either nonhuman primate models or humanized mouse models expressing human GLP-1R.

6.2 Nonhuman primate studies

Pharmacokinetic studies in male cynomolgus monkeys demonstrated oral bioavailability of 5 to 9 percent, sufficient to achieve pharmacologically active plasma concentrations [1]. Repeat-dose toxicology studies in cynomolgus monkeys at multiples of the projected human dose established adequate safety margins. Danuglipron promoted insulin secretion during glucose tolerance tests in cynomolgus monkeys, confirming in vivo engagement of the primate GLP-1R and glucose-dependent insulinotropic activity [1].

6.3 Rodent pharmacokinetic studies

Pharmacokinetic parameters were determined in male Wistar rats after intravenous and oral administration to characterize absorption, distribution, metabolism, and excretion, notwithstanding the absence of GLP-1R pharmacological activity in this species. The in vitro half-life in rat liver microsomes was 81 plus or minus 16 minutes [1].

6.4 Humanized GLP-1R mouse models

Genetically engineered mouse models expressing human GLP-1R in place of the native mouse receptor have been developed to enable preclinical pharmacology testing of species-selective compounds including danuglipron [17]. These humanized models have demonstrated that danuglipron produces glucose-lowering and weight-reducing effects comparable to injectable GLP-1R agonists when tested in the humanized mouse background, validating the species-selectivity mechanism and providing a platform for preclinical dose-response characterization [17].

6.5 Safety pharmacology

In vitro safety pharmacology studies demonstrated that the carboxylic acid moiety in danuglipron substantially reduced hERG potassium channel inhibition relative to earlier analogs in the medicinal chemistry series, providing an acceptable cardiac safety margin [1]. Cardiovascular safety pharmacology in cynomolgus monkeys demonstrated dose-dependent heart rate increases consistent with the GLP-1R agonist class effect, without clinically significant arrhythmias or QT prolongation at exposures exceeding the projected human therapeutic range.

Repeat-dose toxicology studies in rats identified thyroid C-cell hyperplasia at supratherapeutic exposures, a class effect of GLP-1R agonists in rodents driven by species-specific GLP-1R expression on thyroid C-cells. This finding is not directly relevant to danuglipron's pharmacology in rodents (given its inactivity at rodent GLP-1R) and likely reflects off-target activity at high concentrations or represents a conservatively interpreted histopathological finding. The C-cell finding has not been confirmed in primates at clinical exposures [1].

No hepatotoxicity signal was identified in preclinical toxicology studies at the exposures tested, and the drug-induced liver injury observed in clinical development represents a species-discordant or exposure-dependent finding that emerged

only in human studies [9].

7. Clinical Evidence Base

7.1 Phase 1 multiple ascending-dose trial in type 2 diabetes

The pivotal Phase 1 study (NCT03538743) was a randomized, double-blind, placebo-controlled, multiple ascending-dose trial published by Saxena et al. in *Nature Medicine* in June 2021 [2]. The trial enrolled 98 patients with type 2 diabetes mellitus (mean HbA1c approximately 7 to 9 percent; mean BMI approximately 30 to 35; on stable metformin background therapy or treatment-naïve) and randomized them to placebo or danuglipron at doses of 0.5 to 300 mg twice daily for 28 days across eight dose cohorts.

Glycemic endpoints: Danuglipron produced dose-dependent reductions in fasting plasma glucose, postprandial glucose (measured by mixed-meal tolerance test), and HbA1c. The highest tolerated doses (120 to 300 mg twice daily) produced fasting glucose reductions comparable to those observed with injectable GLP-1R agonists at therapeutic doses.

Pharmacodynamic endpoints: Heart rate modestly increased with danuglipron treatment at day 28, consistent with the class effect of GLP-1R agonists. Systolic blood pressure was slightly decreased. Changes in diastolic blood pressure were similar to placebo.

Safety: Most adverse events were mild. The most commonly reported events were nausea, dyspepsia, and vomiting, consistent with the GLP-1R agonist class. There were no clinically meaningful adverse events in laboratory values. No heart-rate-related adverse events were reported [2].

7.2 Phase 2 glycemic control trial in type 2 diabetes

The Phase 2 randomized clinical trial (NCT04707313) was published by Saxena et al. in *JAMA Network Open* in May 2023 [5]. The trial enrolled 411 participants with type 2 diabetes (mean age 58.6 years; 51 percent male; mean HbA1c 8.07 percent; mean BMI 32.8) and randomized them to placebo or danuglipron at target doses of 2.5, 10, 40, 80, or 120 mg twice daily for 16 weeks, with dose escalation over the first 4 to 8 weeks.

HbA1c: All danuglipron groups showed statistically significant dose-responsive reductions in HbA1c at week 16 compared with placebo. The 120 mg twice-daily group achieved a placebo-adjusted least-squares mean HbA1c reduction of 1.16 percentage points (90 percent CI, 0.86 to 1.47). The 80 mg twice-daily group achieved a placebo-adjusted reduction of approximately 0.94 percentage points. The dose-response was approximately log-linear across the studied range [5].

Fasting plasma glucose: The 120 mg twice-daily group achieved a placebo-adjusted least-squares mean fasting plasma glucose reduction of 33.24 mg/dL (90 percent CI, 20.84 to 45.63). Lower doses produced proportionally smaller reductions [5].

Body weight: Clinically meaningful body weight reductions were observed at doses of 80 mg and above. The 120 mg twice-daily group achieved a placebo-adjusted body weight reduction of 4.17 kg over 16 weeks [5].

Safety: The adverse-event profile was consistent with Phase 1 findings. Gastrointestinal events (nausea, vomiting, diarrhea, dyspepsia) were the most common and were dose-dependent. No clinically significant hepatic, renal, or cardiac safety signals were identified.

7.3 Phase 2 dose-escalation scheme comparison

A parallel Phase 2 study published by Saxena et al. in *Diabetes, Obesity and Metabolism* in 2023 compared different dose-escalation strategies targeting 80, 120, and 200 mg twice daily [6]. Starting doses of 5 mg versus 10 mg twice daily and escalation intervals of 1 week versus 2 weeks were evaluated.

Key finding: Gastrointestinal adverse events were primarily related to the target dose (80 to 200 mg twice daily) rather than the starting dose. Two-week escalation steps compared with one-week steps modestly improved tolerability during the titration phase. However, even with optimized escalation, gastrointestinal adverse events remained the principal tolerability limitation at target doses above 80 mg twice daily.

7.4 Phase 2b obesity trial

The Phase 2b obesity study was a randomized, double-blind, placebo-controlled, dose-ranging trial in 628 adults with obesity (BMI 30 or greater, or BMI 27 or greater with at least one weight-related comorbidity) without diabetes [7]. Participants were randomized to danuglipron at target doses of 40 to 200 mg twice daily (with 1-, 2-, or 4-week escalation intervals) or placebo for 26 or 32 weeks. Topline results were announced by Pfizer in December 2023; the full publication by Buckeridge et al. appeared in Diabetes, Obesity and Metabolism in 2025.

Weight loss: All danuglipron groups demonstrated statistically significant placebo-adjusted weight reductions. Least-squares mean percentage decreases ranged from 5.0 to 12.9 percent relative to placebo depending on dose and treatment duration. The highest dose groups achieved placebo-adjusted weight reductions of 8 to 13 percent at 32 weeks [7].

Tolerability: The most frequently reported events were nausea (up to 73 percent) and vomiting (up to 47 percent). Discontinuation rates exceeded 50 percent across all active dose groups, compared with approximately 40 percent in the placebo group. Only 39.3 percent of randomized participants completed treatment. Approximately 38 percent of participants discontinued treatment specifically because of adverse events [7].

Safety: No new safety signals were identified beyond gastrointestinal intolerance. No participants met criteria for drug-induced liver injury in this study. The overall adverse-event profile was consistent with GLP-1R agonism.

7.5 Development discontinuation

In December 2023, Pfizer discontinued the twice-daily immediate-release formulation based on the unacceptable discontinuation rates in the Phase 2b obesity trial and pivoted to a once-daily modified-release formulation designed to reduce C_{max} and improve gastrointestinal tolerability [8].

In July 2024, Pfizer reported that dose-optimization studies of the once-daily modified-release formulation met key pharmacokinetic objectives, confirming a formulation with the potential to deliver a competitive efficacy and tolerability profile in Phase 3 [8].

In April 2025, Pfizer announced discontinuation of all danuglipron development [9]. The discontinuation followed a comprehensive review of the totality of clinical data, including the identification of a single asymptomatic case of potential drug-induced liver injury (DILI) in a dose-optimization study. The participant's liver enzyme elevations resolved after discontinuation of danuglipron. While the overall frequency of liver enzyme elevations across the 1,400-participant danuglipron safety database was in line with approved GLP-1R agonists, the potential DILI case, combined with recent regulatory input and a broader portfolio review, led Pfizer to discontinue the molecule. The discontinuation also followed the earlier discontinuation of Pfizer's other oral GLP-1R agonist, lotiglipron (PF-07081532), which had been terminated due to hepatotoxicity, establishing hepatic safety as a recurring concern in Pfizer's small-molecule GLP-1R agonist program [9, 18].

8. Sourcing and Quality Verification

Research-grade danuglipron (free acid, CAS 2230198-02-2) is supplied by multiple chemical and pharmaceutical research suppliers including MedChemExpress, Selleck Chemicals, Cayman Chemical, BOC Sciences, Tocris, InvivoChem, MedKoo Biosciences, and others. Material is typically supplied at greater than 98 percent purity by HPLC, in milligram quantities as a solid powder. The Tris salt form is also available from selected vendors. Pricing is moderate, in the range of \$100 to \$500 per 10 mg of research-grade material at the time of monograph preparation.

No pharmaceutical-grade formulation is commercially available, as the compound was never approved for clinical use. Investigators requiring larger quantities for in vivo studies in humanized GLP-1R mouse models or in nonhuman primate studies should contact suppliers for custom synthesis at the gram scale.

Investigators should confirm compound identity and purity on every research-grade lot through:

- High-performance liquid chromatography area-percent purity, ideally greater than 98 percent
- Mass spectrometry confirmation of molecular weight (556.2360 for the protonated free acid $[M+H]^+$, or 555.2282 monoisotopic for the neutral species)
- Chiral HPLC or optical rotation confirmation of the correct (S)-oxetane stereochemistry
- Nuclear magnetic resonance spectroscopy (1H and ^{13}C) for structural confirmation against published spectra
- Karl Fischer or loss-on-drying analysis for residual water content
- Residual solvent analysis (gas chromatography) for common synthesis solvents

Third-party analytical laboratories (Janoshik Analytical, Anabolic Lab, others) provide independent confirmation of vendor certificates of analysis. The research-grade danuglipron market is relatively new (compound disclosed in 2022), and investigators should verify that supplied material is the correct (S)-enantiomer and the free acid rather than an alternative salt form unless the salt form is specifically required.

9. Reconstitution and Handling

Danuglipron free acid is sparingly soluble in water at neutral pH. For in vitro research applications, the compound is typically dissolved in dimethyl sulfoxide (DMSO) at concentrations of 10 to 100 mM to prepare stock solutions, which are then diluted into aqueous assay buffer at the desired final concentration with DMSO content maintained below 0.1 to 1 percent (v/v) to avoid solvent effects on cellular assays.

For in vivo research applications in nonhuman primates or humanized GLP-1R mouse models, the compound can be formulated in standard oral vehicles: 0.5 percent methylcellulose in water, polyethylene glycol 400 with Tween 80 and water, or other standard suspending vehicles. The carboxylic acid moiety allows pH-adjusted solutions (pH 7 to 8 with sodium hydroxide or Tris buffer) to improve aqueous solubility for parenteral formulations if required, though oral administration is the physiologically relevant route.

Storage of the solid should be at -20 degrees Celsius in a sealed container with desiccant. DMSO stock solutions should be stored at -20 degrees Celsius and are stable for at least 6 months under these conditions. Aliquoting of stock solutions for single-use is recommended to avoid repeated freeze-thaw cycles.

Aqueous solutions at neutral pH have limited stability owing to the sparingly soluble character of the free acid; solutions should be prepared fresh for each experiment or stored at 2 to 8 degrees Celsius and used within 7 days if stability testing has not been performed on the specific formulation.

The compound is not classified as hazardous under standard laboratory chemical safety classifications. Standard personal protective equipment (laboratory coat, gloves, safety glasses) is appropriate. The compound is pharmacologically active at low concentrations; investigators should exercise care to avoid inadvertent oral or dermal exposure.

10. Stack Interactions and Combinations

Danuglipron interacts with several drug and compound classes through its CYP3A4-mediated metabolism, its OATP transporter-mediated hepatic uptake, and its GLP-1R agonist pharmacology. Investigators conducting research with danuglipron should consider the following interaction categories:

CYP3A4 inhibitors: Strong CYP3A4 inhibitors (ketoconazole, itraconazole, ritonavir, cobicistat, clarithromycin, grapefruit juice) are expected to substantially increase danuglipron plasma concentrations through inhibition of the principal metabolic clearance pathway. Concurrent use should be considered for dose reduction in research protocols. Moderate CYP3A4 inhibitors (erythromycin, diltiazem, verapamil, fluconazole) may produce smaller but measurable effects.

CYP3A4 inducers: Strong inducers (rifampin, carbamazepine, phenytoin, phenobarbital, St. John's wort) are expected to substantially reduce danuglipron exposure through increased metabolic clearance. Concurrent dosing may compromise efficacy in dose-response research.

OATP inhibitors: Compounds that inhibit OATP1B1, OATP1B3, or OATP2B1 (cyclosporine, rifampin at single dose, gemfibrozil) may alter danuglipron hepatic uptake and thereby alter systemic exposure. The direction and magnitude of the interaction depend on whether the predominant effect is reduced hepatic clearance (increasing systemic exposure) or reduced hepatic delivery to the metabolizing enzymes.

Other GLP-1R agonists: Concurrent use with injectable GLP-1R agonists (semaglutide, liraglutide, tirzepatide, exenatide, dulaglutide) is pharmacologically redundant for the GLP-1R agonist effect and would produce additive gastrointestinal adverse events. The combination is not recommended in clinical or research applications.

Insulin and insulin secretagogues: Concurrent GLP-1R agonism with exogenous insulin or with sulfonylureas (glipizide, glyburide, glimepiride) increases hypoglycemia risk. The glucose-dependent nature of GLP-1R-mediated insulin secretion

mitigates but does not eliminate this risk. Dose reduction of the insulin or sulfonylurea may be required.

Gastric emptying-sensitive drugs: GLP-1R agonism delays gastric emptying, which can alter the absorption kinetics of concurrently administered oral medications. Compounds with narrow therapeutic indices or strong dependence on rapid absorption (warfarin, levothyroxine, oral contraceptives, narrow-therapeutic-index antibiotics) should be administered with attention to potential altered absorption.

QT-prolonging agents: GLP-1R agonists as a class produce modest heart rate increases (approximately 2 to 4 beats per minute) but are not associated with QT prolongation. Danuglipron has not shown QT-prolonging activity in clinical studies. However, investigators combining danuglipron with known QT-prolonging agents should monitor electrocardiographic endpoints as a precautionary measure.

Metformin: Concurrent metformin was the background therapy in the Phase 1 and Phase 2 type 2 diabetes studies. No pharmacokinetic interaction between danuglipron and metformin has been reported; the combination produces additive glycemic efficacy through complementary mechanisms (GLP-1R agonism and AMPK activation/hepatic gluconeogenesis suppression) [2, 5].

Hepatotoxic agents: Given the potential drug-induced liver injury signal, co-administration with known hepatotoxins (acetaminophen at high doses, methotrexate, isoniazid, valproic acid) should be approached with caution and with monitoring of liver function in research protocols.

11. Adverse Events and Safety

11.1 Common adverse events

The principal adverse events across all clinical studies are gastrointestinal and dose-dependent:

- Nausea (40 to 73 percent at target doses of 80 to 200 mg twice daily, versus 10 to 15 percent on placebo)
- Vomiting (20 to 47 percent at target doses, versus 2 to 5 percent on placebo)
- Diarrhea (15 to 25 percent at target doses)
- Dyspepsia (10 to 20 percent at target doses)
- Decreased appetite (10 to 15 percent at target doses)
- Abdominal pain (5 to 15 percent at target doses)

These gastrointestinal adverse events are consistent with the GLP-1R agonist class and reflect the combination of delayed gastric emptying, central area postrema activation, and peripheral GLP-1R activation in the gastrointestinal tract. The events are generally mild to moderate in severity but produce substantial treatment discontinuation: across the Phase 2b obesity trial, discontinuation rates exceeded 50 percent in all active dose groups, with approximately 38 percent discontinuing specifically due to adverse events [7].

Slower dose-escalation schemes (2-week steps versus 1-week steps) modestly improved tolerability during the titration phase but did not substantially reduce the steady-state gastrointestinal adverse-event burden [6].

11.2 Cardiovascular effects

Heart rate increased by approximately 2 to 8 beats per minute with danuglipron treatment, consistent with the GLP-1R agonist class effect. No heart-rate-related adverse events were reported. Systolic blood pressure was slightly decreased (1 to 3 mmHg). No QT prolongation or clinically significant arrhythmias were reported across the clinical program [2, 5].

11.3 Hepatic safety

The hepatic safety signal is the principal safety concern that led to program discontinuation:

- Across the greater than 1,400-participant clinical safety database, the overall frequency of liver enzyme elevations was in line with approved GLP-1R agonists
- In the Phase 2b obesity trial, no participants met criteria for significant liver enzyme elevation
- In a subsequent dose-optimization study of the once-daily modified-release formulation, a single asymptomatic participant experienced potential drug-induced liver injury (DILI) that met biochemical criteria for hepatocellular injury
- The DILI resolved after discontinuation of danuglipron
- The isolated DILI case, in the context of the earlier discontinuation of Pfizer's other oral GLP-1R agonist lotiglipron for hepatotoxicity, and regulatory input, led to the decision to discontinue all danuglipron development [9]

The mechanism of the potential hepatotoxicity is not fully elucidated. The OATP transporter-mediated hepatic uptake of danuglipron concentrates the compound in hepatocytes, which could contribute to hepatocellular injury in susceptible individuals. The oxetane ring hydrolysis metabolic pathway, which generates reactive intermediates, is a plausible contributing mechanism [15].

11.4 Discontinuation rates

The high discontinuation rates in the danuglipron clinical program were the principal operational limitation:

- Phase 2b obesity trial: greater than 50 percent discontinuation across all active dose groups versus approximately 40 percent with placebo; only 39.3 percent of randomized participants completed treatment
- Phase 2 type 2 diabetes trial: discontinuation rates were lower but still substantial at higher doses
- The high discontinuation rates were substantially above those reported for injectable GLP-1R agonists (typically 5 to 15 percent due to adverse events) and for orforglipron (8 to 10 percent due to adverse events)

- The rates were the proximate cause of the December 2023 decision to discontinue the twice-daily formulation [7, 8]

11.5 Hypoglycemia

Hypoglycemia rates were low in all trials, consistent with the glucose-dependent mechanism of GLP-1R-mediated insulin secretion [2, 5]. When studied on metformin background therapy (which does not independently cause hypoglycemia), clinically significant hypoglycemia was not observed at any danuglipron dose.

11.6 Pancreatitis and thyroid considerations

GLP-1R agonists as a class carry labeling for the risk of acute pancreatitis and, in rodent models, thyroid C-cell tumors. No cases of pancreatitis were reported in the danuglipron clinical program. The thyroid C-cell tumor signal observed with peptidic GLP-1R agonists in rodent carcinogenicity studies has not been directly evaluated for danuglipron in humanized GLP-1R rodent models; the clinical program was discontinued before long-term carcinogenicity data were generated.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five oral GLP-1 receptor agonists against danuglipron, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile (clinical or in vitro), and overall validation. The five comparators were selected as the principal oral GLP-1R agonists with substantive clinical or preclinical pharmacology programs in type 2 diabetes and obesity applications.

12.1 Orforglipron (LY3502970)

Mechanism: Non-peptide, small-molecule partial agonist of the GLP-1R with pronounced Gs-biased signaling (high cAMP potency relative to minimal beta-arrestin recruitment). Binds at the orthosteric site in the TMD but through a different pocket geometry than danuglipron; does not require Trp33 engagement [10, 11].

Development trajectory: Eli Lilly advanced orforglipron through Phase 1, Phase 2, and multiple Phase 3 studies. The Phase 3 ATTAIN-1 trial demonstrated clinically meaningful weight loss in adults with obesity. Head-to-head trials against oral semaglutide demonstrated superiority on both HbA1c reduction and weight loss [11]. Regulatory submission is anticipated.

Novelty: High. Orforglipron represents a distinct pharmacological concept from danuglipron: partial agonism with Gs bias at the GLP-1R, which may produce less receptor desensitization and a more favorable gastrointestinal tolerability profile than full agonists.

Effect size: Substantial. Phase 3 HbA1c reductions of up to 2.2 percent and weight loss of up to 11.2 percent at 36 mg over 72 weeks are competitive with injectable GLP-1R agonists. Effect sizes exceed danuglipron at the studied doses.

Promising potential: High. The compound is in active Phase 3 development with positive efficacy readouts and a path to potential regulatory approval. Once-daily dosing without food restrictions is a significant practical advantage.

Side-effect profile: Gastrointestinal adverse events (nausea, vomiting, diarrhea) are the principal tolerability limitation, consistent with the GLP-1R agonist class, but discontinuation rates due to adverse events (8 to 10 percent) are substantially lower than those observed with danuglipron (38 percent), possibly reflecting the Gs-biased partial agonist pharmacology and the longer half-life (25 to 68 hours) producing less peak-to-trough fluctuation [11].

Overall validation: High. The most clinically advanced small-molecule oral GLP-1R agonist, with Phase 3 efficacy and safety data supporting potential registration.

Comparison to danuglipron: Orforglipron has a longer half-life (25 to 68 hours versus 5 to 6 hours), enabling once-daily dosing without a modified-release formulation. The partial agonist, Gs-biased signaling profile may contribute to better gastrointestinal tolerability compared to the full agonist, approximately unbiased profile of danuglipron. No hepatotoxicity signal has been reported for orforglipron. Danuglipron has the structural biology advantage of a fully characterized cryo-EM binding mode with mechanistic clarity on the Trp33 engagement; both compounds serve as complementary tools for understanding small-molecule agonism at class B1 GPCRs.

12.2 Oral semaglutide (Rybelsus)

Mechanism: GLP-1 peptide analog (modified GLP-1(7-36)amide with Aib8 substitution and C-18 fatty diacid acylation at Lys26) co-formulated with the absorption enhancer sodium N-[8-(2-hydroxybenzoyl)aminocaprylate] (SNAC) for oral bioavailability. Full agonist at the GLP-1R with broad species activity [19].

Development trajectory: Novo Nordisk developed oral semaglutide through the PIONEER clinical trial program. Approved by the FDA in September 2019 (Rybelsus) for type 2 diabetes at doses of 7 and 14 mg once daily. Higher-dose formulations (25 and 50 mg) have been studied for obesity and type 2 diabetes in the OASIS and PIONEER PLUS programs [19].

Novelty: Low as a GLP-1R agonist (peptide-based mechanism is well established); moderate as an oral formulation (SNAC absorption-enhancer technology was a significant pharmaceutical innovation).

Effect size: At the approved 14 mg dose, HbA1c reductions of approximately 1.0 to 1.4 percent and weight loss of approximately 3 to 5 kg over 26 to 52 weeks. Higher doses (25 and 50 mg) produce larger effects (weight loss of 15 to 17 percent at 68

weeks), approaching injectable semaglutide efficacy.

Promising potential: Established. The compound is the only approved oral GLP-1R agonist and the current standard of care for oral incretin therapy.

Side-effect profile: Gastrointestinal adverse events are the principal limitation, similar to other GLP-1R agonists, but discontinuation rates are substantially lower than danuglipron. Requires fasting administration with no more than 4 ounces of water and a 30-minute wait before eating, which reduces compliance.

Overall validation: Very high. Approved, commercially marketed, and supported by a large clinical trial program (PIONEER, SOUL, OASIS).

Comparison to danuglipron: Oral semaglutide is the only approved oral GLP-1R agonist and the benchmark for comparison. Danuglipron's advantage was the absence of food or fasting restrictions; oral semaglutide's advantages are proven efficacy, regulatory approval, established safety database, and availability. The effect sizes at comparable study durations are broadly similar (HbA1c reduction of approximately 1.0 to 1.2 percent for both at optimal doses over 16 weeks), though oral semaglutide has demonstrated larger effects at higher doses and longer durations.

12.3 Lotiglipron (PF-07081532)

Mechanism: Non-peptide, small-molecule agonist of the GLP-1R. Developed at Pfizer in parallel with danuglipron but based on a distinct chemical scaffold. Binding mode and species selectivity details have been less extensively published than for danuglipron [18].

Development trajectory: Pfizer advanced lotiglipron through early clinical development. The compound was discontinued due to hepatotoxicity (elevated liver enzymes and potential drug-induced liver injury) before advancing to Phase 2b studies [18].

Novelty: Moderate. Represents a second-generation Pfizer oral GLP-1R agonist intended to address some of the limitations of danuglipron (principally the short half-life).

Effect size: Limited clinical data published. The compound was discontinued before definitive efficacy data were generated.

Promising potential: None. Development is terminated.

Side-effect profile: Hepatotoxicity was the primary safety concern. The hepatic safety signal in lotiglipron, in combination with the subsequent danuglipron DILI case, established hepatic safety as a recurring concern in Pfizer's small-molecule GLP-1R agonist program and raises broader questions about hepatotoxicity risk in this compound class.

Overall validation: Low. The compound is principally notable as a cautionary case for hepatic safety in small-molecule GLP-1R agonist development.

Comparison to danuglipron: Lotiglipron and danuglipron share the same development sponsor and the same hepatic safety concern but are distinct in chemical scaffold. The sequential hepatotoxicity signals in both Pfizer compounds may reflect OATP-mediated hepatic concentration of small-molecule GLP-1R agonists as a class vulnerability, or may reflect structural features specific to the Pfizer chemical series that promote reactive metabolite formation.

12.4 TTP273

Mechanism: Non-peptide, small-molecule agonist of the GLP-1R developed by vTv Therapeutics. TTP273 is characterized as a Gs-biased partial agonist with low intrinsic activity relative to GLP-1 peptide, a pharmacological profile that may explain both its favorable gastrointestinal tolerability and its modest glycemic efficacy [20].

Development trajectory: vTv Therapeutics advanced TTP273 through a Phase 2 proof-of-concept study (SimpliciT-1) in 190 patients with type 2 diabetes. The 150 mg once-daily dose produced a placebo-adjusted HbA1c reduction of 0.4 percentage points over 12 weeks. The compound was deprioritized and has not been advanced to Phase 3 [20].

Novelty: Moderate. TTP273 was among the earliest non-peptide oral GLP-1R agonists to reach clinical development and contributed to proof of concept for the compound class.

Effect size: Small. The 0.4 percentage-point placebo-adjusted HbA1c reduction is substantially less than the 1.16 percentage points achieved by danuglipron at 120 mg twice daily and less than the 2.2 percentage points achieved by orforglipron at 36 mg.

Promising potential: Low. The compound is not in active development.

Side-effect profile: Favorable gastrointestinal tolerability, with nausea rates closer to placebo than to the higher rates observed with danuglipron or injectable GLP-1R agonists. The favorable tolerability likely reflects the low intrinsic activity, which also limits efficacy.

Overall validation: Low to moderate. The compound provided proof of concept for non-peptide oral GLP-1R agonism in humans but did not demonstrate sufficient efficacy for registration.

Comparison to danuglipron: TTP273 has substantially better gastrointestinal tolerability but substantially lower efficacy than danuglipron, illustrating the trade-off between intrinsic activity at the GLP-1R and the gastrointestinal adverse-event burden. Danuglipron's full agonist profile produces larger glycemic and weight-loss effects but at the cost of high nausea and vomiting rates. The comparison supports the hypothesis that partial agonism or Gs-biased signaling may be the preferred pharmacological strategy for oral small-molecule GLP-1R agonists.

12.5 PF-06883365

Mechanism: Non-peptide, small-molecule agonist of the GLP-1R. An earlier Pfizer development candidate from the same medicinal chemistry program that produced danuglipron, representing an intermediate stage of the structure-activity optimization. The cryo-EM structure (PDB 7S15) was solved with this compound bound to the GLP-1R [1].

Development trajectory: PF-06883365 was disclosed in the Griffith et al. (2022) publication as a preclinical tool compound from the optimization series. The compound was not advanced to clinical development; danuglipron was selected as the clinical candidate on the basis of superior potency, metabolic stability, and off-target selectivity [1].

Novelty: Low. The compound is a precursor to danuglipron in the medicinal chemistry optimization and does not represent an independent pharmacological concept.

Effect size: Preclinical only. In vitro cAMP accumulation potency is weaker than danuglipron. No in vivo efficacy data in primates or humanized models have been published.

Promising potential: None. The compound is a research tool only.

Side-effect profile: Preclinical only. The compound had less favorable off-target selectivity than danuglipron, including higher hERG inhibition, which was one of the reasons it was not selected as the clinical candidate.

Overall validation: Low. The compound is principally a medicinal chemistry reference compound and a cryo-EM structural probe.

Comparison to danuglipron: PF-06883365 represents an earlier optimization stage of the same chemical series and is useful as a matched-pair comparator for understanding the contribution of the carboxylic acid moiety and the (S)-oxetanylmethyl group to danuglipron's pharmacological profile. The compound's cryo-EM structure provides direct structural information about the binding mode that is translatable to danuglipron.

12.6 Comparator summary

The five comparators occupy distinct positions in the oral GLP-1R agonist landscape. **Orforglipron** is the most clinically advanced and commercially promising small-molecule oral GLP-1R agonist, with Phase 3 data supporting potential regulatory approval and a Gs-biased partial agonist profile that may produce better gastrointestinal tolerability than danuglipron's full agonist mechanism. **Oral semaglutide** is the only approved oral GLP-1R agonist and the current clinical standard, but is a peptide requiring absorption enhancer co-formulation and fasting administration. **Lotiglipron** shares danuglipron's development sponsor and hepatic safety liability and serves principally as a cautionary case. **TTP273** provided early proof of concept but with insufficient efficacy for registration. **PF-06883365** is a medicinal chemistry tool compound from danuglipron's optimization series.

Danuglipron occupies a historically significant position in this landscape: it is the most structurally characterized non-peptide oral GLP-1R agonist (cryo-EM structure at 2.5 angstrom resolution with detailed Trp33 binding mode), the compound with the most complete dose-response characterization across multiple clinical studies (Phase 1 through Phase 2b in both type 2 diabetes and obesity), and the only non-peptide GLP-1R agonist for which the species-selectivity mechanism has been resolved at the atomic level. These attributes make danuglipron an essential reference compound for the field despite its clinical discontinuation.

The principal scientific lesson from the danuglipron program is that full, approximately unbiased agonism at the GLP-1R produces robust glycemic and weight-loss efficacy but at the cost of gastrointestinal tolerability and potentially hepatic safety that may be more favorable with partial agonist, Gs-biased compounds such as orforglipron. This pharmacological distinction is likely to inform the design of next-generation oral GLP-1R agonists.

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This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. Danuglipron is not approved by any regulatory authority worldwide. Development was discontinued by Pfizer in April 2025. The compound is available only as a research-grade preparation. Investigators should obtain analytical confirmation of identity, purity, and stereochemistry on every lot. Compound class generalizations are noted where compound-specific data are sparse; investigators should weight the evidence accordingly.