

RESEARCH MONOGRAPH . COMPOUND PROFILE

Lotiglipron

A selective, potent, orally bioavailable small-molecule agonist of the human glucagon-like peptide-1 receptor developed by Pfizer using Sosei Heptares stabilized-receptor technology, advanced through Phase 2 for type 2 diabetes and obesity, and subsequently discontinued owing to hepatic transaminase elevations in a subset of treated participants.

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ABSTRACT

Lotiglipron (PF-07081532) is an orally administered, nonpeptide, small-molecule agonist of the human glucagon-like peptide-1 receptor (GLP-1R) developed by Pfizer in collaboration with Sosei Heptares. The compound was designed through structure-based drug design leveraging Sosei Heptares proprietary StaR (stabilized receptor) technology platform, which enables crystallographic resolution of G-protein-coupled receptor conformations that are otherwise too unstable for conventional structural characterization. Lotiglipron binds within the transmembrane domain of the GLP-1R, activating the Gs-coupled adenylyl cyclase signaling cascade and increasing intracellular cyclic adenosine monophosphate (cAMP) in a manner functionally analogous to the endogenous incretin peptide GLP-1(7-36)amide but with the pharmacokinetic advantages of oral bioavailability, once-daily dosing without fasting requirements, and a plasma elimination half-life of approximately 21 to 27 hours that supports sustained receptor engagement across the dosing interval.

The compound entered clinical development in 2021 and was advanced through two Phase 1 multiple-ascending-dose studies (Buckeridge et al. 2024) in 74 participants with type 2 diabetes mellitus (T2D) and 26 participants with obesity without diabetes, demonstrating dose-proportional pharmacokinetics across a 10 to 180 mg once-daily dose range, dose-dependent reductions in glycated hemoglobin (HbA1c) of up to 1.61 percentage points at the 180 mg dose over 42 days, and a safety and tolerability profile consistent with the GLP-1R agonist mechanism class. These findings supported advancement to a Phase 2 dose-ranging study

(Amin et al. 2025) in 901 participants (512 with T2D, 389 with obesity), which demonstrated statistically significant reductions in HbA1c of up to 1.44 percentage points (80 mg dose, 16 weeks) and body weight reductions of up to 7.47 percent (200 mg dose, 20 weeks). The Phase 2 study included an open-label semaglutide 14 mg comparator arm; lotiglipron at doses above 20 mg produced HbA1c reductions numerically comparable to or exceeding semaglutide at week 16. However, the Phase 2 study was terminated early following identification of hepatic transaminase elevations (alanine aminotransferase and/or aspartate aminotransferase greater than 3 times the upper limit of normal) in 6.0 to 6.6 percent of lotiglipron-treated participants versus 1.6 percent on placebo, with some individuals reaching elevations greater than 8 times the upper limit of normal. No cases of liver failure, symptomatic hepatitis, or Hy's law were reported. In June 2023, Pfizer announced discontinuation of the lotiglipron clinical program based on the transaminase signal, pharmacokinetic data from Phase 1 drug-drug-interaction studies suggesting impaired hepatic drug transport or metabolism in a subset of participants, and the inability to prospectively identify at-risk individuals.

Lotiglipron is structurally characterized as a benzimidazole-piperidinyl-benzodioxole derivative bearing a chloropyridinyl substituent and an oxetanylmethyl group (molecular formula $C_{31}H_{31}ClN_4O_5$, molecular weight 575.05 g/mol as free base; CAS 2401892-75-7). The compound is not approved in any jurisdiction and is not in active clinical development. Research-grade lotiglipron is available from multiple chemical suppliers and remains a tool compound for the investigation of small-molecule GLP-1R agonist pharmacology, biased signaling, and hepatic metabolism of the oral GLP-1R agonist class. This monograph reviews the chemistry, synthesis, receptor pharmacology,

pharmacokinetics, preclinical and clinical evidence, sourcing and handling, stack interactions, adverse events, and a comparative assessment against five oral or nonpeptide GLP-1R agonist candidates on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Lotiglipron.

Development code: PF-07081532 (Pfizer). The development code is the canonical identifier in the preclinical and early clinical literature and the identifier under which the compound was registered on ClinicalTrials.gov.

Chemical Abstracts Service registry number: 2401892-75-7 (free base). The hydrochloride salt form has been supplied by some chemical vendors; the free base is the primary research-grade material.

International Union of Pure and Applied Chemistry name: 2-((4-((S)-2-(5-chloropyridin-2-yl)-2-methylbenzo[d][1,3]dioxol-4-yl)piperidin-1-yl)methyl)-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid.

1.2 Structural class and chemistry

Lotiglipron is a nonpeptide, small-molecule agonist of the glucagon-like peptide-1 receptor belonging to the benzimidazole structural class. The core architecture comprises a benzimidazole-6-carboxylic acid linked through a methylene bridge to a piperidinyl ring, which in turn bears a 2-substituted benzodioxole carrying a 5-chloropyridin-2-yl group and a geminal methyl substituent. An oxetanylmethyl group is appended to the benzimidazole nitrogen. The carboxylic acid moiety is believed to participate in key ionic interactions with arginine residues in the GLP-1R transmembrane binding pocket, analogous to the pharmacophore elements characterized in the related compound danuglipron (PF-06882961) [1].

Molecular formula: C₃₁H₃₁ClN₄O₅ (free base).

Molecular weight: 575.05 g/mol (free base); 611.52 g/mol (hydrochloride salt).

Physical properties: White to off-white crystalline powder. Soluble in dimethyl sulfoxide; moderately soluble in methanol and ethanol; limited aqueous solubility at physiological pH. The compound is supplied as a lyophilized or crystalline solid by research chemical vendors.

Stereochemistry: Lotiglipron contains two defined stereocenters: the (S)-configuration at the 2-position of the benzodioxole ring system and the (S)-configuration at the oxetan-2-yl group. The compound is supplied as the defined (S,S)-stereoisomer. Investigators acquiring research-grade lotiglipron should confirm stereochemical purity by chiral high-performance liquid chromatography.

1.3 Synthesis

The detailed synthetic route for lotiglipron has not been published in full in the peer-reviewed literature. Patent filings associated with the Pfizer-Sosei Heptares collaboration describe the general synthetic approach for this class of benzimidazole GLP-1R agonists, which typically involves: (a) construction of the benzimidazole-6-carboxylic acid core through condensation of a 4-amino-3-nitrobenzoic acid derivative with an appropriate aldehyde followed by reduction and cyclization; (b) assembly of the 4-substituted piperidinyl-benzodioxole fragment through Suzuki or Buchwald-Hartwig coupling chemistry; (c) reductive amination or alkylation to join the piperidinyl fragment to the benzimidazole core through the methylene linker; and (d) introduction of the oxetanylmethyl group at the benzimidazole nitrogen [2]. The final product is purified by preparative high-performance liquid chromatography or silica gel chromatography and characterized by nuclear magnetic resonance spectroscopy, mass spectrometry, and elemental analysis. The oxetane ring is a metabolic stability-enhancing element commonly employed in contemporary medicinal chemistry to resist oxidative metabolism while maintaining favorable physicochemical properties [3].

2. Abstract

Lotiglipron (PF-07081532) is a selective, potent, orally bioavailable, nonpeptide small-molecule agonist of the human GLP-1 receptor developed by Pfizer through a multi-target research collaboration with Sosei Heptares that leveraged the StaR (stabilized receptor) technology platform for structure-based drug design against G-protein-coupled receptor targets [4, 5]. The compound activates the GLP-1R Gs-coupled signaling pathway, increasing intracellular cAMP and producing the canonical incretin effects of glucose-dependent insulin secretion, suppression of glucagon release, delayed gastric emptying, and central appetite suppression.

The clinical program comprised two Phase 1 multiple-ascending-dose studies (Buckeridge et al. 2024) and one Phase 2 dose-ranging study (Amin et al. 2025) [6, 7]. In Phase 1, 74 participants with T2D and 26 participants with obesity received lotiglipron at target doses of 10 to 180 mg once daily for 28 to 42 days. Pharmacokinetics were dose-proportional, with a median time to peak plasma concentration (Tmax) of 1 to 2 hours on Day 1 and a mean elimination half-life of 20.7 to 26.5 hours at steady state, supporting once-daily administration. Dose-dependent reductions in HbA1c (up to 1.61 percentage points at 180 mg) and fasting plasma glucose were observed in the T2D population. The most common adverse events were gastrointestinal (nausea, vomiting, decreased appetite), consistent with GLP-1R agonist pharmacology; 89.6 percent of adverse events were mild.

In Phase 2, 901 participants (512 T2D, 389 obesity) were randomized to placebo, one of several lotiglipron dose-escalation arms (target maintenance doses 20 to 260 mg), or open-label semaglutide 14 mg (T2D cohort only). The T2D cohort demonstrated HbA1c reductions of up to 1.44 percentage points at 80 mg (week 16), numerically exceeding semaglutide at the same timepoint. The obesity cohort demonstrated body weight reductions of up to 7.47 percent at 200 mg (week 20). However, the study was terminated early following the observation of hepatic transaminase elevations (ALT and/or AST greater than 3 times the upper limit of normal) in 6.0 to 6.6 percent of lotiglipron-treated participants versus 1.6 percent on placebo, with elevations greater than 8 times the upper limit of normal in a smaller subset. No Hy's law cases, symptomatic hepatitis, or liver failure were reported [7].

Pfizer discontinued lotiglipron clinical development in June 2023, citing the transaminase signal and pharmacokinetic data from Phase 1 drug-drug interaction studies suggesting that lotiglipron decreases the hepatic capacity to transport or metabolize drugs (including lotiglipron itself) in a susceptible subset of participants [8]. An exhaustive retrospective review of preclinical in vitro and in vivo toxicity data did not identify signals consistent with liver toxicity, suggesting the transaminase elevations may represent a human-specific phenomenon [7]. The compound is not approved in any jurisdiction and is not in active clinical development. It remains available as a research-grade tool compound for investigation of small-molecule GLP-1R agonist pharmacology.

3. Discovery and Development History

3.1 Origin

Lotiglipron emerged from a multi-target drug discovery collaboration between Pfizer and Sosei Heptares (now Nxera Pharma) initiated in November 2015. The collaboration provided Pfizer access to Sosei Heptares proprietary StaR (stabilized receptor) technology, a platform that engineers thermostabilizing mutations into G-protein-coupled receptors to enable high-resolution crystallographic determination of receptor conformations that are otherwise conformationally heterogeneous and refractory to structural characterization [4]. The StaR platform had previously generated stabilized GLP-1R conformations that enabled structure-based drug design of small-molecule agonists, an approach fundamentally different from the peptide-based GLP-1R agonist programs (semaglutide, liraglutide, dulaglutide, tirzepatide) that dominated the therapeutic landscape.

Pfizer scientists utilized the stabilized GLP-1R crystal structures to design and optimize a series of nonpeptide agonists that bind within the transmembrane domain of the receptor. PF-07081532 was selected from this series for clinical advancement on the basis of potency at the human GLP-1R, selectivity, oral bioavailability, metabolic stability, and a pharmacokinetic profile supporting once-daily dosing without fasting requirements [5, 6].

3.2 Progression to Phase 1

Lotiglipron entered Phase 1 clinical testing in 2021. The Phase 1 program consisted of two randomized, double-blind, placebo-controlled, multiple-ascending-dose studies: Study 1 enrolled participants with T2D; Study 2 enrolled participants with T2D and participants with obesity without diabetes [6]. The dose-escalation design incorporated titration from lower starting doses (10 to 30 mg) to target maintenance doses (up to 180 mg) over 28 to 42 days, reflecting the gastrointestinal tolerability constraints characteristic of the GLP-1R agonist class.

3.3 Advancement to Phase 2

In December 2022, Sosei Heptares announced that PF-07081532 had advanced to Phase 2 clinical trials for type 2 diabetes and obesity, triggering a 10 million USD milestone payment from Pfizer under the collaboration agreement [5]. PF-07081532 was the first clinical candidate from the Pfizer-Sosei Heptares collaboration to reach Phase 2, and one of nine GPCR-targeted drug candidates overall originating from the Sosei Heptares StaR platform to enter clinical trials across all collaboration partners.

3.4 International Nonproprietary Name

The World Health Organization assigned the international nonproprietary name "lotiglipton" to PF-07081532. The "-glipton" stem denotes membership in the oral nonpeptide GLP-1 receptor agonist pharmacological class, a naming convention shared with orforglipton (LY3502970, Eli Lilly) and danuglipton (PF-06882961, Pfizer).

3.5 Discontinuation

In June 2023, Pfizer announced discontinuation of lotiglipton clinical development [8]. The decision was based on three converging findings: (a) laboratory measurements of elevated hepatic transaminases (ALT and AST) in both the Phase 1 drug-drug interaction studies and the ongoing Phase 2 study; (b) pharmacokinetic data from Phase 1 drug-drug interaction studies suggesting that lotiglipton inhibits hepatic drug transport or metabolism in a subset of participants; and (c) the inability to identify a biomarker or genotype that would prospectively identify the at-risk subpopulation, rendering dose individualization or patient selection strategies impractical for registration-directed development. Pfizer simultaneously announced continued development of danuglipton (PF-06882961), its second oral GLP-1R agonist candidate, in a once-daily modified-release formulation [8]. The lotiglipton Phase 2 data were subsequently published by Amin et al. in 2025 [7].

4. Mechanism of Action

Lotiglipron is a selective agonist of the human glucagon-like peptide-1 receptor, a class B1 (secretin family) G-protein-coupled receptor expressed on pancreatic beta cells, enteroendocrine cells, vagal afferent neurons, the area postrema and nucleus of the solitary tract in the brainstem, hypothalamic appetite-regulatory neurons, and at lower density in adipose tissue, kidney, heart, and vascular endothelium [9, 10].

4.1 GLP-1 receptor signaling

The GLP-1R is coupled primarily to the stimulatory G-protein Gs. Agonist binding stabilizes an active receptor conformation that promotes nucleotide exchange at the Gs alpha subunit, activating adenylyl cyclase and increasing intracellular cyclic adenosine monophosphate (cAMP). The cAMP signal activates protein kinase A (PKA) and exchange protein directly activated by cAMP (Epac2), which in pancreatic beta cells potentiate glucose-dependent insulin exocytosis through closure of KATP channels, elevation of intracellular calcium, and direct effects on secretory granule docking and fusion machinery [9, 10]. Simultaneously, GLP-1R activation suppresses glucagon secretion from pancreatic alpha cells (through both paracrine and direct mechanisms), delays gastric emptying through vagal afferent signaling, and reduces appetite and food intake through hypothalamic and brainstem circuits.

Lotiglipron binds within the transmembrane domain of the GLP-1R, occupying a pocket that is distinct from the orthosteric peptide-binding site utilized by native GLP-1(7-36)amide and peptide-based agonists. This allosteric or ago-allosteric binding mode is shared with the other nonpeptide small-molecule GLP-1R agonists (danuglipron, orforglipron, TT-OAD2) and is characterized by engagement of hydrophobic residues in transmembrane helices 1, 2, 3, and 7 and extracellular loop 2 [1, 11]. Cryo-electron microscopy studies of structurally related Pfizer compounds (notably danuglipron) have demonstrated that the carboxylic acid pharmacophore forms a productive ion-pair interaction with arginine-380 in the receptor binding pocket [1]. Lotiglipron shares this carboxylic acid pharmacophore and is expected to engage the same or a closely overlapping binding site.

4.2 Signaling bias

Small-molecule GLP-1R agonists have been reported to exhibit varying degrees of signaling bias relative to native GLP-1. The endogenous peptide activates both the Gs-cAMP pathway and the beta-arrestin recruitment pathway with comparable efficacy, while some nonpeptide agonists show preferential activation of Gs-cAMP with reduced beta-arrestin recruitment [11, 12]. The signaling bias profile of lotiglipron has not been fully characterized in the published literature, but the compound class (benzimidazole-based transmembrane-domain binders) generally produces robust cAMP accumulation. Whether lotiglipron exhibits clinically meaningful signaling bias remains an open question and a subject of ongoing research with the available tool compound.

4.3 Selectivity

Lotiglipron is reported to be selective for the GLP-1R over the closely related glucagon receptor (GCGR) and the glucose-dependent insulintropic polypeptide receptor (GIPR), the two principal paralogs in the class B1 GPCR family [6]. The degree of selectivity (fold selectivity ratios) has not been published in quantitative form; selectivity is inferred from the absence of glucagon-like or GIP-like pharmacological effects in preclinical and clinical studies.

4.4 Downstream metabolic effects

The composite downstream effects of GLP-1R activation by lotiglipron are: (a) glucose-dependent enhancement of insulin secretion (the incretin effect), producing postprandial and fasting glucose lowering without significant hypoglycemia risk in the absence of concomitant sulfonylureas or insulin; (b) suppression of glucagon secretion, reducing hepatic glucose output; (c) delayed gastric emptying, blunting postprandial glucose excursions and contributing to satiety; and (d) central appetite suppression, reducing caloric intake and producing body weight loss with chronic dosing [9, 10]. These effects are the mechanistic basis for the clinical efficacy in T2D (HbA1c reduction) and obesity (body weight reduction) demonstrated in the Phase 1 and Phase 2 programs.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Lotiglipron is administered orally and is absorbed from the gastrointestinal tract without a fasting requirement, a meaningful practical advantage over oral semaglutide (Rybelsus), which requires administration in the fasting state with 120 milliliters of plain water and a 30-minute post-dose fast [6]. The median time to peak plasma concentration (T_{max}) was 1 to 2 hours after the first dose on Day 1 across all dose levels in both Phase 1 studies. At steady state (Day 28 or Day 42), the median T_{max} extended to 2 to 8 hours in Study 1 and 2 to 5 hours in Study 2, reflecting the combination of oral absorption kinetics and accumulation pharmacokinetics at the long half-life [6].

5.2 Dose proportionality and accumulation

Plasma lotiglipron exposure, measured by maximum concentration (C_{max}) and 24-hour area under the concentration-time curve (AUC₂₄), increased in an approximately dose-proportional manner across the 10 to 180 mg once-daily dose range studied in Phase 1 [6]. The long elimination half-life (see below) predicted accumulation with once-daily dosing; steady-state concentrations were approached within approximately 5 to 7 days of repeated dosing at fixed doses.

5.3 Distribution

Detailed distribution parameters (volume of distribution, plasma protein binding, tissue partitioning) have not been published for lotiglipron in the peer-reviewed literature. The molecular properties of the compound (molecular weight 575 g/mol, moderate lipophilicity, carboxylic acid ionizable group) are consistent with moderate plasma protein binding and tissue distribution. Central nervous system penetration is expected based on the appetite-suppressive effects observed in clinical studies, which are mediated through hypothalamic and brainstem GLP-1R activation.

5.4 Metabolism and elimination

The mean plasma elimination half-life of lotiglipron at steady state ranged from 20.7 to 26.5 hours across all dose levels and both Phase 1 studies [6]. This half-life is substantially longer than that of danuglipron (approximately 8 hours in the immediate-release formulation, necessitating twice-daily dosing) and is in a similar range to orforglipron (approximately 25 to 50 hours), supporting once-daily administration.

The metabolic pathways of lotiglipron have not been fully published. Nonclinical data suggested potential for CYP2C19 inhibition by lotiglipron, and a Phase 1 drug-drug interaction study between lotiglipron and clopidogrel (a CYP2C19 substrate and prodrug) was conducted [7]. Pharmacokinetic data from this and other Phase 1 drug-drug interaction studies indicated that lotiglipron can decrease the hepatic capacity to transport or metabolize drugs, including lotiglipron itself, in a subset of participants. This finding was one of the primary bases for the discontinuation decision, as it implied a nonlinear pharmacokinetic phenotype in susceptible individuals that could lead to progressive drug accumulation and elevated hepatic exposure [7, 8].

5.5 Route of administration

The sole route of administration studied clinically was oral. Lotiglipron was administered as an immediate-release tablet formulation, once daily, with or without food. No intravenous, subcutaneous, or other parenteral formulations have been described.

5.6 Special populations

Dedicated pharmacokinetic studies in renal impairment, hepatic impairment, or pediatric populations have not been published. The Phase 1 and Phase 2 studies enrolled adult participants (18 to 70 years of age in the T2D cohorts, 18 to 65 years in the obesity cohorts) with adequate hepatic and renal function at baseline [6, 7].

6. Preclinical Pharmacology

6.1 In vitro pharmacology

Lotiglipron activates the human GLP-1R in heterologous cell-based assays, producing concentration-dependent increases in intracellular cAMP. The compound is marketed by research chemical suppliers (MedChemExpress, Selleckchem, Cayman Chemical, AbMole) as a GLP-1R agonist with nanomolar-range potency, although the specific EC50 values for cAMP accumulation have not been published in peer-reviewed form [13, 14]. Selectivity data indicate that lotiglipron does not activate the glucagon receptor (GCGR) or glucose-dependent insulinotropic polypeptide receptor (GIPR) at concentrations relevant to GLP-1R activation.

6.2 In vivo preclinical pharmacology

Detailed preclinical efficacy data from animal models (glucose tolerance tests, body weight studies, food intake measurements) have not been published in peer-reviewed form for lotiglipron. The progression to Phase 1 clinical studies implies that standard regulatory preclinical pharmacology, safety pharmacology (cardiovascular, respiratory, central nervous system), and toxicology packages were completed to IND-enabling standards, but these data reside in regulatory filings and have not been released publicly.

6.3 Preclinical safety

An exhaustive retrospective review of in vitro and in vivo preclinical toxicity data for lotiglipron, conducted after the clinical transaminase findings, did not identify signals consistent with liver toxicity in nonclinical species [7]. This observation is notable because it indicates that the hepatic transaminase elevations observed in human participants represent a species-specific phenomenon that was not predicted by standard preclinical toxicology assessments. The absence of preclinical hepatotoxicity signal is consistent with the broader experience in pharmaceutical development, where idiosyncratic drug-induced liver injury frequently presents only in human clinical studies and cannot be reliably predicted from animal models or standard in vitro hepatotoxicity assays.

7. Clinical Evidence Base

7.1 Phase 1 multiple-ascending-dose studies

Buckeridge et al. (2024) reported the results of two randomized, double-blind, placebo-controlled, multiple-ascending-dose Phase 1 studies of lotiglipron [6].

Study 1 enrolled participants with T2D (n = 38 on lotiglipron, n = 8 on placebo) treated for 28 days at target doses of 10 to 120 mg once daily with dose titration.

Study 2 enrolled participants with T2D (n = 28 on lotiglipron, n = 8 on placebo) treated for 42 days at target doses of 60 to 180 mg once daily, and participants with obesity without diabetes (n = 18 on lotiglipron, n = 8 on placebo) treated for 42 days at a target dose of 120 mg once daily.

Pharmacodynamic results in T2D: Dose-dependent reductions in HbA1c were observed across both studies. The largest reduction was observed at the 180 mg target dose: least squares mean change from baseline of -1.61 percentage points (90% CI: -2.08, -1.14). Fasting plasma glucose reductions were concordant with the HbA1c findings.

Body weight results: Dose-dependent body weight reductions were observed in both T2D and obesity populations. The magnitude of weight loss over 28 to 42 days was consistent with the early kinetics of GLP-1R agonist-mediated weight loss and was expected to increase with longer treatment duration.

Safety: Most adverse events were mild (89.6%). Nausea was the most frequently reported adverse event in both studies, consistent with the GLP-1R agonist mechanism. Vomiting, decreased appetite, and diarrhea were also reported at frequencies consistent with the class. No clinically meaningful adverse trends were noted in safety laboratory tests, vital signs, or electrocardiogram parameters in these studies [6].

7.2 Phase 2 dose-ranging study

Amin et al. (2025) reported the results of a Phase 2, randomized, double-blind, placebo-controlled, dose-ranging, parallel-group study designed to evaluate the efficacy, safety, and tolerability of lotiglipron at target maintenance doses of 20 to 260 mg administered over a planned 32-week treatment period [7].

Study design: The study enrolled two cohorts: a T2D cohort (n = 512) of adults with T2D inadequately controlled on metformin monotherapy, and an obesity cohort (n = 389) of adults with obesity (BMI 30 kg/m² or greater) or overweight (BMI 27 kg/m² or greater with at least one weight-related comorbidity) without diabetes. In the T2D cohort, participants were randomized to placebo, one of several lotiglipron dose-escalation arms with target maintenance doses of 20, 40, 60, or 80 mg, or open-label semaglutide 14 mg (titrated per label). In the obesity cohort, participants were randomized to placebo or lotiglipron dose-escalation arms with target maintenance doses of 80, 120, 160, 200, or 260 mg using various titration schedules.

HbA1c results (T2D cohort): Statistically significant reductions from baseline in HbA1c versus placebo were observed across all lotiglipron doses and semaglutide 14 mg at week 16 (p less than 0.0001). Baseline mean HbA1c ranged from 7.80 to 8.14 percent across arms. Least squares mean decreases from baseline at week 16 were: 20 mg, -0.81% (90% CI: -1.00, -0.62); 40 mg, -1.01% (90% CI: -1.19, -0.82); 60 mg, -1.12% (90% CI: -1.31, -0.92); 80 mg, -1.44% (90% CI: -1.63, -1.26); semaglutide 14 mg, -1.04% (90% CI: -1.24, -0.84); placebo, -0.07% (90% CI: -0.25, 0.11) [7].

Body weight results (obesity cohort): Statistically significant reductions in body weight versus placebo were observed across all lotiglipron doses at week 20 (p less than 0.01). Least squares mean percent decreases from baseline ranged from -4.29% (80 mg, three-step titration) to -7.47% (200 mg, five-step titration) versus -1.84% on placebo [7].

Comparison to semaglutide: In the T2D cohort, the magnitude of HbA1c reduction at lotiglipron doses above 20 mg was numerically comparable to or exceeding that of semaglutide 14 mg at week 16. This comparison is limited by the open-label design of the semaglutide arm and the early termination of the study.

Dose titration challenges: Participants randomized to the highest target maintenance doses (160 mg and 260 mg in the obesity cohort) reached only 80 mg and 140 mg, respectively, at the time of the week 16 and week 20 assessments, owing to the

gradual dose-escalation protocol and the early study termination [7]. The efficacy at the highest intended doses therefore could not be assessed.

7.3 Cardiovascular and renal endpoints

No dedicated cardiovascular outcome trial (CVOT) or renal outcome study was conducted for lotiglipron. The Phase 1 studies reported no clinically meaningful effects on QTc interval, blood pressure, or heart rate. The GLP-1R agonist class has demonstrated cardiovascular benefit in dedicated outcome trials with injectable agents (li-raglutide, semaglutide, dulaglutide), but no oral small-molecule GLP-1R agonist has completed a cardiovascular outcome trial.

8. Sourcing and Quality Verification

Lotiglipron is not a registered pharmaceutical product in any jurisdiction and is not available in pharmaceutical-grade formulations. Research-grade lotiglipron is supplied by multiple chemical and pharmaceutical research suppliers including MedChemExpress, Selleckchem, Cayman Chemical, AbMole BioScience, ChemScene, MedKoo, and Molnova, at greater than 98 percent purity by HPLC [13, 14]. Supply is in milligram to gram quantities as the free base or as the hydrochloride salt. Pricing is in the range of approximately 100 to 500 USD per 50 mg of research-grade material at the time of monograph preparation, reflecting the synthetic complexity of the compound.

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 (576.06 for the protonated free base $[M+H]^+$)
- Chiral HPLC confirmation of stereochemical purity (greater than 99 percent enantiomeric excess of the (S,S) form)
- Nuclear magnetic resonance spectroscopy (1H and ^{13}C) for structural confirmation
- Karl Fischer or loss-on-drying analysis for residual water content
- Residual solvent analysis for common synthesis solvents

Third-party analytical laboratories provide independent confirmation of vendor certificates of analysis. Because lotiglipron is a discontinued clinical candidate with no generic pharmaceutical market, lot-to-lot variability from research chemical suppliers may be observed, and on-receipt analytical confirmation is appropriate for any investigation requiring dose-response or mechanism-of-action precision.

9. Reconstitution and Handling

Lotiglipron is supplied as a white to off-white crystalline powder. For in vitro cell-based assays, stock solutions are typically prepared at 10 to 50 mM in dimethyl sulfoxide (DMSO), aliquoted into single-use volumes, and stored at -20 degrees Celsius. DMSO stock solutions are stable at -20 degrees Celsius for at least 6 months when protected from moisture and repeated freeze-thaw cycles.

For in vivo animal studies, lotiglipron can be formulated in standard oral gavage vehicles. The carboxylic acid group permits salt formation to enhance aqueous solubility when required. Investigators should determine the solubility and stability of lotiglipron in their specific formulation vehicle under their specific storage conditions, as published formulation data are limited.

Working dilutions from DMSO stock solutions should be prepared in the assay medium immediately before use. The final DMSO concentration in cell-based assays should not exceed 0.1 to 0.5 percent (v/v) to avoid cytotoxicity confounds. Aqueous solutions at physiological pH should be used within 24 hours of preparation unless stability data support longer storage.

The compound should be stored in a desiccated environment at -20 degrees Celsius for long-term storage of the solid. Room-temperature handling for weighing and dissolution is acceptable for short durations (minutes to hours). Light protection is reasonable practice but has not been demonstrated to be required.

10. Stack Interactions and Combinations

Lotiglipron interacts with several drug classes through its effects on hepatic drug metabolism and transport, and through its GLP-1R agonist pharmacology. Investigators conducting research with lotiglipron should consider:

CYP2C19 substrates: Nonclinical data suggested potential for CYP2C19 inhibition by lotiglipron [7]. Concurrent use with CYP2C19 substrates (clopidogrel, omeprazole, esomeprazole, voriconazole, citalopram, diazepam) may produce elevated exposure to the substrate drug. A Phase 1 drug-drug interaction study between lotiglipron and clopidogrel was conducted but full results have not been published.

Hepatic transporter substrates: Pharmacokinetic data from Phase 1 drug-drug interaction studies suggested that lotiglipron can decrease hepatic drug transport capacity in a subset of participants [7, 8]. This implies potential interactions with substrates of hepatic organic anion-transporting polypeptides (OATP1B1, OATP1B3) and other hepatic uptake transporters. Drugs that are OATP substrates (statins including atorvastatin, rosuvastatin, pitavastatin; repaglinide; bosentan) may exhibit elevated systemic exposure when co-administered with lotiglipron.

Metformin: The Phase 2 study enrolled participants on stable metformin monotherapy. No clinically significant pharmacokinetic or pharmacodynamic interaction between lotiglipron and metformin was identified, consistent with the non-overlapping metabolic and elimination pathways of the two compounds [7].

Insulin and sulfonylureas: Concurrent use of lotiglipron with insulin or sulfonylureas would be expected to increase hypoglycemia risk, as the glucose-dependent insulin secretion enhancement by GLP-1R agonism adds to the glucose-independent insulin secretion produced by sulfonylureas and the exogenous insulin effect. This interaction is a class effect of all GLP-1R agonists and was not specifically studied with lotiglipron.

Other GLP-1R agonists: Concurrent use with peptide-based GLP-1R agonists (semaglutide, liraglutide, tirzepatide) is pharmacologically redundant at the receptor level and may produce additive gastrointestinal adverse events. The combina-

tion has not been studied.

QT-prolonging agents: No clinically meaningful QTc prolongation was observed with lotiglipron in Phase 1 studies. However, thorough QT studies were not completed prior to program discontinuation, and investigators combining lotiglipron with known QT-prolonging agents should exercise appropriate monitoring.

Oral contraceptives: GLP-1R agonists delay gastric emptying, which can reduce the absorption rate of co-administered oral medications. This effect has been characterized for injectable GLP-1R agonists and oral contraceptives; the magnitude of the effect with lotiglipron has not been specifically studied.

11. Adverse Events and Safety

11.1 Common adverse events

The principal adverse events observed in Phase 1 and Phase 2 studies were gastrointestinal, consistent with the GLP-1R agonist mechanism class [6, 7]:

- Nausea: the most frequently reported adverse event across both Phase 1 studies and the Phase 2 study; dose-dependent in incidence and severity; generally mild and often transient with continued dosing or dose titration
- Vomiting: dose-dependent; more common during dose-escalation periods
- Decreased appetite: dose-dependent; pharmacologically expected and contributing to the weight-loss effect
- Diarrhea: less common than nausea; generally mild
- Abdominal discomfort: reported at low frequencies across dose levels

In Phase 1, 89.6 percent of all adverse events were rated as mild [6]. The dose-escalation (titration) approach employed in both Phase 1 and Phase 2 studies was designed to mitigate gastrointestinal tolerability by allowing gradual receptor adaptation.

11.2 Hepatic transaminase elevations

The most clinically significant safety finding was the observation of hepatic transaminase elevations in a subset of lotiglipron-treated participants [7, 8].

Incidence: In the Phase 2 study, elevations in ALT and/or AST greater than 3 times the upper limit of normal (ULN) were observed in 24 of 361 participants (6.6%) on lotiglipron in the T2D cohort, 19 of 319 participants (6.0%) on lotiglipron in the obesity cohort, and 1 of 64 participants (1.6%) on placebo in the obesity cohort. Elevations in ALT greater than 8 times ULN were observed in 1.8% of the T2D cohort and 0.5% of the obesity cohort. Elevations in AST greater than 8 times ULN were observed in 0.6% of the T2D cohort and 0.3% of the obesity cohort [7].

Temporal pattern: Most ALT and AST elevations were first observed at weeks 8 and 12, while participants were receiving 40, 60, or 80 mg of lotiglipron. No elevations greater than 3 times ULN were observed with 20 mg lotiglipron or semaglutide [7].

Recovery: A decline in ALT or AST was notable both with continued lotiglipron dosing (in some participants) and with temporary or permanent discontinuation of lotiglipron, suggesting an adaptive or self-limiting hepatic response in many cases [7].

Clinical significance: No on-treatment Hy's law cases (concurrent ALT/AST elevation greater than 3 times ULN and total bilirubin elevation greater than 2 times ULN) were reported. No participants experienced symptomatic hepatitis, liver failure, or required treatment for liver injury. None of the affected participants reported liver-related symptoms or side effects [7, 8].

Mechanism: The mechanism underlying the transaminase elevations was not definitively determined. Temporal alignment between ALT/AST elevations and lotiglipron plasma concentrations, combined with data from Phase 1 drug-drug interaction studies, suggested that lotiglipron can decrease the hepatic capacity to transport or metabolize drugs (including lotiglipron itself) in a susceptible subset of participants, potentially leading to elevated hepatic lotiglipron concentrations and hepatocellular stress [7]. The only distinguishing feature of the affected subset was higher plasma lotiglipron concentrations; no demographic, genetic, or clinical baseline characteristic reliably identified at-risk individuals.

Preclinical concordance: An exhaustive retrospective review of in vitro and in vivo preclinical toxicity data did not identify signals consistent with liver toxicity, indicating that the transaminase elevations are a human-specific phenomenon not predicted by standard preclinical toxicology [7].

11.3 Drug-drug interaction safety findings

Phase 1 drug-drug interaction studies provided additional safety data that contributed to the discontinuation decision. The specific findings from these studies have not been fully published, but Pfizer cited pharmacokinetic data indicating altered hepatic drug metabolism or transport as a contributing factor [8].

11.4 Cardiovascular safety

No clinically meaningful effects on QTc interval, blood pressure, or heart rate were observed in Phase 1 studies. A dedicated thorough QT study was not completed [6].

11.5 Hypoglycemia

Consistent with the glucose-dependent mechanism of GLP-1R agonist-mediated insulin secretion, hypoglycemia was infrequent in both Phase 1 and Phase 2 studies, where participants were not receiving concurrent sulfonylureas or insulin [6, 7].

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five oral or nonpeptide GLP-1R agonist candidates against lotiglipron, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five candidates were selected as the principal oral nonpeptide GLP-1R agonists with substantive clinical or preclinical pharmacology programs, with priority on those that have produced material clinical evidence.

12.1 Orforglipron (LY3502970)

Mechanism: Selective nonpeptide small-molecule GLP-1R agonist. Orforglipron binds within the transmembrane domain of the GLP-1R as a nonpeptide allosteric agonist, engaging a pocket formed primarily by TM1, TM2, TM3, TM7, and ECL2 [15, 16]. Oral bioavailability is approximately 79 percent, substantially higher than oral semaglutide (approximately 1 percent).

Development trajectory: Eli Lilly advanced orforglipron through Phase 2 studies in T2D and obesity, with both reporting clinically meaningful efficacy. The Phase 2 obesity study (Wharton et al. 2023, published in the New England Journal of Medicine) demonstrated body weight reductions of up to 14.7 percent at 36 weeks [17]. Eli Lilly subsequently advanced orforglipron to a comprehensive Phase 3 program (ATTAIN trials) encompassing T2D, obesity, and cardiovascular risk populations [18, 19]. Phase 3 results reported in 2025 demonstrated body weight reductions of 7.5 to 11.2 percent at 72 weeks at doses of 6 to 36 mg [19].

Novelty: High. Orforglipron represents the most advanced oral nonpeptide GLP-1R agonist in clinical development and has a distinct chemical scaffold from the Pfizer benzimidazole series.

Effect size: Body weight reductions of up to 14.7 percent (Phase 2, 36 weeks) and 11.2 percent (Phase 3, 72 weeks); HbA1c reductions comparable to injectable semaglutide. Effect sizes exceed those demonstrated by lotiglipron, though com-

parisons are confounded by differences in treatment duration and dose optimization.

Promising potential: High. Orforglipron is the most advanced oral nonpeptide GLP-1R agonist, with a comprehensive Phase 3 program and a regulatory submission pathway in progress.

Side-effect profile: Gastrointestinal adverse events (nausea, vomiting, diarrhea) are the principal tolerability concern, consistent with GLP-1R agonist pharmacology. No hepatic transaminase signal comparable to lotiglipron has been reported. The compound has been generally well tolerated in Phase 2 and Phase 3 studies.

Overall validation: High. Phase 3 data confirm clinically meaningful efficacy in obesity and T2D with a manageable side-effect profile.

Comparison to lotiglipron: Orforglipron has a longer half-life (25 to 50 hours), higher oral bioavailability, larger effect sizes in clinical studies, a more advanced development trajectory, and the absence of the hepatic transaminase signal that terminated lotiglipron development. Lotiglipron and orforglipron share the oral nonpeptide GLP-1R agonist mechanism but differ in chemical scaffold, binding pose, and metabolic liability. Orforglipron is the clear clinical leader in this comparison.

12.2 Danuglipron (PF-06882961)

Mechanism: Nonpeptide small-molecule GLP-1R agonist from the same Pfizer benzimidazole series as lotiglipron [1]. Danuglipron binds within the transmembrane domain of the GLP-1R; the cryo-EM structure at 2.5 angstrom resolution demonstrates the carboxylic acid ion-pair with arginine-380.

Development trajectory: Pfizer advanced danuglipron through Phase 2 studies for T2D and obesity. A 16-week Phase 2b study demonstrated HbA1c reductions of up to 1.16 percentage points and body weight losses of 4 to 5.5 kg [20]. The twice-daily immediate-release formulation limited patient acceptability; Pfizer subsequently developed a once-daily modified-release formulation [8]. However, in April 2025, Pfizer discontinued the once-daily modified-release program following the observation of elevated liver enzymes in clinical trials, mirroring the hepatic safety concern that terminated lotiglipron [21].

Novelty: Moderate. Danuglipron shares the benzimidazole scaffold with lotiglipron and occupies the same binding site in the GLP-1R.

Effect size: HbA1c reduction of up to 1.16 percentage points (16 weeks, Phase 2b); body weight loss of 4 to 5.5 kg. Effect sizes are numerically smaller than lotiglipron at comparable timepoints, though direct comparison is limited by differences in study design and dose optimization.

Promising potential: Low. Both the twice-daily immediate-release and once-daily modified-release formulations have been discontinued. The compound is no longer in active clinical development.

Side-effect profile: Gastrointestinal adverse events similar to other GLP-1R agonists. Hepatic transaminase elevations were observed in the once-daily modified-release program, contributing to its discontinuation [21]. The recurrence of hepatic signals across two structurally related Pfizer compounds (lotiglipron and danuglipron) raises the possibility of a scaffold-related hepatotoxicity liability in the benzimidazole GLP-1R agonist series.

Overall validation: Low to moderate. Phase 2 clinical data demonstrated proof-of-concept efficacy, but the program has been discontinued owing to tolerability and safety concerns.

Comparison to lotiglipron: Danuglipron and lotiglipron share the benzimidazole scaffold and were developed within the same Pfizer program. Lotiglipron demonstrated larger HbA1c and body weight reductions and had superior pharmacokinetics (once-daily versus twice-daily), but both compounds were ultimately terminated for hepatic safety concerns. The parallel discontinuation of both compounds raises important questions about the hepatotoxicity liability of the benzimidazole GLP-1R agonist chemical class.

12.3 Oral semaglutide (Rybelsus)

Mechanism: Oral formulation of the GLP-1R peptide agonist semaglutide, using the absorption-enhancing excipient sodium N-(8-[2-hydroxybenzoyl]amino)caprylate (SNAC) to promote transient gastric mucosal absorption [22]. Unlike lotiglipron and other small-molecule GLP-1R agonists, oral semaglutide is a peptide that binds the orthosteric site of the GLP-1R.

Development trajectory: Novo Nordisk received FDA approval for oral semaglutide (Rybelsus) in 2019 for T2D at doses of 7 and 14 mg once daily. The compound has since been studied at higher doses (25 and 50 mg) in T2D and obesity, with 25 mg demonstrating body weight reductions of approximately 8 percent at 52 weeks and the 50 mg dose under investigation [22, 23].

Novelty: Low as a chemical entity (semaglutide is an established peptide GLP-1R agonist), but moderate as an oral formulation technology.

Effect size: HbA1c reduction of 1.0 to 1.4 percentage points (14 mg, PIONEER trials); body weight reduction of approximately 4 to 5 percent at 14 mg and approximately 8 percent at 25 mg [22, 23]. Effect sizes at 14 mg are comparable to lotiglipron at 80 mg.

Promising potential: High. Oral semaglutide is an approved, marketed product with an established regulatory and clinical position.

Side-effect profile: Gastrointestinal adverse events consistent with GLP-1R agonist pharmacology. No hepatic transaminase signal. Requires fasting administration (30 minutes before first food, beverage, or other oral medications of the day), a practical inconvenience that lotiglipron avoided.

Overall validation: High. Approved product with extensive Phase 3 data and real-world experience.

Comparison to lotiglipron: Oral semaglutide is the first approved oral GLP-1R agonist and the clinical standard against which oral small-molecule GLP-1R agonists are benchmarked. Lotiglipron offered the potential advantages of no fasting requirement and once-daily dosing without absorption-enhancement technology, but was discontinued before these practical advantages could be validated in late-phase trials.

12.4 TT-OAD2

Mechanism: Partial allosteric agonist of the GLP-1R with biased signaling. TT-OAD2 selectively activates the cAMP/PKA pathway with limited orthosteric probe displacement and minimal Ca²⁺ and ERK1/2 activation [12]. This biased signaling profile is distinct from both lotiglipron and orforglipron and may have implications for tolerability (potentially reduced gastrointestinal side effects through avoidance of beta-arrestin-mediated pathways).

Development trajectory: TT-OAD2 is principally a research tool compound. It has been widely used in academic research to study GLP-1R signaling bias [12]. The compound has not advanced to clinical development.

Novelty: High. TT-OAD2 was among the first reported small-molecule GLP-1R agonists and established the feasibility of nonpeptide agonism at this class B1 GPCR.

Effect size: Preclinical only. Glucose-lowering demonstrated in mouse models. No human efficacy data.

Promising potential: Low as a clinical candidate. High as a research tool for understanding GLP-1R signaling bias.

Side-effect profile: Preclinical only. No human safety data.

Overall validation: Low to moderate. The compound is principally a proof-of-concept and research tool.

Comparison to lotiglipron: TT-OAD2 is mechanistically informative as a partial, biased agonist but has not advanced to clinical development. Lotiglipron has substantially more clinical validation. The biased signaling profile of TT-OAD2 (cAMP-selective, minimal beta-arrestin) represents a theoretical advantage for tolerability that remains to be tested clinically.

12.5 GSBR-1290 (Structure Therapeutics)

Mechanism: Oral nonpeptide small-molecule GLP-1R agonist developed by Structure Therapeutics. GSBR-1290 binds the transmembrane domain of the GLP-1R and produces dose-dependent GLP-1R activation with cAMP accumulation [24].

Development trajectory: Structure Therapeutics advanced GSBR-1290 through Phase 1 studies in healthy volunteers and through a Phase 2 study in T2D and obesity. Early Phase 1 data reported dose-dependent body weight reductions and acceptable tolerability. The compound represents an independent chemical scaffold from both the Pfizer benzimidazole series and the Eli Lilly orforglipron series [24].

Novelty: Moderate to high. Independent chemical scaffold with differentiated medicinal chemistry.

Effect size: Phase 1 body weight reductions demonstrated proof-of-concept. Phase 2 data have been reported at medical conferences. The effect size appears clinically meaningful but has not yet been published in full peer-reviewed form.

Promising potential: Moderate to high. The compound is in active clinical development and represents an alternative oral nonpeptide GLP-1R agonist to orforglipron.

Side-effect profile: Gastrointestinal adverse events consistent with GLP-1R agonist pharmacology have been reported. No hepatic transaminase signal has been publicly reported.

Overall validation: Moderate. Phase 2 data support continued development, but the compound has not reached Phase 3.

Comparison to lotiglipron: GSK-1290 is at a comparable stage of clinical development to where lotiglipron was at discontinuation (Phase 2), but without the hepatic safety signal. The compound represents a potential demonstration that the hepatic transaminase liability is scaffold-specific (benzimidazole series) rather than class-wide (all oral nonpeptide GLP-1R agonists).

12.6 Comparator summary

The five compounds occupy distinct positions in the oral GLP-1R agonist landscape. **Orforglipron** represents the most advanced clinical development trajectory among the nonpeptide small-molecule GLP-1R agonists, with Phase 3 data confirming clinically meaningful efficacy in obesity and T2D and a manageable safety profile. **Danuglipron** shared the benzimidazole scaffold with lotiglipron and was similarly discontinued for hepatic safety concerns, raising scaffold-level questions about this chemical series. **Oral semaglutide** is the approved clinical standard but is a peptide formulation with fasting requirements and low oral bioavailability. **TT-OAD2** is a proof-of-concept tool compound that established the feasibility of small-molecule GLP-1R agonism. **GSK-1290** represents an active, independent clinical program that may help determine whether the hepatic liability is scaffold-specific.

Lotiglipron occupies a defined historical position in this landscape: it demonstrated proof-of-concept clinical efficacy for a once-daily oral nonpeptide GLP-1R agonist with no fasting requirement, achieving HbA1c and body weight reductions comparable to oral semaglutide at the highest studied doses. The hepatic transaminase signal, the inability to identify at-risk individuals, and the concurrent avail-

ability of alternative oral GLP-1R agonist scaffolds (orforglipron, GSBR-1290) without this liability were the rational basis for discontinuation. The compound retains value as a research tool for investigating GLP-1R binding, signaling, and the hepatic metabolism of the benzimidazole agonist class.

The principal question raised by the lotiglipron and danuglipron hepatic signals is whether the benzimidazole scaffold carries an intrinsic liability for hepatotoxicity that is specific to this chemical series, or whether the transaminase elevations reflect a broader vulnerability of small-molecule GLP-1R agonists that has not yet manifested in other scaffolds at the doses and durations studied. The absence of comparable hepatic signals with orforglipron and GSBR-1290 in the available clinical data favors the scaffold-specific hypothesis, but definitive resolution will require longer-duration, larger-population studies with the surviving candidates.

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