

ORIGINAL ARTICLE

Evaluation of an oral small-molecule glucagon-like peptide-1 receptor agonist, lotiglipron, for type 2 diabetes and obesity: A dose-ranging, phase 2, randomized, placebo-controlled study

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Abstract

Aim: The aim was to investigate the effects of lotiglipron, a once-daily, oral small-molecule glucagon-like peptide-1 (GLP-1) receptor agonist, in participants with type 2 diabetes (T2D) or obesity.

Materials and Methods: A phase 2, randomized, double-blind, placebo-controlled, dose-ranging study investigated the efficacy and safety of lotiglipron. The study was terminated early for safety reasons after routine data and monitoring review. The planned analyses for the end points were modified prior to unblinding the study.

Results: In total, 901 participants were treated with at least one dose of the study drug (T2D cohort: $n = 512$, obesity cohort: $n = 389$). Although the majority of participants who were randomly assigned to higher doses did not reach their target maintenance dose, statistically significant changes in HbA1c and body weight were observed. In the T2D cohort, reductions in HbA1c were observed across all lotiglipron doses at week 16 ($p < 0.0001$), with least squares mean decreases up to

Sarah J. DuBrava and Margot Johnson affiliation at the time of study conduct.

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–1.44% (90% confidence interval [CI]: –1.63, –1.26) (lotiglipron 80 mg), versus placebo, –0.07% (90% CI: –0.25, 0.11). In the obesity cohort, decreases in body weight were observed across all lotiglipron doses at week 20 ($p < 0.01$), up to –7.47% (90% CI: –8.50, –6.43) (lotiglipron 200 mg, five-step titration), versus placebo, –1.84% (90% CI: –2.85, –0.83). Across cohorts, the most frequently reported treatment-emergent adverse events were gastrointestinal related (most mild to moderate severity), with nausea being the most common (ranging from 4% [placebo] to 28.8% [80 mg] in the T2D cohort and 12.5% [placebo] to 60.6% [200 mg, four-step titration] in the obesity cohort). Transaminase elevations were observed in a subset of participants (6.6% and 6.0% of participants on lotiglipron in the T2D and obesity cohorts, respectively, compared with 1.6% on placebo in the obesity cohort).

Conclusions: The efficacy (HbA1c and/or body weight) of a range of lotiglipron doses was demonstrated in T2D and obesity cohorts. The safety profile was largely consistent with what has been previously known about the mechanism of action. Our results are unique in reporting elevations in liver transaminases in a subset of participants treated with lotiglipron, with attempts to identify the at-risk population unsuccessful and therefore clinical development of lotiglipron terminated.

ClinicalTrials.gov: NCT05579977.

KEYWORDS

diabetes, glucagon-like peptide-1 receptor agonist, HbA1c, lotiglipron, obesity, PF-07081532, phase 2 study, weight loss

1 | INTRODUCTION

The prevalence of type 2 diabetes (T2D) and obesity continues to increase worldwide,^{1,2} and both are associated with comorbidities and increased risk of mortality if not adequately managed.^{3–8} Glucagon-like peptide-1 receptor (GLP-1R) agonism, as demonstrated by peptidic GLP-1R agonists, is a potent pharmacological pathway to manage glycaemic control, reduce body weight and improve cardiovascular disease outcomes.^{9–14} However, the approved peptidic GLP-1R agonists present a potential barrier for patients because of the need to administer by subcutaneous injection or, in the case of the only currently approved oral formulation (semaglutide [Rybelsus]), the requirement to fast before and after administration.^{15–17} Adherence to medication may be improved by the introduction of oral GLP-1R agonists without the need for pre- and post-treatment fasting.¹⁸ Nonpeptide GLP-1R agonists, which are administered orally without fasting requirements, are currently in clinical development.^{19–24}

Lotiglipron (PF-07081532) is a selective, potent, small-molecule GLP-1R agonist that can be administered orally without fasting requirements. Distinctive features of lotiglipron include a plasma half-life compatible with once-daily (QD) administration along with improved and consistent gastrointestinal (GI) absorption.²⁵ In two phase 1, placebo-controlled, multiple ascending-dose studies investigating lotiglipron (over the course of 28–42 days with doses ranging from 20 to 180 mg QD) in adults with T2D inadequately controlled on metformin and separately in adults with obesity without T2D, lotiglipron demonstrated dose-

dependent reductions in glycated haemoglobin (HbA1c) and plasma glucose in T2D and reductions in body weight (in T2D or obesity),²⁶ with the tolerability profile of mechanism of action (MoA)-based GI adverse events consistent with other oral GLP-1R agonists.^{23,24,27}

The current study was a phase 2 study with a prespecified aim to investigate the efficacy, safety and tolerability of a range of lotiglipron doses planned to be administered over 32 weeks in participants with T2D inadequately controlled on metformin and separately in participants with obesity without T2D.

2 | MATERIALS AND METHODS

2.1 | Study oversight

This study (C3991004; ClinicalTrials.gov: NCT05579977) was conducted in compliance with the ethical principles originating from or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. The study protocol and other relevant documents were approved by the investigators' Institutional Review Boards or ethics committees. All participants provided written informed consent prior to enrolment in the study. An independent review committee (IRC) was used for safety monitoring.

On 25 June 2023, based on observed pharmacokinetic (PK) data from two phase 1 drug–drug interaction (DDI) studies of lotiglipron

(C3991040 [NCT05671653] and C3991047 [NCT05788328])²⁸ and elevated transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) in these same studies and in this study (C3991004), the clinical development of lotiglipron was terminated, and this study was prematurely terminated.²⁹ After this decision, all participants were followed for safety off the study drug, with last patient last visit (LPLV) in the study achieved on 22 September 2023 – with LPLV achieved in the T2D cohort on 22 September 2023 and in the obesity cohort, 1 day earlier, on 21 September 2023.

2.2 | Study participants

The study comprised two cohorts of participants (those with T2D and those with obesity without T2D) and was conducted in seven countries: Bulgaria, Czech Republic, Hungary and Poland enrolled participants only in the T2D cohort; Canada, Japan and the United States, including Puerto Rico, enrolled participants in both cohorts. The participants were recruited to the study from 27 October 2022 to 23 February 2023, with the last participant randomly assigned to the obesity cohort on 15 February 2023 and to the T2D cohort on 3 April 2023. Recruitment across the two cohorts was not balanced by region – countries/sites initiated as approvals were garnered. In the T2D cohort, participants randomly assigned were from North America (38%), Europe (46%) and Asia (16%). In contrast, the majority in the

obesity cohort was recruited from North America (96%), with minor contribution from Asia (4%) and none from Europe. To be eligible, participants had to be 18–75 years of age. The T2D cohort included participants inadequately controlled on metformin doses ≥ 500 mg/day and stable for ≥ 8 weeks prior to screening, with HbA1c $\geq 7.0\%$ and $\leq 10.0\%$ (53–86 mmol/mol), fasting plasma glucose (FPG) ≤ 270 mg/dL (15 mmol/L) and body mass index (BMI) ≥ 23.0 kg/m² (≥ 20.0 kg/m² in Japan). The obesity cohort included participants with BMI ≥ 30.0 kg/m² (all regions), HbA1c $\leq 6.4\%$ (47 mmol/mol) and FPG ≤ 126 mg/dL (7 mmol/L). In both cohorts, participants were excluded for certain concomitant diseases; refer to Table S1 for complete eligibility criteria for both study populations.

2.3 | Study design

This was a phase 2, randomized, double-blind, placebo-controlled, dose-ranging, parallel-group study designed to evaluate the efficacy and safety of lotiglipron in adult participants with T2D and, separately, with obesity without T2D.

The study had 13 arms, with administration of oral lotiglipron (five arms) or matching placebo (one arm) in each cohort, and one additional arm in the T2D cohort receiving open-label oral semaglutide (Rybelsus) as an internal reference standard (Figure 1). Participants in the T2D cohort were randomly assigned in equal numbers to receive

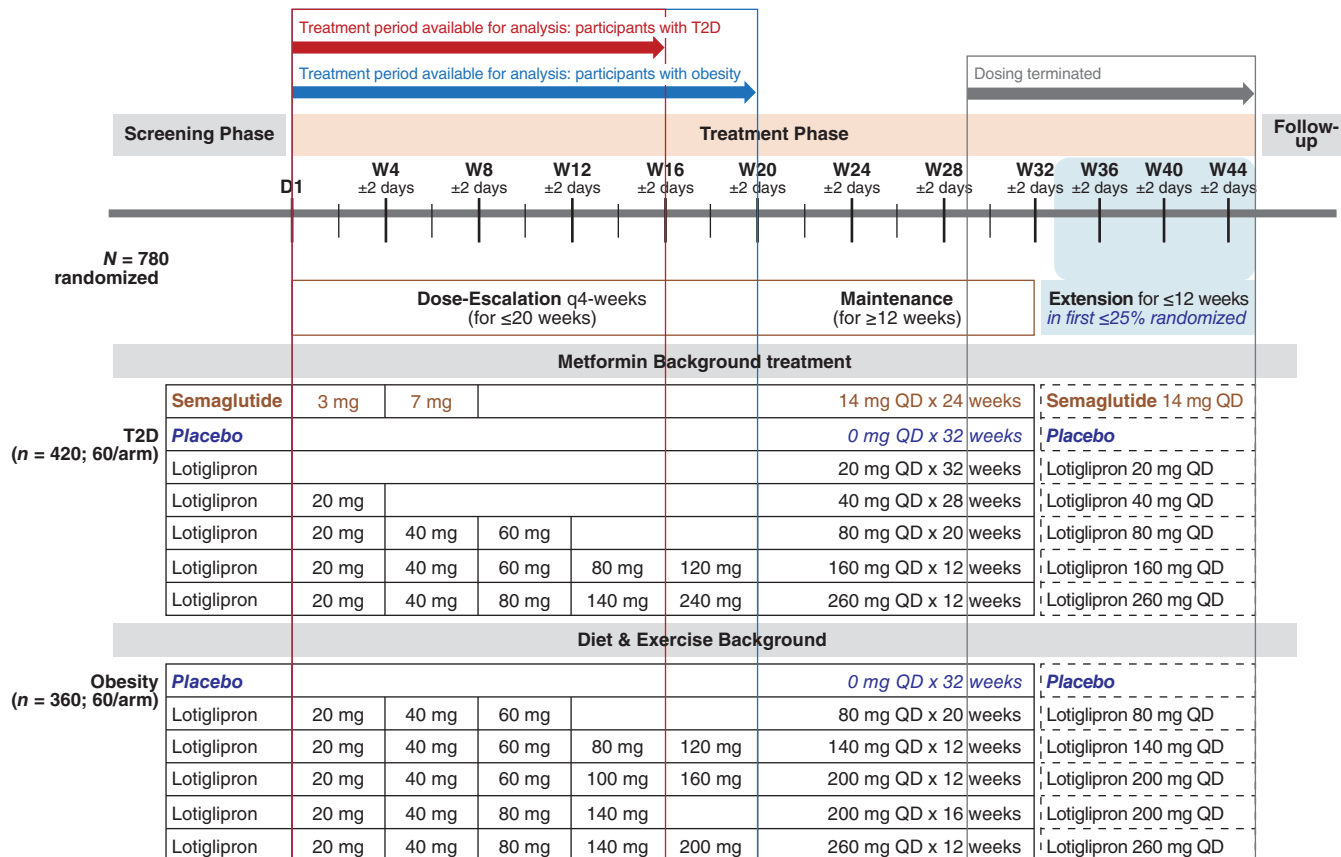


FIGURE 1 Study design. D, day; QD, once daily; T2D, type 2 diabetes; W, week.

lotiglipron QD at one of five maintenance doses (20, 40, 80, 160 or 260 mg) or matching placebo, or semaglutide QD at one maintenance dose (14 mg). Participants in the obesity cohort were randomly assigned in equal numbers to receive lotiglipron QD at one of four maintenance doses, with two dose titration regimens for the 200-mg dose (80 mg, 140 mg, 200 mg five-step titration, 200 mg four-step titration and 260 mg) or matching placebo (Figure 1). The target doses and titration scheme selected for this study were based on observed safety, tolerability, PK and pharmacodynamic data in completed phase 1 clinical studies. The starting lotiglipron dose of 20 mg was found to be well tolerated in a phase I study.²⁶ The target doses evaluated in this study (from 20 to 260 mg QD) were selected to allow adequate bracketing of efficacious doses (from low doses predicted to have sub-maximal efficacy up to doses expected to have near-maximal efficacy, while still having an acceptable safety/tolerability profile). The titration scheme aimed to gradually progress from the starting dose to the target dose in each arm while ensuring participants stay at each dose step for 4 weeks before titrating to the next dose level based on data from marketed GLP-1R agonists, including oral semaglutide,¹⁶ where 4-week intervals at each dose step are generally appropriate to facilitate mitigation of MoA-driven GI adverse events. In addition, the employed titration scheme aimed for ≤ 2 -fold increase in PK exposure with consecutive titration steps.

After a 2-week run-in period in which all participants received single-blind placebo, the randomized study drug regimen was scheduled to be administered for ≥ 32 weeks. Except for the placebo and 20-mg lotiglipron arms, all other arms underwent a titration period of escalating dose levels (every 4 weeks) until reaching their assigned maintenance dose (Figure 1). Participants randomly assigned to lotiglipron or placebo were instructed to self-administer three tablets per dose across all titrated doses with the morning meal. Participants randomly assigned to semaglutide were instructed to take it as directed by the label with required fasting before and after.¹⁶

Across the 12 arms involving administration of lotiglipron or placebo, the double-blind design was retained throughout the study (both titration and maintenance dosing) using four identical-looking tablet strengths and each dose consisting of three tablets, with participants, investigators and site personnel blinded to group assignment. Sponsor staff interacting with the study sites were also blinded to group assignment; however, an IRC, unblinded to treatment assignment, conducted real-time monitoring of safety, biomarker and PK data. The IRC reviews were planned when approximately 25%, 50%, 75% and 100% of the total sample size were randomized, with ad hoc reviews to assess emerging safety signals as dictated by safety data reviews undertaken in a blinded manner by the sponsor staff on a frequency of at least once a month starting at first patient first visit.

2.4 | Study end points and assessments

Due to premature termination of the study prior to week 32 visit and in many participants prior to reaching their assigned maintenance dose, particularly at lotiglipron maintenance doses ≥ 160 mg QD (T2D cohort) and ≥ 140 mg QD (obesity cohort), the planned analyses for the study end points were modified prior to unblinding the study

(Statistical Analyses in Supporting Information S1). Statistical analyses were limited to visits with sufficient data, namely analysis through week 16 (T2D cohort) and week 20 (obesity cohort) (Figure 1).

The primary end point was change from baseline in HbA1c (T2D cohort) and percentage change from baseline in body weight (obesity cohort). In addition, a secondary end point of percentage change in body weight (T2D cohort) was included. Measures of safety in all participants included the assessment of treatment-emergent adverse events (TEAE), and abnormalities in clinical safety laboratory tests, vital signs and standard 12-lead electrocardiograms (ECG). In the obesity cohort, suicidal ideation or behaviour was evaluated using the Columbia Suicide Severity Rating Scale (C-SSRS).

The T2D cohort was instructed to monitor their glucose levels at home ≥ 3 times per week on separate, nonconsecutive days after a fast of ≥ 8 h and/or if symptoms of a hypoglycaemic event were experienced. All other procedures were conducted at prespecified clinic visits during the screening phase (≤ 6 weeks prior to dosing on day 1), placebo run-in (2 weeks prior to dosing on day 1) or treatment phase (week 0/day 1, and on-site visits every 4 weeks thereafter). During the treatment phase all procedures were conducted before the morning dose of the study drug, except collection of post-dose PK samples and ECGs/vitals during on-site visits every 8 weeks. Standard 12-lead ECGs and vital signs were measured in triplicate for those randomly assigned to lotiglipron/placebo. Body weight was measured in duplicate. Spot urine samples were collected for urinalysis, and blood samples were collected for safety, efficacy, biomarker and PK analyses.

2.5 | PK analyses

Blood samples were collected for the measurement of plasma concentrations of lotiglipron (in both cohorts) and semaglutide (in T2D cohort only) pre-dose (every 4 weeks) and post-dose (between 2 and 6 h, every 8 weeks). Plasma concentrations were determined using validated high-performance liquid chromatography with mass spectrometry analytical methods.

2.6 | Statistical analyses

Detailed statistical methods are provided in Supporting Information S1.

3 | RESULTS

3.1 | Participant disposition and baseline characteristics

In total, 1532 participants were screened, with 902 participants randomly assigned to study arms (T2D cohort: $n = 513$, obesity cohort: $n = 389$) (Figure 2). In the T2D cohort, 512 participants were treated with ≥ 1 dose of placebo or study drug; in the obesity cohort, all 389 participants were treated. No participants completed the study treatment phase. The longest study drug exposure was reached by

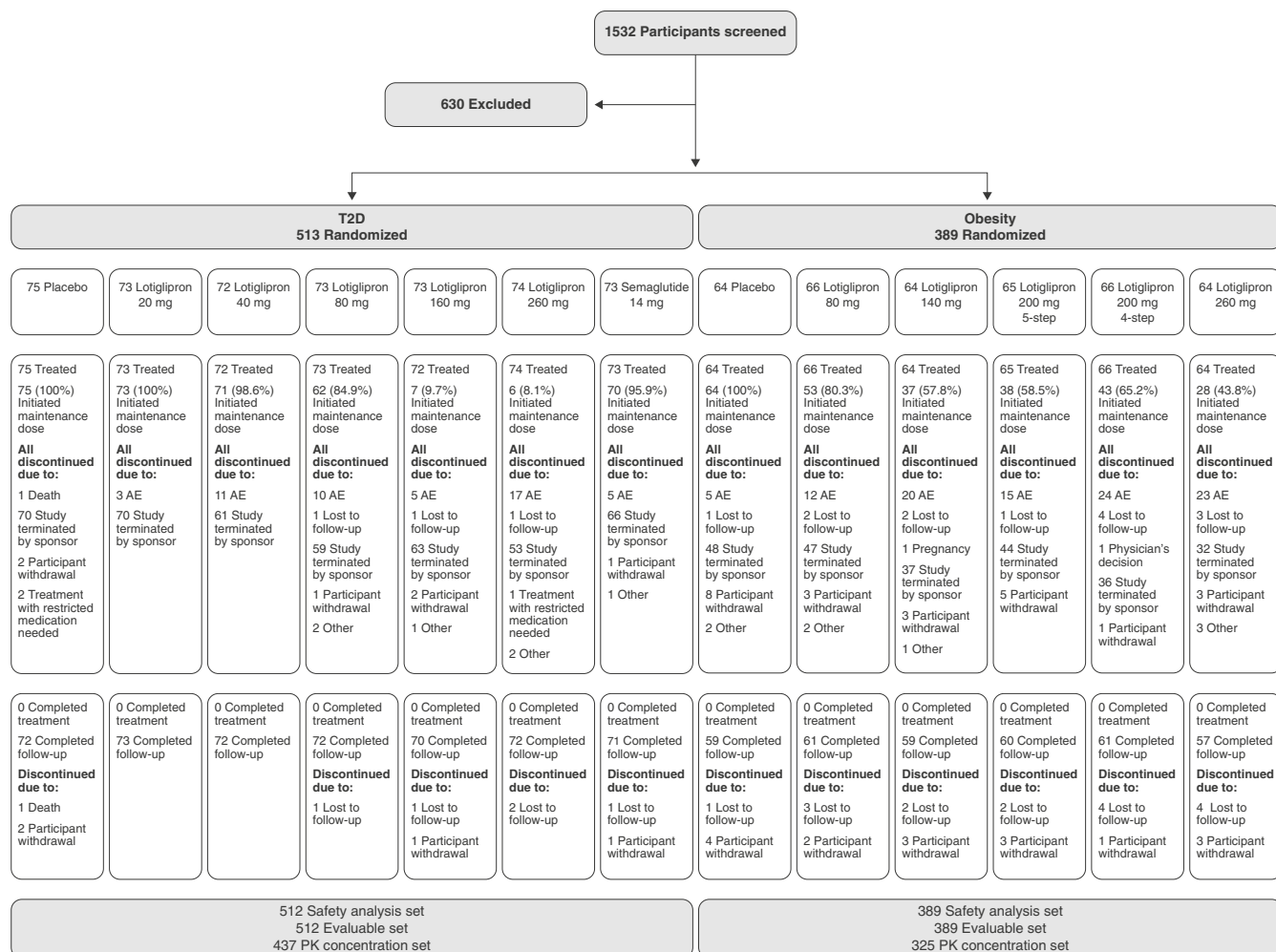


FIGURE 2 Participant disposition. AE, adverse event; T2D, type 2 diabetes.

four participants (two per cohort) who completed the week 28 visit. The number of participants per arm who completed titration and initiated the maintenance phase is shown in Figure 2. Most discontinued treatment due to sponsor's decision to terminate the study (T2D: 86.3%, obesity, 62.7%). The second most common reason was TEAEs (T2D: 10.0%, obesity: 25.4%), with nausea, vomiting, diarrhoea and constipation being the most common (>2% in at least one of the cohorts); however, most participants (>90%) continued to participate in the study after discontinuation of treatment and completed the safety follow-up at least 28 days post last dose.

Demographic and baseline disease characteristics were generally balanced across study arms within each cohort, as expected by the target population (Table 1).

3.2 | Primary efficacy measures in participants with T2D and in participants with obesity

3.2.1 | T2D cohort

In the T2D cohort (with mean baseline HbA1c values ranging 7.80%–8.14%), statistically significant reductions from baseline in HbA1c

versus placebo were observed across all lotiglipron doses and semaglutide 14 mg at week 16 ($p < 0.0001$) (Figure 3A; Table S2), with least squares (LS) mean decreases up to -1.44% (90% CI: -1.63 , -1.26) (lotiglipron 80 mg) compared with placebo at -0.07% (90% CI: -0.25 , 0.11). The magnitude of the effect at week 16 was numerically greater across lotiglipron doses >20 mg versus semaglutide. Notably, participants randomly assigned to maintenance doses of 160 and 260 mg reached only 80 and 140 mg, respectively, at week 16 (Figure 1).

3.2.2 | Obesity cohort

In the obesity cohort (with mean baseline body weight ranging from 104.1 to 110.0 kg) significant reductions from baseline in percentage change in body weight versus placebo across all lotiglipron doses at week 20 were observed ($p < 0.01$) (Figure 3B; Table S2), with LS mean decreases up to -7.47% (90% CI: -8.50 , -6.43) (lotiglipron 200 mg, five-step titration) compared with placebo at -1.84% (90% CI: -2.85 , -0.83). Notably, participants randomly assigned to maintenance doses of 140 mg, 200 mg (five-step titration) and 260 mg reached only 120, 160 and 200 mg, respectively, at week 20 (Figure 1).

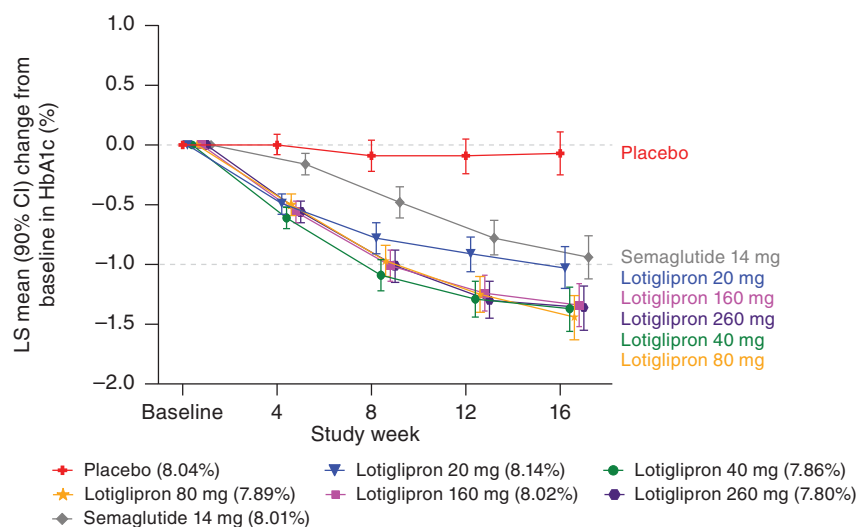
TABLE 1 Demographic and baseline characteristics.

Characteristic	Participants with type 2 diabetes							Participants with obesity						
	Target maintenance dose							Target maintenance dose						
	Placebo	Lotiglipron	Semaglutide					Placebo	Lotiglipron	Semaglutide				
	0 mg (N = 75)	20 mg (N = 73)	40 mg (N = 72)	80 mg (N = 73)	160 mg (N = 72)	260 mg (N = 74)	14 mg (N = 73)	0 mg (N = 64)	80 mg (N = 66)	140 mg (N = 64)	200 mg (five-step) (N = 65)	200 mg (four-step) (N = 66)	260 mg (N = 64)	Overall (N = 389)
Age (years)	60.0 (10.17)	58.8 (10.17)	58.6 (8.47)	57.7 (9.21)	59.6 (9.71)	60.3 (9.76)	59.8 (8.89)	50.9 (13.30)	49.3 (12.97)	48.1 (12.44)	47.6 (13.49)	50.0 (10.74)	48.5 (11.68)	49.1 (12.44)
Sex														
Male	33 (44.0)	43 (58.9)	43 (59.7)	42 (57.5)	39 (54.2)	43 (58.1)	37 (50.7)	28 (43.8)	28 (42.4)	19 (29.7)	29 (44.6)	24 (36.4)	24 (37.5)	152 (39.1)
Female	42 (56.0)	30 (41.1)	29 (40.3)	31 (42.5)	33 (45.8)	31 (41.9)	36 (49.3)	36 (56.3)	38 (57.6)	45 (70.3)	36 (55.4)	42 (63.6)	40 (62.5)	237 (60.9)
Race														
White	58 (77.3)	57 (78.1)	51 (70.8)	54 (74.0)	54 (75.0)	54 (73.0)	57 (78.1)	55 (85.9)	56 (84.8)	44 (68.8)	56 (86.2)	55 (83.3)	52 (81.3)	318 (81.7)
Asian	12 (16.0)	14 (19.2)	17 (23.6)	15 (20.5)	13 (18.1)	14 (18.9)	11 (15.1)	4 (6.3)	3 (4.5)	3 (4.7)	3 (4.6)	4 (6.1)	6 (9.4)	23 (5.9)
Black or African American	4 (5.3)	2 (2.7)	4 (5.6)	4 (5.5)	5 (6.9)	5 (6.8)	5 (6.8)	4 (6.3)	6 (9.1)	15 (23.4)	6 (9.2)	5 (7.6)	4 (6.3)	40 (10.3)
American Indian or Alaska Native	1 (1.3)	0	0	0	0	0	0	1 (1.6)	1 (1.5)	1 (1.6)	0	0	1 (1.6)	4 (1.0)
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	1 (1.6)	0	0	0	1 (0.3)
Multiracial	0	0	0	0	0	0	0	0	0	0	0	1 (1.5)	1 (1.6)	2 (0.5)
Not reported	0	0	0	0	0	1 (1.4)	0	0	0	0	0	1 (1.5)	0	1 (0.3)
Ethnicity														
Hispanic or Latino	14 (18.7)	13 (17.8)	8 (11.1)	7 (9.6)	14 (19.4)	10 (13.5)	8 (11.0)	5 (7.8)	8 (12.1)	10 (15.6)	14 (21.5)	12 (18.2)	10 (15.6)	59 (15.2)
Not Hispanic or Latino	61 (81.3)	60 (82.2)	63 (87.5)	66 (90.4)	58 (80.6)	64 (86.5)	64 (87.7)	59 (92.2)	58 (87.9)	54 (84.4)	51 (78.5)	54 (81.8)	54 (84.4)	330 (84.8)
Not reported	0	0	1 (1.4)	0	0	0	1 (1.4)	0	0	0	0	0	0	0
Type 2 diabetes duration (years)	8.2 (6.41)	9.2 (6.17)	7.3 (5.40)	8.6 (6.12)	8.5 (6.07)	9.1 (6.75)	9.9 (6.50)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
BMI (kg/m ²)	34.3 (6.15)	32.4 (6.12)	33.9 (7.19)	33.8 (7.30)	33.5 (7.68)	34.6 (7.07)	33.3 (6.62)	37.9 (6.69)	37.1 (5.70)	38.4 (7.07)	37.9 (5.68)	37.0 (4.47)	38.3 (7.28)	37.8 (6.20)
Body weight (kg)	95.7 (23.11)	92.2 (18.70)	96.2 (25.12)	97.6 (23.37)	93.5 (23.55)	96.0 (22.60)	94.6 (21.96)	109.7 (22.11)	105.7 (22.28)	106.7 (25.33)	108.2 (21.67)	104.1 (15.92)	109.3 (24.92)	107.3 (22.17)
HbA1c (%)	8.04 (0.971)	8.14 (0.898)	7.86 (0.925)	7.89 (0.948)	8.02 (0.926)	7.80 (0.788)	8.01 (0.929)	5.38 (0.436)	5.37 (0.371)	5.54 (0.382)	5.42 (0.406)	5.42 (0.384)	5.46 (0.408)	5.43 (0.400)
FPG (mg/dL)	173.7 (53.23)	180.7 (39.24)	169.1 (41.40)	169.8 (44.90)	167.4 (43.88)	166.8 (33.95)	171.6 (44.16)	98.7 (11.83)	97.9 (8.75)	99.28 (12.39)	98.3 (10.45)	99.8 (11.45)	101.1 (11.80)	99.2 (11.14)

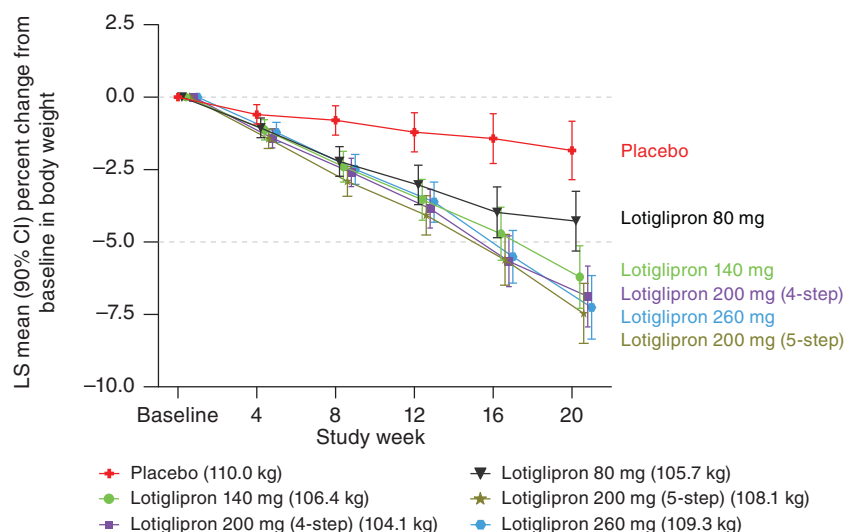
Notes: Safety analysis set. Shown as n (%) for categorical data and mean (standard deviation) for continuous data. Weight and BMI are the average of the measurements at screening visit. For laboratory parameters, baseline is defined as the result closest prior to dosing on day 1. SI conversion factors: to convert HbA1c percentage to mmol/mol, multiply by 10.93 and subtract 23.50; to convert FPG to mmol/L multiply by 0.0555. Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycosylated haemoglobin; N/A, not applicable; SI, International System of Units.

FIGURE 3 Least squares mean change from baseline over time for HbA1c (%) in participants with (A) T2D and percentage change from baseline in body weight in participants with (B) obesity and (C) T2D. Data are for all evaluable participants. Baseline values (shown in legend) are defined as the result (HbA1c) or the average of the duplicate measurements (body weight) closest prior to dosing at visit 3 (day 1). The MMRM model included treatment, cohort, gender, time, baseline $\times$ time interaction and treatment $\times$ time interaction as fixed effects, and baseline as a covariate with time fitted as a repeated effect and participant as a random effect. An unstructured correlation matrix was used unless convergence issues arose; in such cases, a first-order autoregressive followed by a compound symmetry correlation matrix was used. Only planned post-baseline weeks 4, 8, 12 and 16 (T2D cohort) and weeks 4, 8, 12, 16 and 20 (obesity cohort) were included in the model. The on-treatment estimand strategy that estimates the effect if all participants maintain their randomized treatment and adhere to the protocol was applied. CI, confidence interval; HbA1c, glycated haemoglobin; LS, least squares; MMRM, mixed model repeated measures; T2D, type 2 diabetes.

(A) Type 2 diabetes: HbA1c efficacy



(B) Obesity: Weight loss efficacy



(C) Type 2 diabetes: Weight loss efficacy

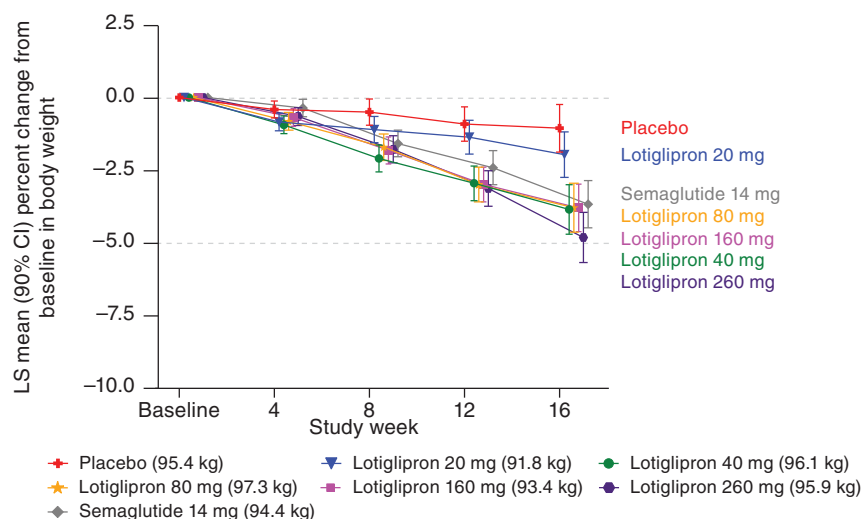


TABLE 2 Treatment-emergent adverse events occurring in $\geq 2\%$ of total participants across lotiglipron arms in either cohort.

Treatment-emergent adverse event	Participants with type 2 diabetes										Participants with obesity					
	Target maintenance dose					Semaglutide					Target maintenance dose					
	Lotiglipron		Overall			Lotiglipron		Overall			Placebo		Lotiglipron			Overall
	0 mg (N = 75)	20 mg (N = 73)	40 mg (N = 72)	80 mg (N = 73)	160 mg (N = 72)	260 mg (N = 74)	14 mg (N = 73)	Overall (N = 512)	Overall (N = 512)	Overall (N = 512)	0 mg (N = 64)	80 mg (N = 66)	140 mg (N = 64)	200 mg (five step) (N = 65)	200 mg (four step) (N = 66)	260 mg (N = 64)
With any TEAE	11 (14.7)	25 (34.2)	45 (62.5)	34 (46.6)	37 (51.4)	47 (63.5)	27 (37.0)	226 (44.1)	226 (44.1)	226 (44.1)	34 (53.1)	49 (74.2)	46 (71.9)	54 (83.1)	59 (89.4)	53 (82.8)
Nausea	3 (4.0)	11 (15.1)	17 (23.6)	21 (28.8)	14 (19.4)	19 (25.7)	10 (13.7)	95 (18.6)	95 (18.6)	95 (18.6)	8 (12.5)	34 (51.5)	30 (46.9)	38 (58.5)	40 (60.6)	32 (50.0)
Diarrhoea	1 (1.3)	8 (11.0)	9 (12.5)	8 (11.0)	4 (5.6)	8 (10.8)	6 (8.2)	44 (8.6)	44 (8.6)	44 (8.6)	12 (18.8)	10 (15.2)	10 (15.6)	16 (24.6)	17 (25.8)	17 (26.6)
Vomiting	1 (1.3)	1 (1.4)	6 (8.3)	11 (15.1)	6 (8.3)	11 (14.9)	6 (8.2)	42 (8.2)	42 (8.2)	42 (8.2)	1 (1.6)	7 (10.6)	10 (15.6)	21 (32.3)	19 (28.8)	22 (34.4)
Constipation	1 (1.3)	2 (2.7)	7 (9.7)	3 (4.1)	4 (5.6)	6 (8.1)	4 (5.5)	27 (5.3)	27 (5.3)	27 (5.3)	5 (7.8)	14 (21.2)	15 (23.4)	15 (23.1)	23 (34.8)	17 (26.6)
Decreased appetite	1 (1.3)	1 (1.4)	5 (6.9)	3 (4.1)	4 (5.6)	7 (9.5)	0	21 (4.1)	21 (4.1)	21 (4.1)	5 (7.8)	5 (7.6)	7 (10.9)	3 (4.6)	8 (12.1)	8 (12.5)
Dyspepsia	1 (1.3)	3 (4.1)	2 (2.8)	4 (5.5)	4 (5.6)	3 (4.1)	2 (2.7)	19 (3.7)	19 (3.7)	19 (3.7)	2 (3.1)	6 (9.1)	4 (6.3)	6 (9.2)	9 (13.6)	4 (6.3)
Abdominal discomfort	0	0	1 (1.4)	1 (1.4)	5 (6.9)	6 (8.1)	1 (1.4)	14 (2.7)	14 (2.7)	14 (2.7)	0	3 (4.5)	1 (1.6)	3 (4.6)	2 (3.0)	3 (4.7)
Gastroesophageal reflux disease	0	0	2 (2.8)	3 (4.1)	4 (5.6)	3 (4.1)	1 (1.4)	13 (2.5)	13 (2.5)	13 (2.5)	1 (1.6)	10 (15.2)	6 (9.4)	5 (7.7)	13 (19.7)	6 (9.4)
Urinary tract infection	1 (1.3)	1 (1.4)	4 (5.6)	1 (1.4)	0	6 (8.1)	4 (5.5)	17 (3.3)	17 (3.3)	17 (3.3)	2 (3.1)	2 (3.0)	2 (3.1)	6 (9.2)	5 (7.6)	3 (4.7)
Abdominal distension	0	1 (1.4)	5 (6.9)	2 (2.7)	2 (2.8)	1 (1.4)	1 (1.4)	12 (2.3)	12 (2.3)	12 (2.3)	4 (6.3)	2 (3.0)	3 (4.7)	1 (1.5)	3 (4.5)	4 (6.3)
Abdominal pain upper	0	3 (4.1)	5 (6.9)	1 (1.4)	1 (1.4)	1 (1.4)	1 (1.4)	12 (2.3)	12 (2.3)	12 (2.3)	1 (1.6)	1 (1.5)	4 (6.3)	6 (9.2)	3 (4.5)	3 (4.7)
Dizziness	2 (2.7)	0	1 (1.4)	1 (1.4)	2 (2.8)	7 (9.5)	0	13 (2.5)	13 (2.5)	13 (2.5)	3 (4.7)	4 (6.1)	2 (3.1)	1 (1.5)	4 (6.1)	4 (6.3)
Headache	0	2 (2.7)	5 (6.9)	2 (2.7)	1 (1.4)	1 (1.4)	2 (2.7)	13 (2.5)	13 (2.5)	13 (2.5)	5 (7.8)	7 (10.6)	4 (6.3)	7 (10.8)	9 (13.6)	5 (7.8)
Lipase increased	0	3 (4.1)	4 (5.6)	1 (1.4)	0	3 (4.1)	3 (4.1)	14 (2.7)	14 (2.7)	14 (2.7)	0	2 (3.0)	0	0	1 (1.5)	2 (3.1)
Hepatic function abnormal	0	0	3 (4.2)	1 (1.4)	2 (2.8)	4 (5.4)	0	10 (2.0)	10 (2.0)	10 (2.0)	0	0	1 (1.6)	0	0	0
Abdominal pain	0	0	5 (6.9)	1 (1.4)	1 (1.4)	2 (2.7)	2 (2.7)	11 (2.1)	11 (2.1)	11 (2.1)	4 (6.3)	3 (4.5)	6 (9.4)	2 (3.1)	10 (15.2)	4 (6.3)
Fatigue	0	0	4 (5.6)	1 (1.4)	2 (2.8)	2 (2.7)	2 (2.7)	11 (2.1)	11 (2.1)	11 (2.1)	5 (7.8)	7 (10.6)	5 (7.8)	6 (9.2)	5 (7.6)	5 (7.8)
Nasopharyngitis	1 (1.3)	0	3 (4.2)	2 (2.7)	1 (1.4)	2 (2.7)	0	9 (1.8)	9 (1.8)	9 (1.8)	0	5 (7.6)	2 (3.1)	4 (6.2)	2 (3.0)	4 (6.3)
Eructation	0	0	1 (1.4)	0	0	1 (1.4)	0	2 (0.4)	2 (0.4)	2 (0.4)	0	3 (4.5)	0	2 (3.1)	4 (6.1)	5 (7.8)
Back pain	1 (1.3)	2 (2.7)	1 (1.4)	1 (1.4)	0	1 (1.4)	1 (1.4)	7 (1.4)	7 (1.4)	7 (1.4)	2 (3.1)	2 (3.0)	1 (1.6)	3 (4.6)	4 (6.1)	3 (4.7)
COVID-19	0	2 (2.7)	0	1 (1.4)	1 (1.4)	2 (2.7)	0	6 (1.2)	6 (1.2)	6 (1.2)	5 (7.8)	3 (4.5)	2 (3.1)	1 (1.5)	2 (3.0)	5 (7.8)
Upper-respiratory-tract infection	2 (2.7)	1 (1.4)	1 (1.4)	0	1 (1.4)	0	3 (4.1)	8 (1.6)	8 (1.6)	8 (1.6)	3 (4.7)	2 (3.0)	1 (1.6)	4 (6.2)	5 (7.6)	0

TABLE 2 (Continued)

Treatment-emergent adverse event	Participants with type 2 diabetes										Participants with obesity								
	Target maintenance dose										Target maintenance dose								
	Placebo	Lotiglipron	Semaglutide					Overall	Placebo	Lotiglipron	Semaglutide					Overall			
	0 mg (N = 75)	20 mg (N = 73)	40 mg (N = 72)	80 mg (N = 73)	160 mg (N = 72)	260 mg (N = 74)	14 mg (N = 73)	0	6 (1.2)	0 mg (N = 64)	80 mg (N = 66)	140 mg (N = 64)	200 mg (five step) (N = 65)	200 mg (four step) (N = 66)	260 mg (N = 64)	Overall (N = 389)			
Alanine aminotransferase increased	0	0	1 (1.4)	2 (2.7)	1 (1.4)	2 (2.7)	0	0	6 (1.2)	2 (3.1)	1 (1.5)	2 (3.1)	1 (1.5)	5 (7.6)	1 (1.6)	12 (3.1)			
Flatulence	1 (1.3)	0	1 (1.4)	1 (1.4)	0	4 (5.4)	0	0	7 (1.4)	2 (3.1)	1 (1.5)	1 (1.6)	1 (1.5)	3 (4.5)	4 (6.3)	12 (3.1)			
Bronchitis	1 (1.3)	1 (1.4)	0	0	0	2 (2.7)	0	0	4 (0.8)	1 (1.6)	4 (6.1)	1 (1.6)	3 (4.6)	0	0	9 (2.3)			
Gastroenteritis	0	0	0	1 (1.4)	0	0	2 (2.7)	0	3 (0.6)	2 (3.1)	1 (1.5)	1 (1.6)	3 (4.6)	2 (3.0)	1 (1.6)	10 (2.6)			
Arthralgia	0	1 (1.4)	0	1 (1.4)	0	1 (1.4)	0	0	3 (0.6)	0	2 (3.0)	0	2 (3.1)	3 (4.5)	0	7 (1.8)			
Aspartate aminotransferase increased	0	0	1 (1.4)	2 (2.7)	0	0	0	0	3 (0.6)	1 (1.6)	1 (1.5)	2 (3.1)	0	3 (4.5)	1 (1.6)	8 (2.1)			
Insomnia	0	0	0	0	0	1 (1.4)	0	0	1 (0.2)	0	1 (1.5)	0	3 (4.6)	1 (1.5)	2 (3.1)	7 (1.8)			

Notes: Safety analysis set. Data are number of participants *n* (%). Treatment-emergent adverse events, all causalities, with $\geq 2\%$ occurrences across all lotiglipron arms in either target population (T2D or obesity). Participants are counted only once per treatment per event; includes all data collected since the first dose of study drug at visit 3 (day 1); MedDRA, version 26.0, coding dictionary applied.

Abbreviations: COVID-19, coronavirus disease 2019; MedDRA, Medical Dictionary for Regulatory Activities; T2D, type 2 diabetes; TEAE, treatment-emergent adverse event.

3.3 | Secondary efficacy measures in participants with T2D

In the T2D cohort (with mean baseline body weight ranging from 91.8 to 97.3 kg) significant reductions from baseline in percentage change in body weight versus placebo were observed with all lotiglipron doses >20 mg, at week 16 ($p < 0.001$) (Figure 3C; Table S2).

3.4 | Safety and tolerability

A total of 707 TEAEs were reported in 303 (59.2%) participants in the T2D cohort; TEAEs by randomized arms are presented in Table S3. Most participants reported TEAEs of mild ($n = 197$, 38.5%) or moderate ($n = 99$, 19.3%) severity (data not shown), with severe TEAEs reported in 7 (1.4%) participants and serious TEAEs reported in 11 (2.1%) participants (Table S3). One death due to cardiac arrest was reported in a participant randomly assigned to placebo. Discontinuations of the study drug due to TEAEs were reported in 51 (10%) participants, mostly in the lotiglipron 40-, 80- and 260-mg groups (Table S3).

A total of 1258 TEAEs were reported in 317 (81.5%) participants in the obesity cohort (Table S3). Most participants reported TEAEs of mild ($n = 166$, 42.7%) or moderate ($n = 128$, 32.9%) severity (data not shown). Severe TEAEs and serious TEAEs were reported in 23 (5.9%) and 10 (2.6%) participants, respectively (Table S3). No deaths were reported. Discontinuation of the study drug due to TEAEs was reported in 97 (24.9%) participants, most frequently in the lotiglipron 140-mg, 200-mg five-step, 200-mg four-step and 260-mg groups (Table S3). More rapid titration of lotiglipron in the 200-mg four-step group exhibited a higher discontinuation rate compared with slower titration in the 200-mg five-step group (36.4% vs. 23.1%).

In the T2D cohort, the most frequently reported TEAEs ($\geq 5\%$ of participants) were GI-related (nausea, 18.6%; diarrhoea, 8.6%; vomiting, 8.2%; constipation, 5.3%) (Table 2), with most mild to moderate in severity (nausea, 18.4%; diarrhoea, 8.4%; vomiting, 7.8%; constipation, 5.3%; data not shown). Severe TEAEs were reported in two participants (one in the lotiglipron 80-mg group with severe diarrhoea and vomiting and one in the lotiglipron 260-mg group with severe nausea and vomiting). In the obesity cohort, the most frequently reported TEAEs were nausea (46.8%), constipation (22.9%), diarrhoea (21.1%), vomiting (20.6%), gastroesophageal reflux disease (10.5%), headache (9.5%), decreased appetite (9.3%), fatigue (8.5%), dyspepsia (8.0%), abdominal pain (7.5%) and urinary tract infection (5.1%) (Table 2). Of those, severe TEAEs were reported in 12 participants.

The incidence of the most common GI-related TEAEs (nausea, diarrhoea, vomiting and constipation) is shown over time (by titration step) in each cohort by maintenance dose (Figure S1). In the T2D cohort, no clear increase in incidence with increasing lotiglipron doses was observed for any of these GI-related TEAEs (Figure S1A–D). In the obesity cohort, the proportion of GI-related TEAEs was higher than that in the T2D cohort, and there appeared to be a dose-dependent trend for vomiting (primarily with doses of lotiglipron

≥ 80 mg showing an increase over time) but not for the other GI-related TEAEs (constipation showed a numerically decreasing incidence over time across most lotiglipron doses) (Figure S1E–H). Across both cohorts, the incidence of GI-related TEAEs generally decreased as titration continued.

Protocol-defined hypoglycaemic TEAEs are summarized for participants with T2D after pooling of data across each titration dose for lotiglipron and semaglutide (Table S4). Overall incidence of hypoglycaemia was ≤ 2 participants per titration dose. There was one protocol-defined severe hypoglycaemic event in the T2D cohort in the lotiglipron 20-mg group (Table S4). One protocol-defined probable symptomatic hypoglycaemia event was reported in the obesity cohort in the lotiglipron 200-mg group (data not shown).

The mean baseline and percentage change from baseline for serum amylase and lipase (data not shown), along with the proportions of participants noted to have elevated serum lipase or serum amylase, are similar to those reported with other oral GLP-1R agonists, and there were no reports of incident pancreatitis.^{16,23,24}

Lotiglipron administration led to transaminase elevations in a subset of participants in both cohorts, with no on-treatment Hy's law cases reported. A total of 44 participants (24 of 361 [6.6%] on lotiglipron in the T2D cohort, 19 of 319 [6.0%] on lotiglipron in the obesity cohort and 1 of 64 [1.6%] on placebo in the obesity cohort) were observed to have elevation in ALT and/or AST $>3\times$ upper limit of normal (ULN) (one participant had AST level $>3\times$ ULN but ALT $<3\times$ ULN). The magnitude of ALT elevation was higher than that of AST elevation in the majority of cases. The incidence of ALT $>3\times$ ULN was 4.5% in participants in the T2D cohort and 5.2% in participants in the obesity cohort compared with the incidence of AST $>3\times$ ULN of 2.4% and 1.6% in the respective cohorts (Tables S5 and S6). Elevations in ALT $>8\times$ ULN (T2D: 1.8%, obesity: 0.5%) and AST $>8\times$ ULN (T2D: 0.6%, obesity: 0.3%) were observed. The change in individual ALT and AST levels over time by assigned treatment and cohort shows that most ALT and AST elevations were first observed at weeks 8 and 12 while participants were receiving 40, 60 or 80 mg of lotiglipron doses with no elevations $>3\times$ ULN observed with 20-mg lotiglipron or semaglutide (Figures S2 and S3). The proportion of participants with ALT or AST $>3\times$ ULN did not further increase with increasing lotiglipron doses. Furthermore, a decline in ALT or AST was notable despite continued lotiglipron dosing as well as with temporary or permanent discontinuation of lotiglipron shown in Figures S2 and S3, with measurements occurring off the study drug noted with an 'x' on the applicable spaghetti lines. In both cohorts, although participants with increases in ALT or AST were observed to have lost body weight, there were many participants who lost considerably more body weight but were not observed to have elevated ALT or AST (data not shown). No changes in potential clinical concern were observed in other laboratory parameters.

At baseline, all 389 participants in the obesity cohort were evaluated using the C-SSRS; one in the lotiglipron 260-mg group reported suicidal ideation without intent to act. Post baseline, in 383 participants (98.5%) assessed, one participant in the placebo group reported self-injurious behaviour without suicidal intent, and one participant in

the 260-mg group reported suicidal ideation without intent to act (same participant who reported ideation at baseline).

No clinically significant adverse trends in vital signs or ECGs were apparent (data not shown).

3.5 | Pharmacokinetics

Lotiglipron trough concentrations (across both cohorts) generally increased with increasing doses and were in alignment with expected exposures (Figure S4). Semaglutide trough concentrations (T2D cohort) also increased with increasing doses (data not shown).

Participants who had ALT or AST levels $>3\times$ ULN exhibited, on average, higher lotiglipron dose-normalized trough and post-dose concentrations compared with participants who did not meet this criterion; this separation was evident as early as week 0 (post-dose) and week 4 (trough) and continued at week 8 and week 12 (Figure S5). The largest difference in trough and post-dose concentrations between the two groups was observed at week 8, aligning with the timing at which the majority of ALT and AST elevations were generally observed (Figures S2 and S3).

The IRC for this study conducted four planned reviews (after ~25%, 50%, 75% and 100% of the total sample size was randomized). The decision to terminate this study and the clinical development of lotiglipron was based on the recommendation from the IRC after its second ad hoc (and sixth and final) review of the unblinded safety and PK data from this study. At this second ad hoc review, the IRC also reviewed the safety and PK data from the two phase 1 DDI studies.

4 | DISCUSSION

Although this phase 2 study was terminated prematurely, the study demonstrated the efficacy of lotiglipron across a range of doses in two study cohorts, with significant reductions in HbA1c and body weight at week 16 in participants with T2D and significant reductions in body weight at week 20 in participants with obesity. In the T2D cohort, separation from placebo occurred as early as week 4 (HbA1c) and week 8 (body weight), with improvement in HbA1c at week 16 numerically greater than semaglutide with lotiglipron doses >20 mg. Observed data for semaglutide were in line with results of other studies with oral semaglutide 14 mg, validating its use as an internal reference standard.²⁷ The HbA1c efficacy of lotiglipron across doses >20 mg generally was in line with the reported range of efficacy at week 16 of other small-molecule, oral, GLP-1R agonists.^{19,20,23} The percentage of weight loss from baseline nearly reached or exceeded 4.0% at week 16 across all doses >20 mg. In the obesity cohort, separation from placebo in body weight occurred as early as week 8, with significant weight loss ranging from 4.3% to 7.5% at week 20, which is likely too early to determine the nadir effect of lotiglipron. However, similar weight loss, at week 20, has been observed with another small-molecule, oral, GLP-1R agonist.²⁴

Consistent with the pharmacology of GLP-1R agonists, the most frequently reported TEAEs were GI-related (most mild to moderate severity), and GI-related TEAEs, in general, were the most common cause for discontinuation of the study drug (apart from study termination) in both cohorts. In addition, observed changes in serum amylase and lipase were similar to those reported with other oral GLP-1R agonists.^{16,23,24} Based on drug discontinuations with different titration steps (200 mg four step vs. 200 mg five step), slower titration resulted in better tolerability than a more rapid titration. GI tolerability appeared to be better in participants with T2D compared with obesity without T2D. This can be hypothesized to be related to slower gastric motility associated with T2D³⁰ and/or the development of tolerance to GI-related TEAEs with background use of metformin. Across cohorts, the incidence of GI-related TEAEs generally decreased as titration continued and was generally comparable to other studies with oral GLP-1R agonists, though acknowledging differences in study designs.^{19,23,24,27} Nonetheless, we cannot rule out the possibility that tolerability differences between the two cohorts stem from disproportionate randomization of study participants across the three main geographic regions (with most participants in the obesity cohort randomized in North America).

Although no on-treatment Hy's law cases were observed in this study, lotiglipron doses ≥ 40 mg were associated with incident elevations in liver transaminases in 5% of the participants randomly assigned, with no clear traits identified in this subpopulation, including the relationship between weight loss and elevation in transaminases. Participants who had ALT or AST levels $>3\times$ ULN exhibited, on average, higher lotiglipron dose-normalized trough and post-dose plasma concentrations compared with participants who did not meet this criterion, with a maximum difference between the two groups observed at week 8, aligning with the timing at which the majority of ALT and AST elevations were generally observed. This also aligns with the lack of a clear adverse liver signal in the earlier phase 1b studies with a dosing duration of 4–6 weeks.²⁶ The MoA underlying the elevated transaminases is not clearly understood; however, temporal alignment between ALT and AST elevations and lotiglipron concentrations, as well as data from two phase 1 DDI studies (mentioned in Section 2.1 and to be presented in a separate publication), suggests lotiglipron can decrease the liver's capacity to transport or metabolize drugs, including lotiglipron itself, in a subset of participants. In additional analyses conducted to identify an underlying cause for the elevated liver transaminases in the subset of participants (e.g. timing of ALT/AST elevations over the course of treatment and follow-up [off treatment], influence of changes in body weight and relationship to lotiglipron concentrations), the only aspect that separated the subset with ALT/AST elevations from the rest of the population randomly assigned was higher plasma lotiglipron concentrations (Figure S5). An exhaustive retrospective review of in vitro and in vivo preclinical toxicity and absorption, distribution, metabolism and excretion data for lotiglipron did not observe any signals consistent with liver toxicity in these nonclinical data, suggesting the elevated transaminases may be unique to humans.

4.1 | Limitations

The study was terminated prior to observation at week 32 and prior to many participants reaching a maintenance dose. Statistical analyses, including those for efficacy, were thus limited to visits with sufficient data, and evaluation of the protocol-defined efficacy and safety end points at week 32 was not possible. As a result, dose-response assessments of drug effects on the primary end points, HbA1c (T2D) and body weight (obesity), are not clear. Notwithstanding these limitations, in both cohorts the efficacy of lotiglipron was robust with statistically significant results across multiple doses. As is typical for phase 2 dose-ranging studies, this study did not permit dose modifications, though a temporary pause in dosing, lifestyle modifications and the use of pharmacological agents to help manage MoA-based GI-related TEAEs were permitted. As a result, the GI-related TEAE profile likely represents the worst case. This study observed an effect on liver transaminases in a subset of participants, with the reason for differential effects among participants an open research question.

5 | CONCLUSIONS

This phase 2 study of lotiglipron demonstrated glycaemic and body weight efficacy in participants with T2D and body weight efficacy in those with obesity (without T2D). The safety profile was largely consistent with what has been previously known about the MoA. Our results are unique in reporting liver ALT/AST elevations without elevated bilirubin in a subset of participants treated with lotiglipron, with attempts to identify the at-risk population unsuccessful and therefore clinical development of lotiglipron terminated.

AUTHOR CONTRIBUTIONS

Neeta B. Amin, Margot Johnson and Nikolaos Tsamandouras contributed to the conception and design of the study. All authors contributed to the acquisition, analysis or interpretation of the data. Amina Z. Haggag, Timothy R. Smith, Szilard Vasas and Witold Zmuda were the primary clinical investigators, and Sarah J. DuBrava was the study statistician. All authors contributed to drafting, revising or reviewing the manuscript, and approved the final version.

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CONFLICT OF INTEREST STATEMENT

Neeta B. Amin, Gina Buckley, Robert Frederich, Alexandra Palmer, Tilman Schuster, Nikolaos Tsamandouras and Qi Zhu are full-time employees of Pfizer and may own shares/stock options in Pfizer. Sarah J. DuBrava and Margot Johnson were full-time employees of Pfizer at the time of this study and may own shares/stock options in Pfizer. Amina Z. Haggag was a primary investigator and owns Pfizer stock. Szilard Vasas was a primary investigator of this study and others sponsored by Novo Nordisk, IONIS Pharma, Arrowhead Pharmaceuticals and New Amsterdam. Timothy R. Smith was a primary investigator of this study and others sponsored by Lilly, Amgen, Novo Nordisk, Novartis, Boehringer Ingelheim, AbbVie, Reata and Vertex. Witold Zmuda was a primary investigator and reports no other conflicts of interest.

DATA AVAILABILITY STATEMENT

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See <https://www.pfizer.com/science/clinical-trials/trial-data-and-results> for more information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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