

Oral small molecule GLP-1 receptor agonist aleniglipron in people with overweight or obesity: a randomized, double-blind, placebo-controlled phase 2b trial

Received: 22 April 2026

Accepted: 19 May 2026

Published online: 05 June 2026

 Check for updates

Julio Rosenstock¹✉, Ildiko Lingvay², Donna Ryan³, Ania M. Jastreboff⁴, Robert Kushner⁵, Andres Acosta⁶, Thomas C. Blevins⁷, Melissa Choi⁸, Faith L. Holmes⁹, Timothy Smith¹⁰, Lisa Connery¹¹, Yao Li¹², Mike Ke Liu¹², Aline Barth¹², Jamie Butcher¹², Antonio Civitarese¹², Huibin Yue¹² & Blai Coll¹² on behalf of the ACCESS Trial Investigators*

Aleniglipron is an oral, small-molecule glucagon-like peptide-1 receptor agonist (GLP1-RA) in development for obesity treatment. The ACCESS phase 2b placebo-controlled, double-blind study randomized 230 adults (mean BMI 39.5 kg m⁻², 54% female) with obesity or overweight to examine the effects of once-daily aleniglipron escalated every 4 weeks to 45, 90 or 120 mg. At week 36, the trial met its primary endpoint with a placebo-adjusted LS mean (95% confidence interval) body-weight change from baseline of -8.2% (-11.1 to -5.3%), -9.8% (-12.5 to -7.2%) and -11.3% (-13.9 to -8.6%) for the aleniglipron 45-, 90- and 120-mg arms, respectively ($P < 0.0001$, all doses versus placebo), with no apparent weight-loss plateau at the end of the double-blind period. Continued weight loss was observed at the interim analysis (median treatment duration of 20 weeks) of the ongoing open-label extension. Gastrointestinal events were generally mild to moderate and decreased in frequency over time, with little to no recurrence of vomiting after reintroduction following permitted dose interruptions. Treatment-related discontinuations were 10.4% across aleniglipron arms, with no events of drug-induced liver injury. Clinically relevant weight reductions of up to 11.3% with a tolerability profile consistent with the GLP-1RA class support further development of aleniglipron for obesity treatment. ClinicalTrials.gov registration: [NCT06693843](https://clinicaltrials.gov/ct2/show/study/NCT06693843).

The incidence of obesity is increasing globally, leading to elevated risk for mortality and comorbidities and increased healthcare costs. GLP-1 RAs that mimic the effects of GLP-1, an incretin hormone that decreases appetite, increases satiety and delays gastric emptying, have been approved for chronic weight management, as well as for type 2 diabetes. In addition, GLP-1RAs have been demonstrated to reduce cardiovascular risk, improve metabolic-dysfunction-associated steatohepatitis (MASH) and moderate-to-severe sleep apnea and

consistently show clinically meaningful improvements in markers of systemic inflammation¹⁻⁷. Available peptide-based GLP-1 RAs are increasingly used for obesity treatment but are not widely accessible to broader populations. Most GLP-1 RAs are injectable, which limits patient access because of resistance to this method of administration, inconvenient storage procedures (refrigeration) and scalability limitations due to complex manufacturing processes and cost considerations.

A full list of affiliations appears at the end of the paper. ✉ e-mail: juliorosenstock@dallasdiabetes.com

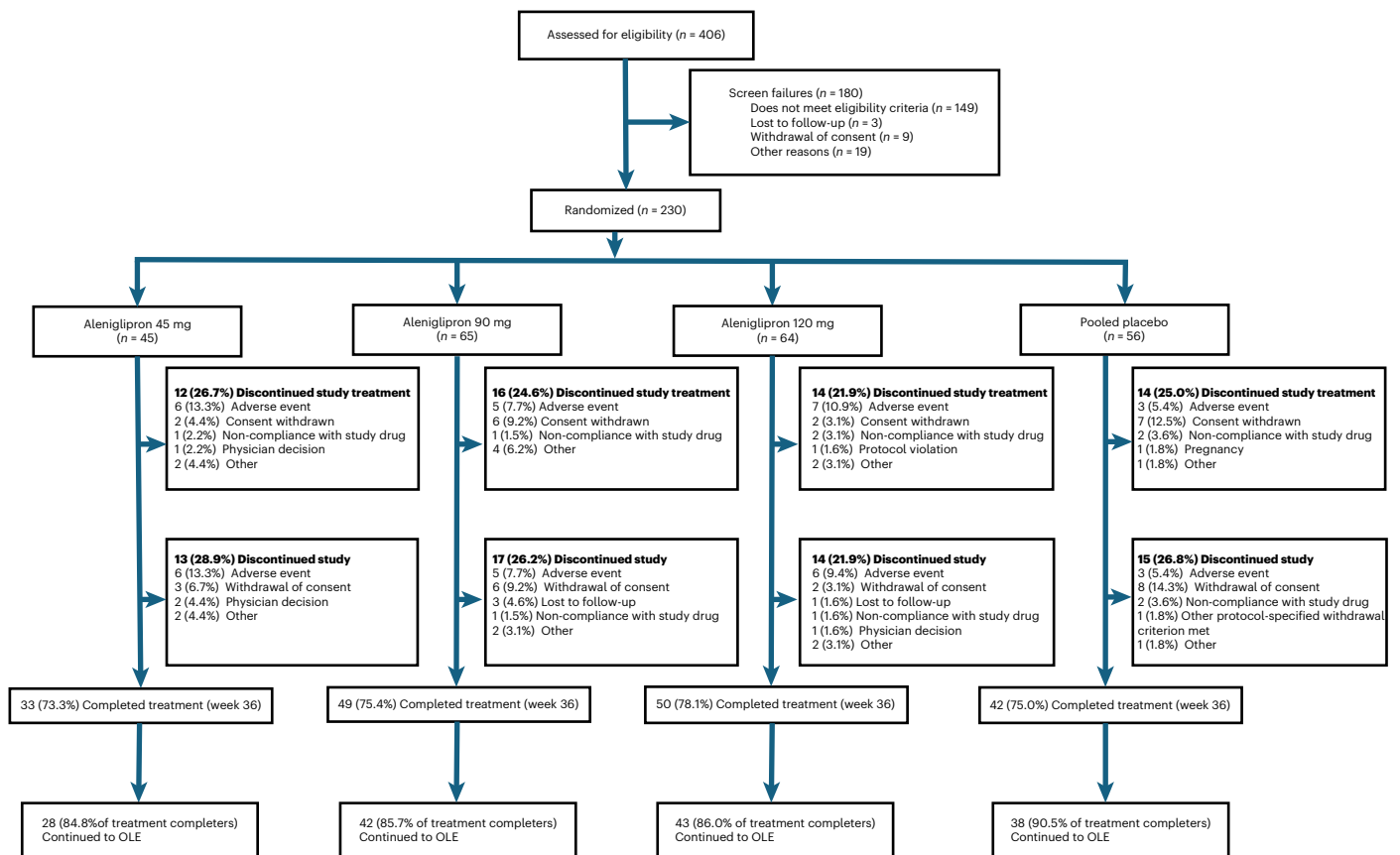


Fig. 1 | CONSORT diagram. CONSORT diagram illustrating screening and randomization to the aleniglipron treatment arms. Participants who completed treatment were allowed to enroll in the open-label extension phase of the ACCESS trial, or completed the end-of-study visit if they did not continue to open-label extension.

Small-molecule GLP-1 RAs can be orally administered, can be manufactured at scale and could address access and treatment gaps. Several oral GLP-1 RA compounds at different stages of clinical development, including two which are FDA-approved, oral semaglutide and orforglipron, with the latter being a small molecule demonstrating -12.4% body weight loss by 72 weeks (refs. 1–3,5,8,9). Oral therapies with this degree of effectiveness could offer more convenient obesity treatments with broader accessibility.

Aleniglipron (GSR-1290) is a potent, highly selective small-molecule GLP-1RA in development for obesity treatment. Aleniglipron was designed using structure-based drug discovery to provide chemical stability, enhance scalability and improve accessibility (Extended Data Fig. 1). The ACCESS phase-2b study evaluated once-daily oral aleniglipron over 36 weeks to assess the efficacy, safety and tolerability of three maintenance doses (45, 90, 120 mg daily) compared with placebo in adults with obesity or overweight and one or more weight-related comorbidity. Additionally, a predefined, open-label extension (OLE) estimated longer-term safety, durability of weight loss beyond 36 weeks and whether starting at a lower dose (2.5 mg) of aleniglipron in the placebo arm improves tolerability.

Results

Trial design and participants

Between 28 October 2024 and 7 February 2025, 406 adults were screened and 230 participants underwent randomization across 38 sites in the United States (Fig. 1 and Supplementary Table 1). The mean (\pm s.d.) age of the randomized participants was 49.8 ± 13.7 years, body mass index (BMI) was 39.5 ± 6.9 kg m $^{-2}$, body weight was 114.8 ± 22.6 kg and waist circumference was 121.2 ± 14.5 cm; 125 participants (54%) were female (Table 1).

Similar percentages of participants completed the study treatment in the 45-mg (33 (73.3%)), 90-mg (49 (75.4%)) and 120-mg (50 (78.1%)) aleniglipron arms and the pooled placebo group (42 (75.0%)) (Fig. 1).

Participants were randomized to three dose-level cohorts (45, 90 or 120 mg) at a ratio of 3:4:4, then to aleniglipron or placebo at a ratio of 3:1 in each cohort (Figs. 1 and 2). Each participant received ascending daily doses of aleniglipron, starting at 5 mg or placebo, with titration every 4 weeks until the maintenance dose was reached over a 36-week period (Fig. 2). Randomization was stratified by baseline BMI (≤ 35 kg m $^{-2}$; > 35 kg m $^{-2}$) and sex. For analyses, participants assigned to the placebo in each cohort were pooled for comparison with each aleniglipron treatment group.

The primary endpoint (efficacy estimand) was the percentage change in body weight from baseline to week 36. The secondary endpoints (efficacy estimand) were the percentages of participants who achieved $\geq 5\%$, $\geq 10\%$ and $\geq 15\%$ reductions in body weight by week 36, and changes in absolute body weight, waist circumference and BMI from baseline to week 36. Additional secondary safety endpoints were treatment-emergent adverse events (TEAEs), serious adverse events (SAEs) (Extended Data Table 1), adverse events of special interest (AESIs), laboratory parameters, electrocardiograms and vital signs. AESIs included major adverse cardiovascular events, heart-failure syndrome, acute pancreatitis, hypoglycemia, thyroid malignancies, C-cell hyperplasia, supraventricular arrhythmia, cardiac conductive disorders, hepatobiliary disorders, severe gastrointestinal (GI) adverse events (AEs), acute renal events, depressive disorder, suicidal ideation and hypersensitivity (Extended Data Table 1).

Primary outcomes

The primary endpoint, a statistically significant reduction in body weight from baseline to week 36 compared with placebo, was met

Table 1 | Participant demographics and baseline clinical characteristics at start of double-blind period

Characteristics Mean (s.d.) or n (%)	Aleniglipron 45 mg n=45	Aleniglipron 90 mg n=65	Aleniglipron 120 mg n=64	Placebo n=56	Overall n=230
Age, years, mean (± s.d.)	49.0 (±12.7)	47.9 (±12.5)	52.3 (±13.9)	49.9 (±15.8)	49.8 (±13.8)
Sex, female, n (%)	25 (55.6)	35 (53.8)	35 (54.7)	30 (53.6)	125 (54.3)
Race or ethnic group, n (%)					
White	37 (82.2)	53 (81.5)	56 (87.5)	46 (82.1)	192 (83.5)
Black or African American	5 (11.1)	8 (12.3)	5 (7.8)	6 (10.7)	24 (10.4)
Asian	1 (2.2)	2 (3.1)	0 (0.0)	1 (1.8)	4 (1.7)
Multiple	1 (2.2)	1 (1.5)	1 (1.6)	1 (1.8)	4 (1.7)
Not Hispanic or Latino	38 (84.4)	56 (86.2)	55 (85.9)	45 (80.4)	194 (84.3)
Hispanic or Latino	7 (15.6)	9 (13.8)	9 (14.1)	11 (19.6)	36 (15.7)
Body weight, kg, mean (± s.d.)	115.6 (± 24.7)	117.9 (±23.6)	113.1 (±20.5)	112.3 (±22.0)	114.8 (±22.6)
Body mass index, kg m ⁻² , mean (± s.d.)	39.7 (±6.9)	39.8 (±7.5)	39.0 (±6.4)	39.4 (±7.0)	39.5 (±6.9)
Waist circumference, cm, mean (± s.d.)	120.1 (±15.3)	121.8 (±15.0)	121.2 (±12.5)	121.2 (±15.6)	121.2 (±14.5)
HbA1c, %, mean (± s.d.)	5.7 (±0.3)	5.7 (±0.4)	5.7 (±0.3)	5.5 (±0.4)	5.6 (±0.4)
HbA1c ≥5.7%, n(%)	23 (±51.1)	39 (±60.0)	32 (±50.0)	19 (±33.9)	113 (±49.1)
Fasting glucose level (mg dl ⁻¹), mean (± s.d.)	96.0 (±13.53)	96.0 (±11.10)	94.3 (±10.04)	94.0 (±10.27)	95.0 (±11.1)
Systolic blood pressure, mmHg, mean (± s.d.)	127.0 (±11.3)	126.4 (±12.6)	125.3 (±14.8)	125.3 (±12.6)	125.9 (±13.0)
Diastolic blood pressure, mmHg, mean (± s.d.)	83.3 (±7.9)	81.9 (±8.0)	80.2 (±8.8)	80.3 (±7.9)	81.3 (±8.2)
Heart rate (beat min ⁻¹), mean (± s.d.)	72.1 (±10.4)	72.7 (±9.6)	69.1 (±9.4)	71.6 (±9.7)	71.3 (±9.8)
eGFR (ml min ⁻¹ 1.73 m ² , mean (± s.d.)	99.0 (±20.4)	100.2 (±17.1)	98.8 (±18.2)	100.5 (±17.4)	99.6 (±18.1)
Total cholesterol (mg dl ⁻¹), mean (± s.d.)	190.3 (±39.4)	192.4 (±37.8)	189.4 (±38.8)	176.8 (±32.7)	187.3 (±37.5)
High-density lipoprotein (mg dl ⁻¹), mean (± s.d.)	48.5 (±12.0)	48.3 (±11.54)	51.5 (±14.42)	48.7 (±12.00)	49.3 (±12.59)
Low-density lipoprotein (mg dl ⁻¹), mean (± s.d.)	116.7 (±31.73)	117.0 (±33.5)	111.8 (±31.4)	105.4 (±30.4)	112.6 (±32.0)
Very low-density lipoprotein cholesterol (mg dl ⁻¹), mean (± s.d.)	25.0 (±11.8)	27.1 (±23.2)	26.2 (±15.1)	22.6 (±15.3)	25.4 (±17.3)
Triglycerides (mg dl ⁻¹), mean (± s.d.)	125.0 (±58.7)	130.1 (±81.3)	128.9 (±69.1)	111.1 (±65.0)	124.1 (±70.0)

eGFR, estimated glomerular filtration rate.

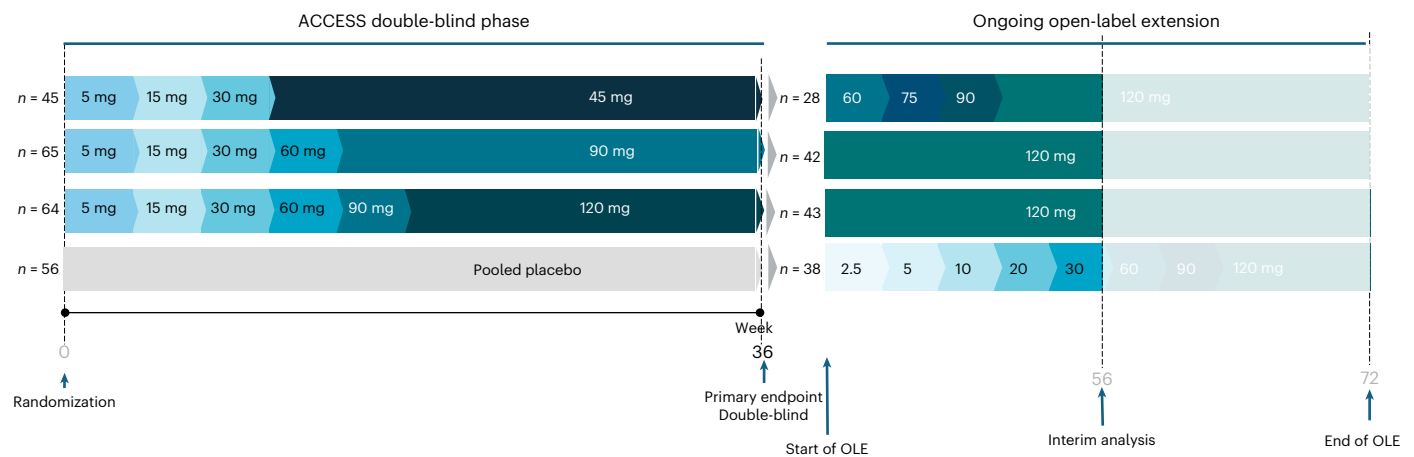


Fig. 2 | Study design. Study design of ACCESS, showing double-blind phase and number of participants who then continued into the open-label extension phase.

across all aleniglipron doses in the efficacy estimand. The least squares (LS) mean change in body weight from baseline to week 36 with aleniglipron was -9.0% for 45 mg (95% confidence interval (CI), -11.2 to -6.8%), -10.7% for 90 mg (-12.5 to -8.8%) and -12.1% for 120 mg (-13.9 to -10.3%) compared with placebo (-0.8% , -2.7 to 1.1%) (Fig. 3a). The placebo-adjusted LS mean (95% CI) change in body weight from baseline to week 36 for 45 mg was -8.2% (-11.1 to -5.3% ;

-9.2 kg), -9.8% (-12.5 to -7.2% ; -11.0 kg) for 90 mg and -11.3% (-13.9 to -8.6% ; -12.4 kg) for 120 mg aleniglipron (all $P < 0.0001$) (Fig. 3b). The treatment regimen estimand showed similar results, with a LS mean (95% CI) body-weight change from baseline of -8.8% (-11.1 to -6.6%) in the 45-mg aleniglipron arm, -10.2% (-12.1 to -8.4%) in the 90-mg arm and -11.4% (-13.3 to -9.6%) in the 120-mg arm (Extended Data Table 2).

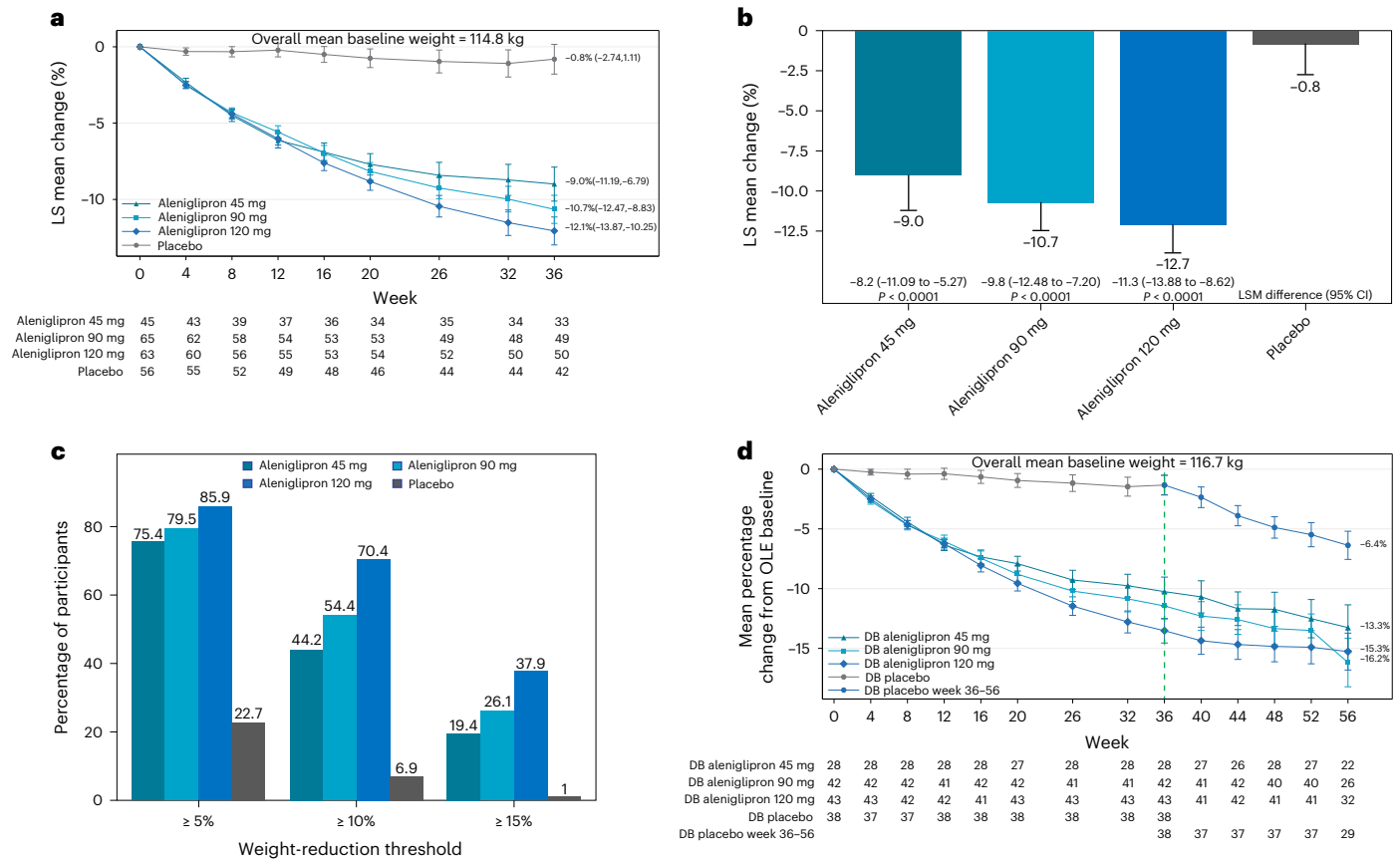


Fig. 3 | Body-weight reduction. **a**, Body-weight reduction in double-blind period (efficacy estimand). The number of participants at each assessment is denoted below the graph. **b**, Body-weight reduction and placebo-adjusted body-weight reduction at week 36 of the double-blind period (efficacy estimand). Error bars are the standard error of the LS mean change from the MMRM model. The confidence intervals and *P* values are from the MMRM model. **c**, Categorical body-weight reduction in the double-blind period. Model-estimated response rates were calculated using Rubin's rule by combining the percentages of participants who met the target in imputed data sets analyzed with logistic regression. 5 mg arm, *n* = 33. 90 mg arm, *n* = 49. 120 mg arm, *n* = 50. Pooled placebo, *n* = 42. In **a–c**, the baseline is defined as the last measurement before the first dose of the study drug. Under the efficacy estimand, values more than two days after intercurrent

events (permanent discontinuation of treatment) are considered invalid and set to missing. Standard error bars are displayed, with the LS mean percentage change from baseline from the MMRM model. The confidence intervals or *P* values were not adjusted for multiplicity. **d**, Body-weight reduction in the open-label extension (summary descriptives). Baseline is defined as the last measurement before the first dose of study drug in the double-blind phase. Results are based on the average of triplicate measurements of weight taken at each visit. The dotted green line indicates the beginning of open-label extension. 95% CIs were not adjusted for multiplicity and were not used for hypothesis testing. Error bars indicate the s.d. The number of participants at each assessment is shown below the graph. Week 56 data, as indicated by the sample size, reflect that not all participants have reached this time point assessment as the study is ongoing.

Secondary outcomes

Body-weight loss. Body-weight loss of $\geq 5\%$, $\geq 10\%$ and $\geq 15\%$ occurred in 86%, 70% and 38% of participants on 120 mg aleniglipron, versus 23%, 7% and 1% in the placebo arm, respectively (Fig. 3c and Extended Data Table 3).

Mean absolute body weight, mean waist circumference and mean BMI in the aleniglipron arms were all statistically significantly reduced compared with their values in the placebo arm (Extended Data Table 4).

Clinical parameters. There were no clinically meaningful changes in lipid profiles from baseline to week 36 (Extended Data Table 5). The overall mean baseline hemoglobin A1c (HbA1c) of 5.63% was reduced in participants on aleniglipron by -0.27% , -0.32% and -0.36% in the 45-mg, 90-mg and 120-mg arms, respectively, compared with 0.01% in placebo.

Safety and tolerability. The most commonly occurring TEAEs with aleniglipron were GI-related, including nausea, diarrhea, vomiting and constipation (Table 2). As shown in Extended Data Figure 2 (heatmap of tolerability), most participants in the three aleniglipron arms were following the titration schedule in the protocol. Of note, participants

with dose interruptions (indicated in the panels as white cells) generally did not experience vomiting upon reinitiation. This tolerability profile was aligned with the number of AEs leading to treatment discontinuations (Table 2), with an overall rate of 10.4% in the aleniglipron-treated arms. Treatment discontinuations due to TEAEs were mostly related to GI AEs (Table 2), and there was no dose–response relationship across aleniglipron dose arms. The treatment discontinuations due to TEAEs predominantly occurred at earlier titration steps across all doses, and GI AEs were attenuated at later time points (Fig. 4).

Treatment-emergent SAEs occurred in one participant (2.2%) in the 45-mg arm, none in the 90-mg arm, four participants (6.3%) in the 120-mg arm and three participants (5.4%) in the pooled placebo group (Table 2). No deaths occurred during the trial.

Participants in the aleniglipron-treated arms showed clinically meaningful reductions in both systolic and diastolic blood pressure, and there was no evidence of QTc prolongation (Extended Data Table 5). At week 36 (pre-dose), heart-rate increases of 0.8 ± 1.3 , 2.2 ± 1.1 and 2.1 ± 1.1 beats per minute (b.p.m.) were observed in the 45-, 90- and 120-mg groups, respectively, compared with -1.2 ± 1.1 b.p.m. in the placebo group, representing a placebo-adjusted difference of only 2.0–3.4 b.p.m. (Extended Data Table 5). Additionally, heart-rate measurements

Table 2 | Common TEAEs by preferred term (safety analysis set) during the double-blind study period (baseline to week 36)

	Aleniglipron 45mg (n=45) n (%)	Aleniglipron 90mg (n=65) n (%)	Aleniglipron 120mg (n=63) n (%)	Pooled placebo (n=56) n (%)
Any SAEs	1 (2.2)	0 (0.0)	4 (6.3)	3 (5.4)
Any study drug-related SAEs	0 (0.0)	0 (0.0)	1 (1.6)	1 (1.8)
Any AESIs	12 (26.7)	11 (16.9)	17 (27.0)	15 (26.8)
Any TEAEs	42 (93.3)	60 (92.3)	58 (92.1)	44 (78.6)
Any TEAE leading to discontinuation of treatment	6 (13.3)	5 (7.7)	7 (11.1)	3 (5.4)
Any GI-related TEAE leading to dose discontinuation	6 (13.3)	5 (7.7)	3 (4.8)	1 (1.8)
Any GI-related TEAEs	40 (88.9)	55 (84.6)	50 (79.4)	31 (55.4)
Common TEAEs (≥5%; preferred term)				
Nausea	32 (71.1)	44 (67.7)	41 (65.1)	12 (21.4)
Vomiting	18 (40.0)	29 (44.6)	20 (31.7)	3 (5.4)
Diarrhea	19 (42.2)	26 (40.0)	14 (22.2)	13 (23.2)
Constipation	18 (40.0)	20 (30.8)	19 (30.2)	8 (14.3)
Headache	10 (22.2)	11 (16.9)	17 (27.0)	10 (17.9)
Dyspepsia	8 (17.8)	8 (12.3)	6 (9.5)	5 (8.9)
Gastroesophageal reflux disease	7 (15.6)	8 (12.3)	10 (15.9)	0 (0.0)
Abdominal distension	4 (8.9)	11 (16.9)	6 (9.5)	3 (5.4)
Abdominal pain	4 (8.9)	11 (16.9)	7 (11.1)	2 (3.6)
Fatigue	3 (6.7)	7 (10.8)	10 (15.9)	3 (5.4)
Upper respiratory tract infection	5 (11.1)	4 (6.2)	6 (9.5)	4 (7.1)
Eruktion	3 (6.7)	6 (9.2)	5 (7.9)	1 (1.8)
Dizziness	2 (4.4)	2 (3.1)	6 (9.5)	3 (5.4)

were collected 2–4 h after the dose, with a placebo-adjusted difference ranging from 2.0 to 3.8 b.p.m. (Extended Data Table 5).

No drug-induced liver injury or persistent elevation of liver enzyme levels (between baseline and week 36) was observed across all aleniglipron treatment arms. All fluctuations in ALT or AST levels reaching three or more times the upper limit of normal (ULN) ($n = 8$) or five times the ULN ($n = 1$) returned to baseline values without stopping treatment with the study drug. There were no cases of liver enzyme elevations of ten or more times the ULN (Extended Data Table 6).

Exploratory outcomes

C-reactive protein. An exploratory analysis of changes in high-sensitivity C-reactive protein (hsCRP) showed clinically meaningful reductions in the three aleniglipron arms, ranging from –28.8% to –46.4%, compared with a reduction of –6.9% in the placebo group (Extended Data Table 5).

Open-label extension efficacy and safety: interim analysis.

A prespecified interim analysis of the OLE after a median follow-up of 20 weeks indicated further weight loss beyond 36 weeks (Fig. 3d and Supplementary Table 2), achieving a total mean weight loss from randomization to the interim analysis of $13.3 \pm 8.9\%$, $16.2 \pm 10.4\%$ and $15.3 \pm 8.7\%$ in the 45-, 90- and 120-mg aleniglipron groups, respectively, at week 56. Percentages of GI-related TEAEs were lower than those seen in the initial phase of the study (weeks 0–36) (Extended Data Table 7).

In addition, participants from the placebo arm who initiated aleniglipron at a lower dose of 2.5 mg had a body-weight reduction of 6.4% at week 56 (Fig. 3d) after a median follow-up of 20 weeks with a titrated dose of around 30 mg by that time. At the time of the interim analysis, there were no reported vomiting events, and 39.9% of participants reported nausea with no AE-related study drug discontinuations (Extended Data Table 7 and Extended Data Fig. 3).

Discussion

The ACCESS study demonstrated that once-daily aleniglipron at doses of 45 mg, 90 mg or 120 mg led to dose-dependent, clinically meaningful reductions in body weight in adults with obesity or overweight over a 36-week period. Of note, 86% of participants randomized to the 120-mg aleniglipron arm had a body-weight reduction of at least 5%, the recommended cut-off in FDA guidance for an effective obesity medication¹⁰, with 70% and 38% of participants achieving weight reductions of 10% and 15%, respectively. Other cardiovascular risk factors were also notably improved with aleniglipron treatment, such as systolic blood pressure, hsCRP and HbA1c, which could positively contribute to the known cardiovascular benefits and potential diabetes-prevention effects of approved GLP-IRAs^{6,8,11}.

Despite the observed and anticipated attenuation of effect beyond week 36, there were no apparent signs of a weight-loss plateau. Additionally, the ongoing OLE, a unique feature of the program, provided evidence showing additional weight reduction, with an interim analysis revealing up to 16.2% body-weight loss at week 56. This result suggests that further weight-loss benefits could be attainable with a longer treatment duration.

In the absence of head-to-head studies of GLP-1 RAs, any comparisons must be interpreted with caution because of differences in routes of administration, pharmacokinetic characteristics and specific study populations and designs^{4,12,13}. However, for other small-molecule GLP-IRAs, an estimated 10.5% body-weight reduction at 36 weeks (phase 3, 72-week study) following a 4-week titration step has been reported⁹. In ACCESS, the 120-mg aleniglipron arm consisted of a participant population with a high number of males, a group in which efficacy has typically been lower¹³; however, in this group, there was still an 11.3% reduction in body weight. This result, along with the lack of apparent plateauing, positions aleniglipron as a solid candidate as an obesity treatment.

The safety and tolerability profiles of aleniglipron in this study reflect the known AEs for the GLP-1 RA class of drugs¹⁴. The most

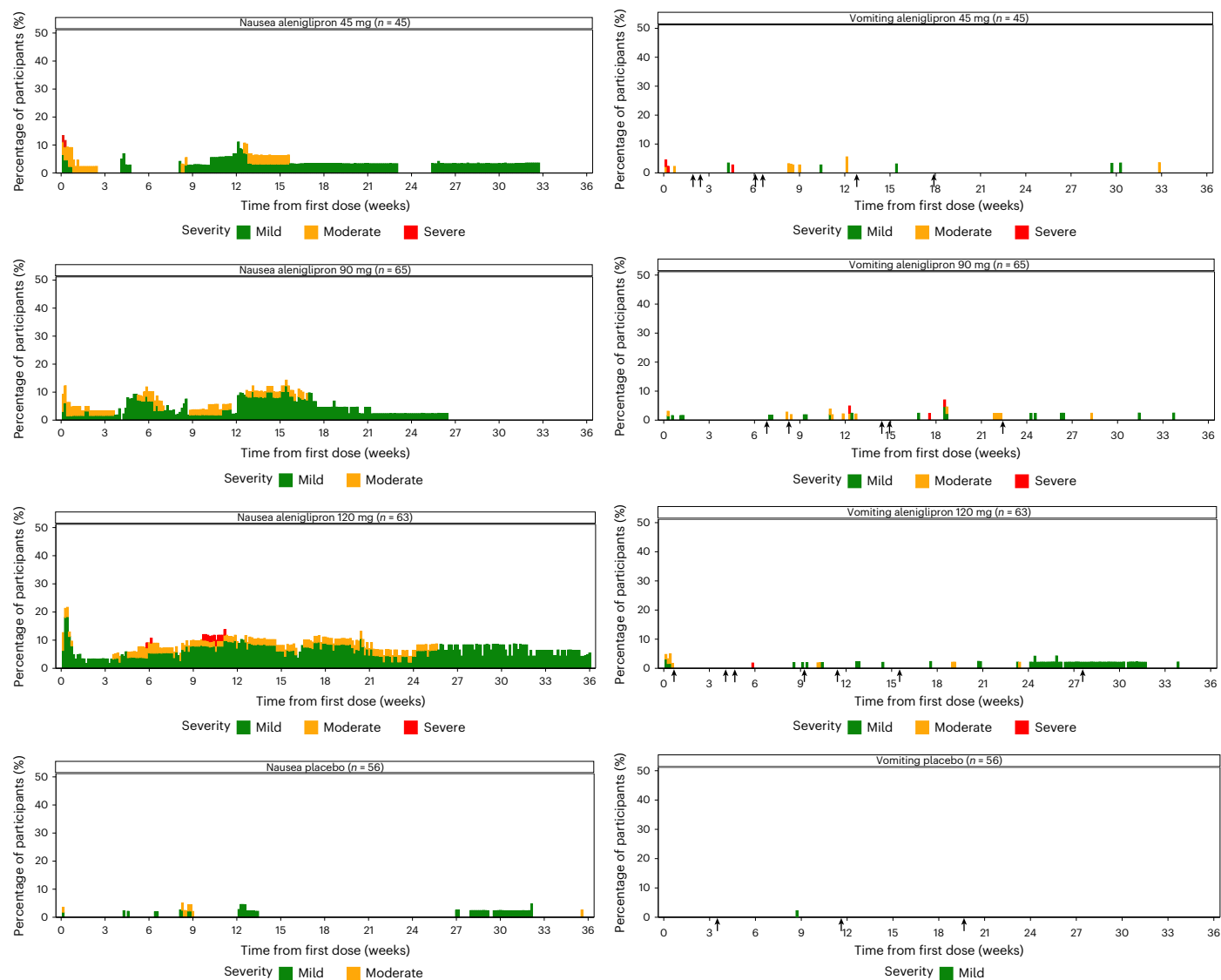


Fig. 4 | The prevalence of GI TEAEs (nausea and vomiting) and timing of study drug discontinuations due to adverse events. Arrows indicate any AE leading to study drug discontinuations. The y axis represents the prevalence rate, calculated as the proportion of participants who experienced nausea (left) or vomiting (right) on a daily basis among participants who took the target dose of the study drug on the day on the x axis. TEAEs are defined as AEs that started or

worsened in severity after the first dose of study drug, and onset date is within 7 days after the last dose of study drug. Intermittent events with ‘intermittent’ or ‘occasional’ in the verbatim field in electronic data capture were not included. TEAEs are enumerated from onset to resolution or the end of the study (if not resolved), and the maximum severity is selected.

important variable in assessing safety and tolerability is the percentage of participants experiencing an AE leading to treatment discontinuation (10.4%). Notably, there was no increase in the number of discontinuations as participants reached higher doses of aleniglipron. Most discontinuations due to TEAEs occurred during the initial titration steps to a higher dose and could therefore be considered modifiable with a new titration strategy of starting at a lower dose with smaller increases to the next dose, as the placebo crossover data in the extension phase suggested. In the OLE study, an interim analysis of the placebo group, which began at a lower starting dose of aleniglipron (2.5 mg versus 5 mg) with smaller dose-escalation increments, demonstrated improved tolerability with no TEAE-related discontinuations and few GI events while achieving clinically relevant body-weight reductions over a 20-week median follow-up.

Notably, the proactive collection of GIAEs through an electronic diary (e-diary) provided more rigorous evaluations of AEs but introduced potential ascertainment bias and possibly higher reporting compared with non-solicited AE reporting¹⁵. The heat maps of dose

levels overlaid with vomiting events add clarity to the interpretation of the AE profile and add valuable insights into the participant experience on aleniglipron. Upon examination of each participant’s dosing across the study, it becomes clear that, although some required dose interruptions or reductions, when the dose was reinitiated or titrated up again, vomiting rarely recurred. This suggests that participants on aleniglipron can successfully restart treatment or continue to increase dosing after an interruption. This could increase the likelihood of remaining on treatment for extended periods, which is essential for clinically meaningful and lifelong treatment of obesity.

In the current study, there was no apparent dose–response relationship for the most common GI AEs across all aleniglipron treatment arms, and treatment discontinuations due to any TEAE were limited. One hypothesis for the absence of a dose–response relationship in the tolerability profile is that the three treatment arms used the same titration schemes, with most events occurring early in the titration phase. Consistent with other programs in the GLP-1RA class of medicines, in this study, a low percentage of persistent vomiting events (below 10%) was

observed once the maintenance dose was reached^{6,9}. Of note, there was no persistent elevation of liver enzyme levels or drug-induced liver injury.

Study limitations included the prospective collection of GI AEs through an e-diary, which could have led to ascertainment bias and higher numbers of recorded GI-related AEs. This also impacted the placebo arm, in which participants reported a 20% incidence of nausea. The percentage of female participants was lower in this study than in other GLP-1RA obesity studies, which might have led to attenuated body-weight-loss results, given that female participants tend to lose more weight than do male participants^{9,13,15–17}. The high percentage of white participants, and the fact that all the study sites were in the United States, might limit the generalizability of the results.

The results of the ACCESS trial support the upcoming phase 3 trial design, starting at a 2.5 mg dose rather than 5 mg, which is also expected to further improve tolerability during the early stages of titration.

In summary, aleniglipron, an orally administered small-molecule GLP-1RA, demonstrated clinically meaningful weight reductions with a favorable safety and tolerability profile that does not worsen after aleniglipron reintroduction following dose interruption. The development of oral small-molecule GLP-1RAs with lower manufacturing costs, simple storage conditions and greater manufacturing scalability, such as aleniglipron, could help expand access around the world for people with obesity or overweight.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at <https://doi.org/10.1038/s41591-026-04476-6>.

References

1. Wegovy. *Prescribing Information*. March 2026. <https://www.novo-pi.com/wegovy.pdf> (Novo Nordisk, 2026).
2. Foundayo. *Prescribing information*. April 2024. <https://pi.lilly.com/us/foundayo-uspi.pdf> (Eli Lilly, 2026).
3. Mounjaro. *Prescribing information*. April 2026. <https://pi.lilly.com/us/mounjaro-uspi.pdf> (Eli Lilly, 2026).
4. Kong, F. et al. Comprehensive evaluation of GLP-1 receptor agonists: an umbrella review of clinical outcomes across multiple diseases. *Nat. Commun.* **17**, 972 (2026).
5. Saran, A., Raisinghani, R., Paliwal, S. & Sharma, S. GLP-1R agonists: recent advances, current gaps, and future challenges. *Mol. Divers.* **30**, 101–112 (2026).
6. Deanfield, J. et al. Semaglutide and cardiovascular outcomes by baseline and changes in adiposity measurements: a prespecified analysis of the SELECT trial. *Lancet* **406**, 2257–2268 (2025).
7. Wharton, S. et al. Treatment with orforglipron, an oral glucagon like peptide-1 receptor agonist, is associated with improvements of CV risk biomarkers in participants with type 2 diabetes or obesity without diabetes. *Cardiovasc. Diabetol.* **24**, 240 (2025).
8. McGowan, B. M. et al. Efficacy and safety of once-weekly semaglutide 2·4 mg versus placebo in people with obesity and prediabetes (STEP 10): a randomised, double-blind, placebo-controlled, multicentre phase 3 trial. *Lancet Diabetes Endocrinol.* **12**, 631–642 (2024).
9. Wharton, S. et al. Orforglipron, an oral small-molecule GLP-1 receptor agonist for obesity treatment. *N. Engl. J. Med.* **393**, 1796–1806 (2025).
10. *Obesity and Overweight: Developing Drugs and Biological Products for Weight Reduction. Draft Guidance*. January 2025. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/obesity-and-overweight-developing-drugs-and-biological-products-weight-reduction> (US FDA, 2026).
11. Lincoff, A. M. et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. *N. Engl. J. Med.* **389**, 2221–2232 (2023).
12. Guo, H. et al. Comparative efficacy and safety of GLP-1 receptor agonists for weight reduction: A model-based meta-analysis of placebo-controlled trials. *Obes. Pillars.* **13**, 100162 (2025).
13. Alexander, G.C. et al. Heterogeneity of treatment effects of glucagon-like peptide-1 receptor agonists for weight loss in adults: a systematic review and meta-analysis. *JAMA Intern. Med.* **186**, 567–577 (2026).
14. Shetty, R. et al. Adverse drug reactions of GLP-1 agonists: a systematic review of case reports. *Diabetes Metab. Syndr.* **16**, 102427 (2022).
15. Jastreboff, A. M. et al. Once-monthly maridebart cafraglutide for the treatment of obesity — a phase 2 trial. *N. Engl. J. Med.* **393**, 843–857 (2025).
16. le Roux, C. W. et al. Glucagon and GLP-1 receptor dual agonist survodutide for obesity: a randomised, double-blind, placebo-controlled, dose-finding phase 2 trial. *Lancet Diabetes Endocrinol.* **12**, 162–173 (2024).
17. Jastreboff, A. M. et al. Triple-hormone-receptor agonist retatrutide for obesity — s phase 2 trial. *N. Engl. J. Med.* **389**, 514–526 (2023).

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

© The Author(s) 2026, modified publication 2026

¹The University of Texas Southwestern Medical Center, Dallas, TX, USA. ²University of Texas Southwestern Medical Center, Internal Medicine, Dallas, TX, USA. ³Pennington Biomedical Research Foundation, Baton Rouge, LA, USA. ⁴Yale School of Medicine, Internal Medicine, Endocrinology, New Haven, CT, USA. ⁵Northwestern University Feinberg School of Medicine, Chicago, IL, USA. ⁶Mayo Clinic, Medicine, Rochester, MN, USA. ⁷Texas Diabetes and Endocrinology, Austin, TX, USA. ⁸Trialmed, Minneapolis, MN, USA. ⁹Elligo Health Research, Austin, TX, USA. ¹⁰StudyMetrix Research, St. Peters, MO, USA. ¹¹Alliance for Multispecialty Research, Knoxville, TN, USA. ¹²Structure Therapeutics, South San Francisco, CA, USA. *A list of authors and their affiliations appears at the end of the paper. ✉e-mail: juliorosenstock@dallasdiabetes.com

the ACCESS Trial Investigators

Thomas C. Blevins⁷, Melissa Choi⁸, Faith L. Holmes⁹, Timothy Smith¹⁰ & Lisa Connery¹¹

A full list of members and their affiliations appears in the Supplementary Information.

Methods

Trial design and participants

Between 28 October 2024 and 7 February 2025, 406 adults were screened and 230 participants underwent randomization across 38 sites in the United States. The research protocol and statistical analysis plan (included as supplementary material) were approved by the central institutional review board Advarra. This study was carried out according to the principles of the Declaration of Helsinki. Each participant provided written informed consent. This was a dose-ranging phase 2b, randomized, placebo-controlled, parallel group, 36-week study. Eligible participants were adults aged ≥ 18 and < 80 years, with obesity (BMI ≥ 30 kg m⁻²) or with overweight (≥ 27 kg m⁻²) and one or more weight-related comorbidity and stable weight (no more than 5% weight gain or loss) in the previous 3 months. Weight-related comorbidities included hypertension, dyslipidemia, obstructive sleep apnea, cardiovascular disease, heart-failure syndrome and MASH. Other key inclusion criteria included HbA1c $< 6.5\%$ at screening. Key exclusion criteria were a previously documented diagnosis of diabetes; body weight ≤ 80 kg at screening; and prior or planned surgical treatment for obesity. Excluded medications are listed in the protocol. All participants and study personnel were blinded to study drug assignment. Drug–drug interaction exclusion and inclusion criteria are described in the supplementary information (Supplementary Tables 3 and 4) and in the protocol (provided as supplementary information including, summary of any changes to protocol).

Full inclusion criteria. Participants were eligible for study inclusion only if all the following criteria applied at screening and baseline (before dosing). If abnormal values were obtained in the first instance, assessment could be repeated once (at the discretion of the investigator and sponsor) to confirm eligibility.

- Signed informed consent before initiation of any study-related activities, capable of understanding the full nature and purpose of the trial (including possible risks and adverse effects) and willing to comply with all study procedures and adhere to the protocol schedule and restrictions.
- Men and women, age ≥ 18 years and < 80 years, with:
 - BMI ≥ 30 kg m⁻² or
 - BMI ≥ 27.0 kg m⁻² and a previous or current diagnosis of one or more comorbidity:
 - Hypertension (as defined by a resting systolic blood pressure (BP) of ≥ 140 mmHg and a resting diastolic BP of ≥ 90 mmHg or receiving BP lowering medication for the treatment of hypertension)
 - Dyslipidemia as defined by a fasting triglyceride ≥ 200 mg dl⁻¹ (2.2 mM), fasting low-density lipoprotein (LDL) cholesterol of ≥ 100 mg dl⁻¹ (2.5 mM) or a high-density lipoprotein (HDL) cholesterol < 40 mg dl⁻¹ (1.0 mM), or receiving treatment with an approved lipid-lowering medication
 - Documented obstructive sleep apnea or receiving treatment for obstructive sleep apnea
 - Cardiovascular disease, including documented coronary artery atherosclerotic disease, peripheral arterial atherosclerotic disease, stroke or transient ischemic attacks
 - Documented diagnosis of MASH (confirmed by clinical, laboratory, imaging or biopsy findings)
- Screening HbA1c $< 6.5\%$
- Reproductive status:
 - Female participants of non-childbearing potential, defined as either surgically sterilized (having undergone hysterectomy, bilateral salpingectomy, bilateral tubal ligation or bilateral oophorectomy ≥ 6 weeks before screening) or postmenopausal (defined as no menses for ≥ 12 months, without an alternative medical cause, and a

follicle-stimulating hormone level > 40 IU l⁻¹ at the screening visit for postmenopausal women ≤ 55 years).

- Female participants of childbearing potential must have had a negative urine pregnancy test (or negative serum pregnancy test) during screening and day 1. Additionally, they must not have been or planned to be breastfeeding. They agreed not to donate ova, to not attempt to become pregnant and, if engaging in sexual intercourse with a male partner, to use a highly effective method of contraception from the time of signing the informed consent form (ICF) until ≥ 30 days after the last dose of the study drug.
- Male participants agreed to not donate sperm and, if engaging in sexual intercourse with a female partner who could become pregnant, to use a highly effective method of contraception from signing the ICF until ≥ 90 days after the last dose of study drug.

Exclusion criteria. Participants were excluded from the study if any of the following criteria applied at the screening visit or before dosing:

Diabetes-related medical conditions.

- Previous documented diagnosis of diabetes mellitus (except for gestational diabetes and the participant had HbA1c $< 6.5\%$).
- Use of metformin for any indication.

Obesity-related medical conditions.

- Self-reported change in body weight $> 5\%$ within 3 months before screening.
- Body weight ≤ 80 kg at screening.
- Had a prior or planned surgical treatment for obesity (excluding liposuction or abdominoplasty, if performed > 1 year prior to screening).
- Had or planned to have endoscopic and/or device-based therapy for obesity including, but not limited to, mucosal ablation, gastric artery embolization, intragastric balloon and duodenal–jejunal endoluminal liner, or had device removal within the 6 months prior to screening.
- Had obesity induced by other endocrine disorders (such as Cushing's syndrome, Prader–Willi syndrome or melanocortin-4-receptor deficiency).

Other medical conditions

- History or presence of significant cardiovascular, pulmonary, hepatic, renal, hematological, GI, endocrine, immunologic, dermatologic or neurological disease, including any acute illness or major surgery within the past 3 months, or any clinical laboratory abnormality determined by the investigator or medically certified delegate to be clinically significant.
- Any chronic disorder or severe disease that, in the opinion of the investigator, might have jeopardized the participant's safety, compliance with the protocol and/or ability to complete the study.
- History of treatment for cancer in the past 5 years (excluding surgically resected skin squamous cell or basal cell carcinoma, in situ cervical cancer or in situ prostate cancer).
- Serum calcitonin level at screening of ≥ 20 ng l⁻¹ if estimated glomerular filtration rate (eGFR) ≥ 60 ml⁻¹ min⁻¹ 1.73 m⁻² or ≥ 35 ng l⁻¹ if eGFR < 60 ml⁻¹ min⁻¹ 1.73 m⁻², or a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2.
- Had a thyroid-stimulating hormone level outside the range of 0.4 to 6.0 mIU l⁻¹ at screening.
- History of chronic pancreatitis or idiopathic acute pancreatitis, or documented history of biliary stones. A participant with

a history of acute pancreatitis caused by gallstones may have been included in the study if the participant had a cholecystectomy to resolve the problem.

14. Chronic malabsorption, regardless of etiology.
 15. History of Crohn's disease, ulcerative colitis or other inflammatory bowel disease.
 16. Impaired renal function at screening defined as eGFR <30 ml⁻¹ min⁻¹ 1.73 m⁻² per the Chronic Kidney Disease Epidemiology Collaboration.
 17. Fasting serum triglyceride level of >500 mg dl⁻¹ at screening.
 18. Documented diagnosis of heart failure and at Screening New York Heart Association Class III or IV.
 19. Within the year before the screening visit, any of the following: episode of acute coronary event, transient ischemic attack, stroke, peripheral arterial vascular disease leading to revascularization or other significant cardiovascular event as determined by the investigator.
 20. A seated BP, after resting for 5 minutes, of >160 mm Hg systolic or >100 mm Hg diastolic. The measurement was performed in triplicate, and the average of all three measurements was used to determine eligibility.
 21. A pulse rate >100 b.p.m. If elevated, the measurements may have been repeated two more times, and the average of all three measurements was used to determine eligibility.
 22. Evidence of abnormality on the screening visit ECG deemed clinically significant by the investigator, history of known arrhythmia or prolonged QT interval corrected using Fridericia's formula (QTcF) (males >450 ms; females >470 ms), based on the average of triplicate electrocardiograms, or risk factors for torsade de pointes (including a family history of long QT syndrome or sudden cardiac death). A personal or family history of long QT syndrome, family history of sudden death in a first-degree relative (parents, siblings or children) before the age of 40 years, or a personal history of unexplained syncope within the last year. Use of prescription or over-the-counter medications at screening that are known to significantly prolong the QT or QTc interval.
 23. Had an ECG considered by the investigator with abnormalities that might have interfered with the interpretation of changes in ECG intervals at screening.
 24. Ongoing or history of frequent intermittent or chronic tachyarrhythmia syndromes (such as atrial fibrillation, supraventricular tachycardia, and positional orthostatic tachycardia syndrome). Participants with a history of premature atrial contractions or premature ventricular contractions may have been included.
 25. Liver enzyme results elevated more than twice above the ULN for AST or ALT, or more than 1.5 times the ULN for bilirubin (total, conjugated or unconjugated) (except for cases of known Gilbert's syndrome). Testing could be repeated twice.
 26. Documented diagnosis of cirrhosis.
 27. Presence or had sequelae of GI, liver, kidney or other conditions known to interfere with the absorption, distribution, metabolism or excretion of drugs.
 28. Any history of ileus.
 29. Positive test results for an active viral infection: severe acute respiratory syndrome coronavirus 2, HIV-1 or HIV-2 with positive antibodies, hepatitis B virus with a positive hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV) with positive antibodies and viral load at the screening visit.
 30. A history of significant active or unstable major depressive disorder or other severe psychiatric disorder (for example, schizophrenia, bipolar disorder or other serious mood or anxiety disorder) in the past 2 years.
 31. A lifetime history of a suicide attempt or psychiatric hospitalization.
 32. A Patient Health Questionnaire-9 (PHQ-9) score of 15 or more prior to randomization.
 33. On the Columbia Suicide Severity Rating Scale (C-SSRS) during screening (within the last 28 days):
 - A 'yes' answer to question 4 (active suicidal ideation with some intent to act, without specific plan) on the 'suicidal ideation' portion of the C-SSRS or
 - A 'yes' answer to question 5 (active suicidal ideation with specific plan and intent) on the 'suicidal ideation' portion of the C-SSRS or
 - A 'yes' answer to any of the suicide-related behaviors (actual attempt, interrupted attempt, aborted attempt, preparatory act or behavior) on the 'suicidal behavior' portion of the C-SSRS and
 - the ideation or behavior occurred
- Prior or concomitant therapy.**
34. Use of medications intended to promote weight loss, within 6 months prior to screening, including, but not limited to, the following:
 - Saxenda (liraglutide 3.0 mg) or other GLP-1RA
 - Wegovy or Ozempic (semaglutide)
 - Xenical or Alli (orlistat)
 - Meridia (sibutramine)
 - Acutrim (phenylpropranolamine)
 - Sanorex (mazindol)
 - Adipex or Lomaira (phentermine)
 - Belviq (lorcaserin)
 - Qsymia (phentermine-topiramate combination)
 - Contrave (naltrexone when combined with bupropion)
 - Zepbound or Mounjaro (tirzepatide)
 - Other similar body-weight-loss medication, including over-the-counter medications (for example, Alli)
 35. Had current treatment with or history of treatment with (within 3 months prior to screening) medications that may cause significant weight gain, including, but not limited to, tricyclic antidepressants, atypical antipsychotics and mood stabilizers. However, participants at a stable dose (greater than 6 months and with no expectation that the dose will change within the next year) and who are weight stable for the last 6 months on these medications may be included in the study. Examples of medications causing weight gain that must be at stable doses for at least 6 months and with no expectation of changing within the next year include:
 - Imipramine
 - Amitriptyline
 - Mirtazapine
 - Paroxetine
 - Phenelzine
 - Chlorpromazine
 - Thioridazine
 - Clozapine
 - Olanzapine
 - Valproic acid and its derivatives
 - Lithium

Selective serotonin reuptake inhibitors other than paroxetine are permitted. Bupropion, when not combined with naltrexone is permitted.
 36. Taking daily doses of amphetamine and amphetamine-like stimulants for attention-deficit/hyperactivity disorder, which include Adderall (amphetamine-mixed amphetamine salts), Ritalin (methylphenadate), Vyvance (lisdexamfetamine) and Strattera (atomoxetine) is allowed.

37. Use of strong CYP3A4 inducers or moderate to strong CYP3A4 inhibitors, drugs that are sensitive P-gp or BCRP substrates, or drugs that are P-gp inducers or P-gp inhibitors. See Supplementary Table 3 for details. Concomitant medications that are sensitive CYP3A4 substrates may require monitoring with or without dose reductions, according to the individual respective product labeling, as summarized in Supplementary Table 3. Concomitant use of lovastatin and simvastatin is not allowed (however, use of other statins is not prohibited).
38. History of substance abuse within 12 weeks before screening.
39. Participants recovering from opiate abuse or taking methadone, buprenorphine–naloxone (Suboxone) or pentazocine (Talwin). However, participants prescribed a medically appropriate use for opiates are allowed.
40. Positive drug-abuse screen (excluding marijuana (tetrahydrocannabinol (THC)) before the first dose of study drug, unless the participant is prescribed one of these classes of drugs (narcotics) for a medically appropriate indication.

Prior or concurrent clinical study experience.

41. Were currently enrolled in any other clinical study or had participated in another clinical trial of an investigational drug or device within 60 days before the first study drug administration. At least 6 months before the first study drug administration, if the clinical trial included a GLP-1RA, GIP receptor agonist (RA), glucagon RA, amylin RA, peptide YY RA, neuropeptide Y RA or any combination thereof and/or any investigational product currently being used for participants with overweight, obesity or type 2 diabetes.

Other exclusions.

42. Pregnant, breastfeeding or intending to become pregnant.
43. Female of childbearing potential and not using an adequate contraceptive method (adequate contraceptive measures as required by local regulation or practice) for the duration of the trial and for ≥ 30 days following the last dose of study drug.
44. Male not using adequate contraceptive method for the duration of the trial and for ≥ 90 days following the last dose of study drug.
45. Consumption of grapefruit, tangelo or Seville orange (or products containing grapefruit, tangelo or Seville orange) in the 10 days before the first administration of study drug and throughout the study.
46. Demonstrated clinically significant allergic reactions (for example, food, drug, or atopic reactions, asthmatic episodes) that required intervention, (for example, emergency room visit, epinephrine administration) and which, in the opinion of the investigator, would interfere with the participant's ability to participate in the trial.
47. Known hypersensitivity to any of the study drug ingredients.

Procedures

Participants were randomized to three dose level cohorts (45, 90 or 120 mg) at a ratio of 3:4:4, then to aleniglipron or placebo at a ratio of 3:1 in each cohort (Fig. 3 and Extended Data Fig. 1). Each participant received ascending daily doses of aleniglipron starting at 5 mg, with titration occurring every 4 weeks to the assigned dose, or placebo over 36 weeks (Fig. 3). Randomization was stratified by baseline BMI ($\leq 35 \text{ kg m}^{-2}$, $>35 \text{ kg m}^{-2}$) and sex. For analyses, all participants assigned to placebo in each cohort were pooled to compare with each aleniglipron treatment group. Mitigation strategies for AEs were provided throughout the study (through dietary counselling, prescription of antiemetic or anti-diarrheal medication and per investigator judgment).

Participants who experienced AEs that precluded continuation at the prescribed dose were allowed to take a lower tolerated dose and could be rechallenged with the next highest full dose in the morning after 1 or 2 days. If dose re-initiation resulted in intolerable AEs, the dose could be down-titrated, but participants needed to tolerate a daily dose of at least 30 mg to remain on the study drug.

An e-diary specifically designed to inquire about the presence of GI symptomatology (for example, nausea, vomiting, constipation, diarrhea) and their intensity (using a visual analog scale), was proactively used to record and transmit data on AEs and participant-reported outcomes, daily for 7 days, after each dose titration step (every 4 weeks), as well as recording daily medication taken (including date and time of dosing).

The electronic data-capture system MediData Rave was used for data collection.

Study objectives and endpoints

The primary endpoint (efficacy estimand) was the percentage change in body weight from baseline to week 36. The secondary endpoints were percentages of participants who achieved $\geq 5\%$, $\geq 10\%$ and $\geq 15\%$ reductions in body weight at week 36, and changes in body weight (absolute), waist circumference and BMI from baseline to week 36. Additional secondary safety endpoints were TEAEs, SAEs, AESIs, laboratory parameters, electrocardiograms and vital signs.

Exploratory objectives were change in lipid profile, hsCRP, resting blood pressure, fasting glucose and HbA1c.

Open-label extension

ACCESS Participants who completed the double-blind treatment period on study drug (or placebo) and signed informed consent ($n = 151$) were eligible to enroll in the ACCESS OLE to assess the longer-term safety of aleniglipron, durability and maintenance of weight loss for an additional planned 36 weeks (from weeks 36 to 72). Participants in the active study arms continued treatment with aleniglipron titrated every 4 weeks until a dose of 120 mg was reached. Participants in the placebo group were initiated on multiple-ascending daily doses of aleniglipron, starting at a lower dose (2.5 mg versus 5 mg in the ACCESS trial), and the dose was titrated every 4 weeks up to 120 mg (Fig. 3). The results of a pre-specified interim analysis performed after a median follow-up of 20 weeks are reported in this manuscript.

Statistical methods

We estimated that 230 participants would provide $>90\%$ power to detect a treatment difference of -5% body-weight change between the aleniglipron treatment group and placebo from baseline to week 36, assuming an s.d. of 6%, a two-sided alpha level of 0.05, 35 completers in one aleniglipron treatment group and 35 completers in the placebo group. No multiplicity adjustments were made, and CIs were not used for hypothesis testing.

The full analysis set included all randomized participants who received one or more doses of aleniglipron or placebo and had one or more post-dose assessments. The safety-analysis set included all participants who received one or more doses of aleniglipron or placebo. Safety and tolerability data are presented for all participants in the safety analysis set.

The efficacy estimand, predefined in the statistical analysis plan, estimates the treatment effect of aleniglipron relative to placebo at week 36 in participants who met the inclusion criteria and would have completed the treatment period. Data collected before the occurrence of any intercurrent events (ICEs) (+2 days) were used for the analysis. ICEs (hypothetical strategy) were defined as permanent discontinuation of study drug, initiation of another anti-obesity medication or bariatric surgery; data subsequent to the ICE were handled by the hypothetical strategy (regarded as invalid and set to missing). Missing data were imputed implicitly.

The primary endpoint based on the efficacy estimand was analyzed using a mixed model for repeated measures (MMRM) with treatment group, randomization strata (baseline BMI and sex), visit, treatment-by-visit interaction and baseline measurement as covariates. An unstructured covariance model was used.

The treatment regimen estimand, predefined in the statistical analysis plan, was to estimate the treatment effect of aleniglipron relative to placebo at week 36 in participants who met the inclusion criteria, regardless of adherence to treatment. The ICE definition was the same as that in the efficacy estimand, except data following an ICE were handled by the treatment strategy, and all subsequent data were included in the analysis. Missing data were imputed based on observed data, assuming that the benefit accrued up to the ICE is retained but there is no additional residual benefit after the ICE.

The continuous endpoints based on the two estimands were analyzed using an MMRM similar to the primary endpoint analysis above. For the body-weight categorical endpoints, logistic regression was used to analyze the data. Missing values at week 36 were imputed according to the multiple-imputation approach, and values were combined using Rubin's rule⁴⁸.

All tests of treatment effects were conducted at a two-sided alpha level of 0.05, and two-sided 95% CIs were calculated. Lipid parameters, fasting glucose and hsCRP were log-transformed before fitting the MMRM, as described in the SAP.

Because of the exploratory nature of the OLE study, no estimand or model-based approach was planned. The change from the double-blind baseline in body weight was summarized on the basis of observed data. Summary descriptives (number, mean, median, s.d., minimum and maximum) were presented by visit and treatment group separately.

All data processing, summarization and analyses were performed using the SAS Enterprise Guide Version 8.2 (or higher) statistical software package.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

Deidentified individual patient data for variables necessary to address a specific research question may be shared with an approved data-sharing request. Researchers will submit a request containing the research objectives, endpoints or outcomes of interest, statistical analysis plan, data requirements, publication plan and their qualifications. Gasherbrum Bio does not grant external requests for individual deidentified patient data for re-evaluating safety and efficacy endpoints already addressed in the product labeling or assessing safety or efficacy for an indication in current development.

Requests are reviewed by a committee of internal advisors, and if not approved, might be further arbitrated by a panel of external advisors. Upon approval, information necessary to address the research question will be provided under the terms of a data-sharing agreement.

Data-sharing requests will be considered beginning 36 months after the study publication (manuscript accepted for publication) and either (1) the product has been granted marketing authorization in at least two regulatory jurisdictions, or (2) clinical development for the product and/or indication discontinues and the data will not be submitted to regulatory authorities. There is no end date for eligibility to submit a data-sharing request for this study. Data can be requested from info@structuretx.com. Requests will be acknowledged and reviewed within 60 days of receipt of request. Source data are provided with this paper.

References

18. Little, R.J., & Rubin, D.B. *Statistical Analysis with Missing Data* (John Wiley & Sons, 1987).

Acknowledgements

We thank the trial participants, investigators and study-site personnel for their contributions, and J. Ludovic Croxford, C. Gode, C. Anglen and R. Stevens for providing editorial and medical writing support.

Author contributions

J.B., A.C. and B.C. contributed to study design and data collection and interpretation and helped conduct the study; J.R., I.L., D.R., A.J., R.K., A.A., M.L. and A.B. contributed to study design or data interpretation; T.B., M.C., F.H., T.S. and L.C. contributed to data collection and interpretation and helped conduct the study; Y.L. and H.Y. contributed to data collection, analysis and interpretation. The first draft of the manuscript was written by the first author and authors employed by the sponsor. All authors critically reviewed and contributed to revisions; all authors provided final approval for the manuscript.

Funding

Supported by Structure Therapeutics. The sponsor designed the trial, collected and analyzed the data, and participated in manuscript preparation.

Competing interests

J.R. reports clinical research grants from Amgen, Applied Therapeutics, AstraZeneca, Biomea Fusion, Boehringer Ingelheim, Corcept, Corxel, Eli Lilly, Hanmi, Merck, Novo Nordisk, Pfizer, Regeneron, Roche, Regor, Sanofi, Structure Therapeutics and Terns; J.R. serves or has served on scientific advisory boards and received honorarium or consulting fees from Amgen, Applied Therapeutics, Arrowhead, Biomea Fusion, Boehringer Ingelheim, Corcept, Eccogene, Eli Lilly, Hanmi, i2O Therapeutics, Novo Nordisk, Regeneron, Roche, Sanofi, Structure Therapeutics and Terns, and has received honoraria for lectures from Eli Lilly, Novo Nordisk and Sanofi. I.L. reports received research funding (paid to institution) and/or product from NovoNordisk, Boehringer-Ingelheim, Dexcom, Roche, Pfizer and Lilly; research related consulting fees (paid to institution) from NovoNordisk; advisory or consulting fees and/or other support from Aadvarak Therapeutics, Abbvie, Adarx, Altasciences, Alveus Therapeutics, Amgen, Antag Therapeutics, Arrowhead Pharmaceuticals, Astra Zeneca, Baim Institute, Bain Capital, Bayer, Betagenon, Bioio, Biomea, Boehringer-Ingelheim, Boston Scientific, Carmot, Corxel, Cytokine Pharma, Eli Lilly, Genentech, Janssen/J&J, Juvena, Kailera Therapeutics, Keros Therapeutic, Mediflix, Metsera, Neurocrine, Novo Nordisk, Penguin Bio, Pfizer, Regeneron, Response Pharmaceutical, Roche, Sanofi, Shionogi, Sparrow, Skye Bioscience, Source Bio, Structure Therapeutics, SUMMIT, Tenvie, TERNS Pharma, Verdiva Bio, Viking Therapeutics and Zealand Pharma. D.R. reports having received consulting honoraria from Abbvie, Altimmune; Amgen, AstraZeneca, Biohaven, Boehringer Ingelheim, Calibrate, Carmot Therapeutics, Currax Pharmaceuticals, CinRx, Eli Lilly, Epitomee, Fractyl Health, i2o, ICON, Kailera, Novo Nordisk, Pfizer, PPD, Protagonist, Regor, Rhythm, Souffle, Source Bio, Structure Therapeutics, Tenvie, Viking Therapeutics, WondrHealth, Weight Watchers and Zealand Pharma. She has received stock options from Calibrate, Epitomee and Ro Health. A.M.J. conducts multicenter trials with Amgen, Boehringer Ingelheim, Eli Lilly, Novo Nordisk and Rhythm Pharmaceuticals and serves on scientific advisory boards for Amgen, AstraZeneca, Boehringer Ingelheim, Biohaven, Eli Lilly, i2o, Intellihealth/Flyte, Metsera, Novo Nordisk, Pfizer, Regeneron, Roche/Genentech, Scholar Rock, Structure Therapeutics, Syntis Bio, Viking, Wave, WW International and Zealand Pharmaceuticals; academic cofounder State 4 Therapeutics. R.K. reports a position of a medical board member, advisor or consultant for Abbvie, Antag, AstraZeneca,

Boehringer Ingelheim, Currax, Eli Lilly, Novo Nordisk, Structure, Viking and Weight Watchers. A.A. reports participation on an advisory board or data monitoring board for Amgen, Boehringer Ingelheim, Currax, Structure Therapeutics and Regeneron; grant support to the institution from Vivus, Novo Nordisk, Phenomix Sciences and Terns Pharmaceutical; and consulting fees to the institution from Amgen, RareStone and Bausch Health. T.C.B. reports speaker or advisory relationships with BI, Eli Lilly, Mannkind, and Sanofi and research funding from BI, Amgen, Dreamed, Sanofi, AstraZeneca, Eli Lilly, Novo Nordisk, Sequel, Insulet, Structure, vTv, Medtronic, and Tandem Diabetes Care. M.C. reports no competing interests. F.L.H. reports no competing interests. T.S. is a primary investigator of studies sponsored by Lilly, Amgen, Novo Nordisk, Novartis, Boehringer Ingelheim, AbbVie, Reata and Vertex. L.C. reports clinical investigator activity for Eli Lilly and Structure Therapeutics. Y.L., M.L., A.B., J.B., A.C., H.Y. and B.C. are employees of Structure Therapeutics and report no other competing interests.

Additional information

Extended data is available for this paper at <https://doi.org/10.1038/s41591-026-04476-6>.

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41591-026-04476-6>.

Correspondence and requests for materials should be addressed to Julio Rosenstock.

Peer review information *Nature Medicine* thanks Michael Nauck, Peng Wei and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Primary Handling Editor: Ashley Castellanos-Jankiewicz, in collaboration with the *Nature Medicine* team.

Reprints and permissions information is available at www.nature.com/reprints.

Extended Data Table 1 | SAEs and AESIs in the double-blind period of the ACCESS study

Preferred Term n (%)	Aleniglipron 45 mg (N=45)	Aleniglipron 90 mg (N=65)	Aleniglipron 120 mg (N=63)	Placebo (N=56)
SAEs in the double-blind period of the ACCESS study				
Any treatment-emergent SAE	1(2.2)	0	4(6.3)	3(5.4)
Appendicitis	0	0	1(1.6)	0
Cellulitis	0	0	1(1.6)	0
Parotitis	0	0	1(1.6)	0
Sepsis	0	0	1(1.6)	0
Bronchitis	0	0	0	1(1.8)
Metabolic encephalopathy	0	0	1(1.6)	0
Trigeminal neuralgia	1(2.2)	0	0	0
Acute kidney injury	0	0	2(3.2)	0
Cervical vertebral fracture	0	0	1(1.6)	0
Atrial fibrillation	0	0	0	1(1.8)
Cholecystitis	0	0	0	1(1.8)
Cholelithiasis	0	0	0	1(1.8)
AESIs in the double-blind period of the ACCESS study				
Any treatment-emergent AESI	12(26.7)	11(16.9)	17(27.0)	15(26.8)
Cough	2(4.4)	0	1(1.6)	4(7.1)
Dyspnoea	1(2.2)	0	0	0
Rhinitis allergic	1(2.2)	0	0	0
Wheezing	0	0	0	2(3.6)
Pruritus	0	1(1.5)	1(1.6)	0
Rash	1(2.2)	1(1.5)	0	0
Dermatitis contact	0	0	1(1.6)	0
Eczema	0	0	1(1.6)	0
Seasonal allergy	0	1(1.5)	0	1(1.8)
Hypotension	0	0	1(1.6)	0
Alanine aminotransferase increased	1(2.2)	2(3.1)	1(1.6)	1(1.8)
Blood bilirubin increased	0	0	1(1.6)	0
Blood bilirubin unconjugated increased	0	0	1(1.6)	0
Blood fibrinogen decreased	0	1(1.5)	0	2(3.6)
Aspartate aminotransferase increased	0	0	0	1(1.8)
International normalized ratio increased	0	0	0	1(1.8)
Prothrombin time prolonged	0	0	0	1(1.8)
Hepatobiliary disorders	0	1(1.5)	1(1.6)	1(1.8)
Hypertransaminasemia	0	1(1.5)	0	0
Metabolic dysfunction-associated liver disease	0	0	1(1.6)	0
Cholecystitis	0	0	0	1(1.8)
Cholelithiasis	0	0	0	1(1.8)
Severe gastrointestinal adverse events	3(6.7)	3(4.6)	1(1.6)	0
Vomiting	3(6.7)	2(3.1)	1(1.6)	0
Nausea	2(4.4)	1(1.5)	1(1.6)	0
Dyspepsia	0	1(1.5)	1(1.6)	0
Palpitations	0	1(1.5)	2(3.2)	1(1.8)
Atrial fibrillation	0	0	0	1(1.8)
Sinus tachycardia	0	0	0	1(1.8)
Syncope	0	0	3(4.8)	0
Electrocardiogram abnormal	0	1(1.5)	0	0
Acute kidney injury	0	0	3(4.8)	0

Extended Data Table 1 (continued) | SAEs and AESIs in the double-blind period of the ACCESS study

Preferred Term n (%)	Aleniglipron 45 mg (N=45)	Aleniglipron 90 mg (N=65)	Aleniglipron 120 mg (N=63)	Placebo (N=56)
Renal impairment	1(2.2)	0	0	0
Hypoglycemia	2(4.4)	0	2(3.2)	0
Depression	0	1(1.5)	0	1(1.8)
Depressive symptom	0	0	1(1.6)	0
Suicidal ideation	0	0	1(1.6)	0
Cholecystitis	0	0	0	1(1.8)
Heart Failure Syndrome	0	0	0	1(1.8)
Bronchitis	0	0	0	1(1.8)

SAE = serious adverse event. AESI = adverse event of special interest.

Extended Data Table 2 | Body weight reduction from baseline at Week 36 (treatment estimand)

	Aleniglipron 45 mg (N=45)	Aleniglipron 90 mg (N=65)	Aleniglipron 120 mg (N=63)	Pooled placebo (N=56)
Percent change in body weight*				
LSM ^a (SE), (95% CI)	-8.8 (1.13) (-11.08, -6.60)	-10.2 (0.94) (-12.07, -8.37)	-11.4 (0.92) (-13.26, -9.62)	-1.0 (0.99) (-2.93, 0.96)
LSM difference ^b (SE), (95% CI)	-7.9 (1.50) (-10.81, -4.90)	-9.2 (1.36) (-11.91, -6.55)	-10.5 (1.35) (-13.11, -7.80)	
Category of weight reduction, MBE % of participants (95% CI)**				
≥ 5%	70.1 (55.19, 81.69)	77.6 (65.82, 86.22)	77.0 (64.93, 85.79)	18.3 (10.18, 30.55)
≥ 10%	35.1 (22.64, 50.07)	45.6 (33.80, 57.84)	61.2 (48.59, 72.47)	4.3 (1.24, 13.83)
≥ 15%	13.5 (6.29, 26.75)	21.5 (13.09, 33.33)	30.8 (20.57, 43.40)	0.8 (0.05, 11.72)
≥ 20%	5.6 (1.66, 17.36)	8.6 (3.80, 18.34)	15.0 (8.09, 26.12)	0.9 (0.06, 12.31)

LSM = least squares mean; SE = standard error; CI = confidence interval; MBE = model-based estimate. *LSM, SE, and 95% CI are results from a mixed model for repeated measures (MMRM) with treatment, sex, baseline body mass index stratum, visit week, treatment-by-visit week interaction as fixed factors, and baseline body weight as covariate. An unstructured covariance structure was used. **Model estimated response rate is the average predicted probability from a logistic regression model. Missing values were imputed by categorizing the imputed values of the missing body weight at Week 36 through predicted values obtained from the MMRM analysis of percent change in body weight. 95% CI were not adjusted for multiplicity and were not used for hypothesis testing. ^aLSM is change from baseline. ^bLSM difference is change from baseline and placebo-adjusted.

Extended Data Table 3 | Categorical body weight reduction (efficacy estimand)

	Aleniglipron 45 mg (N=45)	Aleniglipron 90 mg (N=65)	Aleniglipron 120 mg (N=63)	Pooled-Placebo (N=56)
% of participants with $\geq 5\%$ reduction in body weight				
Observed % (n/N')	75.8 (25/33)	79.6 (39/49)	86.0 (43/50)	19.0 (8/42)
Model Estimated (95% CI) ^a	75.4 (58.31, 87.02)	79.5 (66.16, 88.49)	85.9 (73.57, 92.98)	22.7 (12.20, 38.26)
% of participants with $\geq 10\%$ reduction in body weight				
Observed % (n/N')	42.4 (14/33)	55.1 (27/49)	72.0 (36/50)	4.8 (2/42)
Model Estimated (95% CI) ^a	44.2 (28.45, 61.24)	54.4 (40.41, 67.66)	70.4 (56.21, 81.50)	6.9 (2.09, 20.62)
% of participants with $\geq 15\%$ reduction in body weight				
Observed % (n/N')	18.2 (6/33)	26.5 (13/49)	40.0 (20/50)	0 (0/42)
Model Estimated (95% CI) ^a	19.4 (9.28, 36.23)	26.1 (15.74, 40.01)	37.9 (25.38, 52.29)	1.0 (0.07, 14.15)

CI = confidence interval. ^aModel estimated response rates were calculated with Rubin's rule by combining the percentages of participants who met the target in imputed data sets analyzed with logistic regression. 95% CI were not adjusted for multiplicity and were not used for hypothesis testing.

Extended Data Table 4 | Secondary weight-loss endpoints (efficacy estimand)

Change from baseline at Week 36, LSM (SE), (95% CI)	Aleniglipron 45 mg (N=45)	Aleniglipron 90 mg (N=65)	Aleniglipron 120 mg (N=63)	Pooled placebo (N=56)
Waist circumference, cm	-9.7 (1.39) (-12.45, -6.98)	-9.5 (1.15) (-11.78, -7.23)	-12.1 (1.14) (-14.39, -9.88)	-4.1 (1.23) (-6.53, -1.69)
Placebo-adjusted LSM (SE)	-5.6 (1.81)	-5.4 (1.63)	-8.0 (1.63)	n/a
Absolute body weight, kg	-10.4 (1.29) (-12.95, -7.86)	-12.2 (1.07) (-14.35, -10.13)	-13.6 (1.06) (-15.73, -11.54)	-1.2 (1.13) (-3.42, 1.04)
Placebo-adjusted LSM (SE)	-9.2 (1.71)	-11.0 (1.55)	-12.4 (1.54)	n/a
BMI, kg m ⁻²	-3.6 (0.45) (-4.48, -2.71)	-4.1 (0.37) (-4.86, -3.39)	-4.8 (0.37) (-5.53, -4.07)	-0.4 (0.39) (-1.15, 0.40)
Placebo-adjusted LSM (SE)	-3.2 (0.59)	-3.8 (0.54)	-4.4 (0.54)	n/a

BMI = body mass index. Least squares means (LSM) and their associated standard error (SE), 95% confidence interval (CI) are results from a mixed model for repeated measures. Unstructured covariance structure was used. 95% CI were not adjusted for multiplicity and were not used for hypothesis testing.

Extended Data Table 5 | Changes in laboratory parameters, ECG, vital signs from baseline at Week 36 (efficacy estimand)

Change from baseline at Week 36, LSM (SE), (95% CI)	Aleniglipron 45 mg (N=45)	Aleniglipron 90 mg (N=65)	Aleniglipron 120 mg (N=63)	Pooled placebo (N=56)
Systolic blood pressure (mmHg)	-7.9 (1.71) (-11.25, -4.48)	-8.9 (1.42) (-11.68, -6.07)	-9.0 (1.40) (-11.74, -6.21)	-1.5 (1.52) (-4.49, 1.49)
Diastolic blood pressure (mmHg)	-3.3 (1.11) (-5.53, -1.14)	-4.1 (0.92) (-5.90, -2.26)	-3.5 (0.91) (-5.33, -1.73)	-0.3 (0.99) (-2.23, 1.66)
QTcF Interval, Aggregate (ms) ^a				
Pre-dose	-7.4 (2.03) (-11.41, -3.41)	-2.5 (1.68) (-5.79, 0.83)	-6.1 (1.68) (-9.44, -2.80)	-0.5 (1.78) (-3.96, 3.04)
2-4 h Post-dose	-6.9 (1.99) (-10.78, -2.96)	-5.8 (1.67) (-9.12, -2.57)	-6.3 (1.67) (-9.56, -3.01)	-5.0 (1.78) (-8.51, -1.51)
ECG Heart Rate (beats/min) ^a				
Pre-dose	0.8 (1.27) (-1.69, 3.34)	2.2 (1.06) (0.13, 4.30)	2.1 (1.06) (-0.03, 4.15)	-1.2 (1.12) (-3.44, 0.99)
2-4 h Post-dose	8.7 (1.44) (5.87, 11.54)	9.4 (1.21) (7.07, 11.82)	10.5 (1.21) (8.13, 12.89)	6.7 (1.30) (4.18, 9.27)
Free Fatty Acid (mEq/L)	-0.07 (0.036) (-0.146, -0.003)	0.00 (0.029) (-0.057, 0.059)	-0.03 (0.029) (-0.089, 0.026)	-0.04 (0.031) (-0.101, 0.021)
Hemoglobin A1C (%)	-0.27 (0.047) (-0.363, -0.178)	-0.32 (0.039) (-0.395, -0.241)	-0.36 (0.039) (-0.434, -0.280)	0.01 (0.042) (-0.070, 0.098)
Percent change from baseline at Week 36, MBE (SE), (95% CI)	Aleniglipron 45 mg (N=45)	Aleniglipron 90 mg (N=65)	Aleniglipron 120 mg (N=63)	Pooled placebo (N=56)
Cholesterol	-3.9 (2.2) (-8.2, 0.6)	-8.3 (1.8) (-11.8, -4.8)	-7.5 (1.8) (-10.9, -4.0)	-2.5 (2.0) (-6.4, 1.5)
HDL Cholesterol	2.2 (2.5) (-2.6, 7.3)	-1.6 (2.0) (-5.4, 2.5)	-0.2 (2.0) (-4.1, 3.9)	0.9 (2.2) (-3.4, 5.3)
Triglycerides	-13.5 (4.5) (-21.9, -4.1)	-9.3 (3.9) (-16.7, -1.3)	-12.3 (3.7) (-19.4, -4.6)	-5.9 (4.3) (-14.1, 3.1)
LDL Cholesterol	-4.2 (3.1) (-10.1, 2.0)	-8.2 (2.4) (-12.9, -3.2)	-9.0 (2.4) (-13.6, -4.1)	-0.9 (2.8) (-6.3, 4.8)
Fasting Glucose	-6.3 (1.5) (-9.2, -3.2)	-5.6 (1.3) (-8.0, -3.0)	-6.6 (1.2) (-9.0, -4.1)	0.9 (1.4) (-1.9, 3.7)
hsCRP	-33.4 (10.1) (-50.6, -10.0)	-28.8 (8.6) (-43.9, -9.8)	-46.4 (6.6) (-58.0, -31.8)	-6.9 (12.1) (-28.0, 20.4)

QTcF=QT Corrected for Heart Rate using Fridericia's Formula; ECG = electrocardiogram; MBE = model-based estimate; HDL = high-density lipoprotein; LDL = low-density lipoprotein. Least squares means (LSM) and their associated standard error (SE), 95% confidence interval (CI) are results from a mixed model for repeated measures based on the efficacy estimand. 95% CI were not adjusted for multiplicity and were not used for hypothesis testing. ^aChange in pre-dose and post-dose parameters at Week 36 are made in comparison to baseline values before any dose of study drug.

Extended Data Table 6 | Summary of participants with maximum post-baseline ALT or AST $\geq 3\times$, $\geq 5\times$, and $\geq 10\times$ upper limit of normal

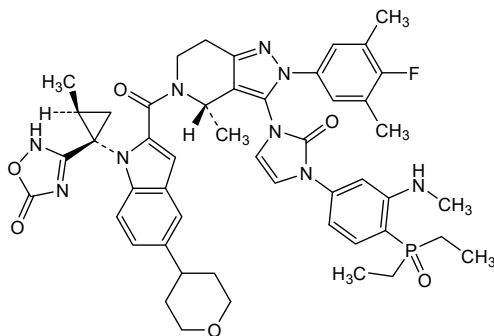
Liver enzymes	Aleniglipron 45 mg (N=45) n (%)	Aleniglipron 90 mg (N=65) n (%)	Aleniglipron 120 mg (N=63) n (%)	Pooled placebo (N=56) n (%)
$\geq 3\times$ ULN (either ALT/AST)	1 (2.3)	3 (4.8)	2 (3.2)	2 (3.6)
ALT	1 (2.3)	3 (4.8)	2 (3.2)	1 (1.8)
AST	0 (0)	0 (0)	0 (0)	1 (1.8)
$\geq 5\times$ ULN (either ALT/AST)	0 (0)	1 (1.6)	0 (0)	0 (0)
ALT	0 (0)	1 (1.6)	0 (0)	0 (0)
AST	0 (0)	0 (0)	0 (0)	0 (0)
$\geq 10\times$ ULN (either ALT/AST)	0 (0)	0 (0)	0 (0)	0 (0)
ALT	0 (0)	0 (0)	0 (0)	0 (0)
AST	0 (0)	0 (0)	0 (0)	0 (0)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit normal. % = n/N' where N' is the number of participants with a lab measurement at baseline or post-baseline for the given parameter. Baseline is defined as the last measurement prior to the first dose of study drug.

Extended Data Table 7 | Common TEAEs by preferred term (safety analysis set) during the OLE study period

Aleniglipron starting dose in OLE period	Aleniglipron 60 mg (N=28) n (%)	Aleniglipron 120 mg (N=42) n (%)	Aleniglipron 120 mg (N=43) n (%)	Aleniglipron 2.5 mg (N=38) n (%)
Arm in the double-blind treatment period	45 mg	90 mg	120 mg	Placebo
Any TEAE	16 (57.1)	27 (64.3)	23 (53.5)	31 (81.6)
Any TEAE leading to discontinuation of treatment	0	1 (2.4)	0	0
Common TEAEs (≥5%; preferred term)				
Nausea	5 (17.9)	5 (11.9)	5 (11.6)	15 (39.9)
Vomiting	2 (7.1)	5 (11.9)	7 (16.3)	0
Diarrhea	2 (7.1)	7 (16.7)	3 (7)	10 (26.3)
Constipation	3 (10.7)	6 (14.3)	1 (2.3)	12 (31.6)

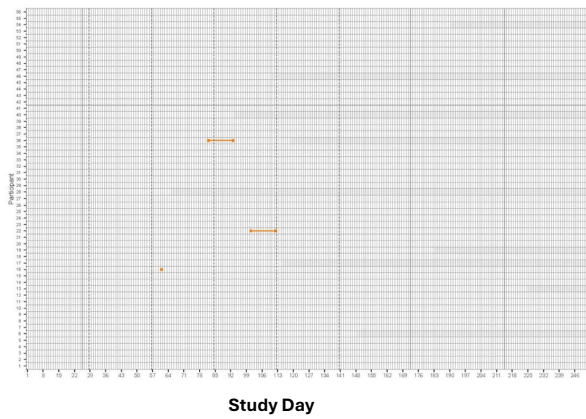
TEAE = treatment-emergent adverse event.



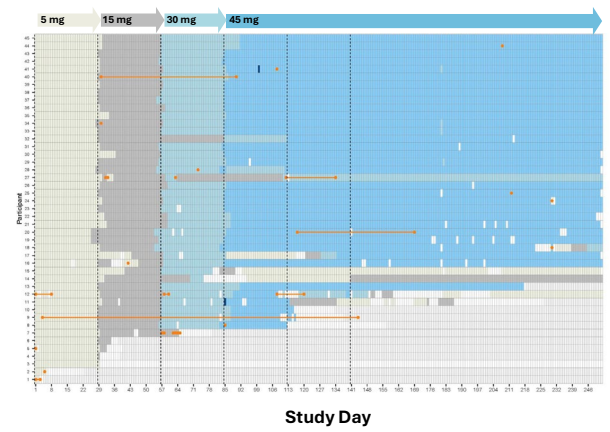
Extended Data Fig. 1 | Aleniglipron compound structure. Aleniglipron (GSBR-1290) is a potent, β -arrestin-biased, highly selective small molecule GLP-1 RA. Using structure-based drug discovery, aleniglipron was designed to optimize

substituent positioning and provide conformational stability, eliminate chiral centers requiring chiral separation supporting efficient synthesis, oral exposure, and selective and biased receptor engagement.

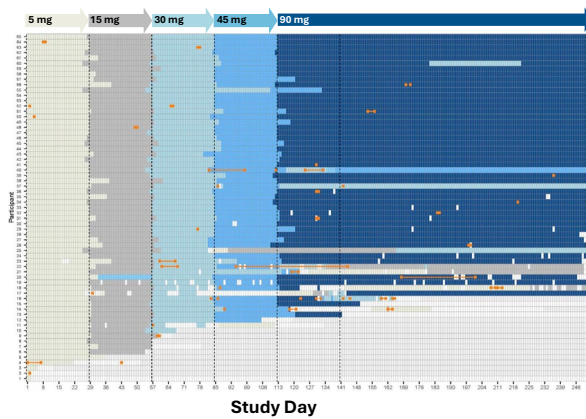
A. Placebo



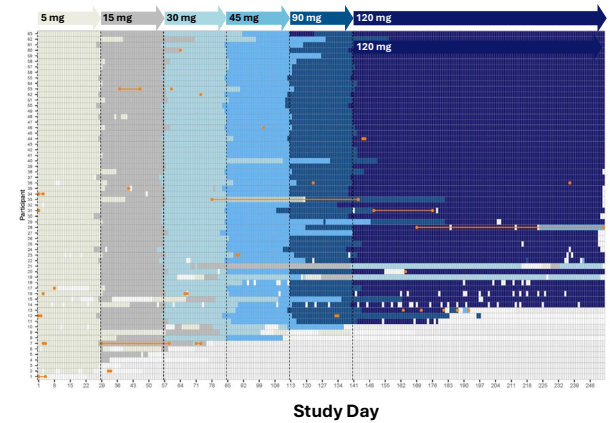
B. 45 mg Aleniglipron



C. 90 mg Aleniglipron



D. 120 mg Aleniglipron



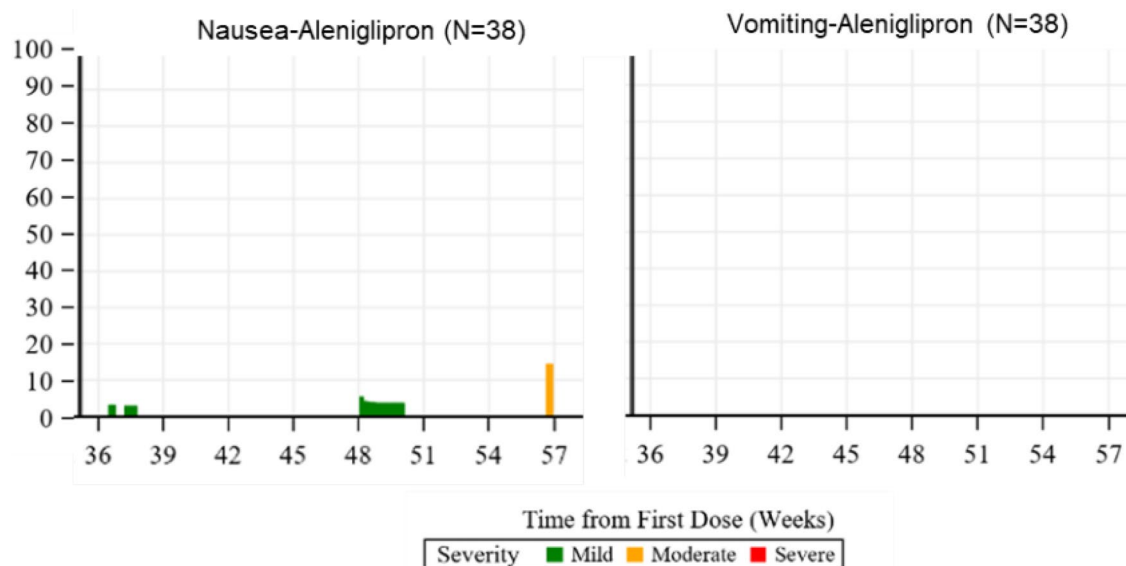
Actual dose: 5 mg 15 mg 30 mg 45 mg 90 mg 120 mg Skipped Vomiting

Extended Data Fig. 2 | Heat map of vomiting over time and by dose arm.

A. Placebo arm. **B.** 45 mg aleniglipron arm. **C.** 90 mg aleniglipron arm.

D. 120 mg aleniglipron arm. Colored arrows at top of each panel indicate targeted dose titration. Colored boxes in panels indicate actual dose level: White box, skipped dose or placebo. Beige, 5- < 15 mg. Medium grey, 15- < 30 mg. Light blue, 30- < 60 mg. Medium blue, 60- < 90 mg. Dark blue, 90- < 120 mg.

Navy blue \geq 120 mg. Light grey indicates early study discontinuation. Orange lines indicate intermittent events of vomiting of 1 day duration. Dots represent events of vomiting every 4 weeks. Each row indicates an individual participant, represented with mock participant numbers beginning at 1 for each panel.



Extended Data Fig. 3 | Tolerability to 2.5 mg starting dose of aleniglipron after a median follow up of 20 weeks in the OLE period (previous placebo group initiating aleniglipron at 2.5 mg daily for 4 weeks, followed by uptitration to 5 mg, 10 mg, 20 mg, 30 mg daily at 4 week intervals). Figure represents prevalence of nausea or vomiting over time. Y axis represents the prevalence rate calculated as the proportion of participants who experienced nausea or vomiting on a daily basis among participants who were dosed the study drug at target

dose on the respective day. TEAEs are defined as AEs that started or worsened in severity after the first dose of OLE study drug, and onset date is within 7 days after the last dose of study drug. Intermittent events with 'INTERMITTENT' or 'OCCASIONAL' in the verbatim field in electronic data capture were not included. TEAEs are enumerated from onset to resolution or data cutoff (if ongoing) and the maximum severity is selected.

Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our [Editorial Policies](#) and the [Editorial Policy Checklist](#).

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a Confirmed

- The exact sample size (n) for each experimental group/condition, given as a discrete number and unit of measurement
- A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
- The statistical test(s) used AND whether they are one- or two-sided
Only common tests should be described solely by name; describe more complex techniques in the Methods section.
- A description of all covariates tested
- A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
- A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
- For null hypothesis testing, the test statistic (e.g. F , t , r) with confidence intervals, effect sizes, degrees of freedom and P value noted
Give P values as exact values whenever suitable.
- For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
- For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
- Estimates of effect sizes (e.g. Cohen's d , Pearson's r), indicating how they were calculated

Our web collection on [statistics for biologists](#) contains articles on many of the points above.

Software and code

Policy information about [availability of computer code](#)

Data collection

Data analysis

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio [guidelines for submitting code & software](#) for further information.

Data

Policy information about [availability of data](#)

All manuscripts must include a [data availability statement](#). This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our [policy](#)

De-identified individual patient data for variables necessary to address a specific research question may be shared with an approved data sharing request. Researchers will submit a request containing the research objectives, endpoints/outcomes of interest, statistical analysis plan, data requirements, publication plan, and qualifications of the researcher(s). Gasherbrum Bio, Inc. does not grant external requests for individual de-identified patient data for the following purposes:

- re-evaluating safety and efficacy end points already addressed in the product labelling,
- assessing safety or efficacy for an indication in current development

Requests are reviewed by a committee of internal advisors, and if not approved, may be further arbitrated by a panel of external advisors. Upon approval, information necessary to address the research question will be provided under the terms of a data sharing agreement.

Data sharing requests will be considered beginning 36 months after the study publication (manuscript accepted for publication) and either 1) the product has been granted marketing authorization in at least two regulatory jurisdictions, or 2) clinical development for the product and/or indication discontinues and the data will not be submitted to regulatory authorities. There is no end date for eligibility to submit a data sharing request for this study. Access can be requested from info@structuretx.com. Requests will be acknowledged and reviewed within 60 days of receipt of request.

Research involving human participants, their data, or biological material

Policy information about studies with [human participants or human data](#). See also policy information about [sex, gender \(identity/presentation\), and sexual orientation](#) and [race, ethnicity and racism](#).

Reporting on sex and gender	Sex was determined by self-reporting; we did not collect alternative data to reconcile sex and gender. The Informed Consent Form signed by all participants described that data collected during the study, including sex of participants, may be shared as part of study reporting, but with no personal identifying information attached.
Reporting on race, ethnicity, or other socially relevant groupings	Race and ethnicity were self reported, and included: White Black or African American Asian Multiple Not Hispanic or Latino Hispanic or Latino
Population characteristics	Key covariates in the therapeutic area of chronic weight management were collected: Baseline BMI • ≤35 kg/m ² • >35 kg/m ² Sex • Male • Female
Recruitment	The study was conducted at 38 clinical trial sites across the US that use conventional recruiting strategies including previously existing potential participants database, media outreach. Self selection may create bias in that those who volunteer for clinical trials may have different motivations compared with patients who may use a drug, if approved, in the real world. A double-blind, placebo-controlled trial helps to alleviate the impact of self-selection bias.
Ethics oversight	A central IRB, Advarra, was used for ethics oversight. The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline E6: Good Clinical Practice (GCP). Participants were reimbursed for travel, meals, and other study-related expenses in accordance with IRB approval.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

Life sciences Behavioural & social sciences Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see [nature.com/documents/nr-reporting-summary-flat.pdf](https://www.nature.com/documents/nr-reporting-summary-flat.pdf)

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	We estimated that 230 participants would provide >90% power to detect a treatment difference of -5% body weight change between the aleniglipron treatment group and placebo from baseline to Week 36, assuming an SD of 6%, a 2-sided alpha level of 0.05, 35 completers for one aleniglipron treatment group and 35 completers for the placebo group.
Data exclusions	The full analysis set included all randomized participants who received ≥1 dose of aleniglipron or placebo and had ≥1 post dose assessment. The safety analysis set included all participants who received ≥1 dose of aleniglipron or placebo. Safety and tolerability data are presented for all participants in the safety analysis set. One patient randomized to aleniglipron 120 mg treatment group did not receive any study treatment and was excluded from the efficacy and safety analysis population

Replication	The reproducibility of findings was supported by the use of a predefined protocol and statistical analysis plan, standardized study procedures, and systematic data monitoring to ensure consistency and data integrity. Full methodological and analytic details are provided in the protocol and SAP. No experimental replication was required.
Randomization	Participants were randomized to three dose level cohorts (45, 90, or 120 mg) at a ratio of 3:4:4, then to aleniglipron or placebo at a ratio of 3:1 within each cohort. Randomization was stratified by baseline BMI (≤ 35 kg/m ² / >35 kg/m ²) and sex.
Blinding	All participants and study personnel were blinded to study drug assignment.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
<input checked="" type="checkbox"/>	<input type="checkbox"/> Antibodies
<input checked="" type="checkbox"/>	<input type="checkbox"/> Eukaryotic cell lines
<input checked="" type="checkbox"/>	<input type="checkbox"/> Palaeontology and archaeology
<input checked="" type="checkbox"/>	<input type="checkbox"/> Animals and other organisms
<input type="checkbox"/>	<input checked="" type="checkbox"/> Clinical data
<input checked="" type="checkbox"/>	<input type="checkbox"/> Dual use research of concern
<input checked="" type="checkbox"/>	<input type="checkbox"/> Plants

Methods

n/a	Involved in the study
<input checked="" type="checkbox"/>	<input type="checkbox"/> ChIP-seq
<input checked="" type="checkbox"/>	<input type="checkbox"/> Flow cytometry
<input checked="" type="checkbox"/>	<input type="checkbox"/> MRI-based neuroimaging

Clinical data

Policy information about [clinical studies](#)

All manuscripts should comply with the ICMJE [guidelines for publication of clinical research](#) and a completed [CONSORT checklist](#) must be included with all submissions.

Clinical trial registration	ClinicalTrials.gov identifier NCT06693843
Study protocol	The full protocol will be made available as a supplemental file submitted with this manuscript.
Data collection	Between October 28, 2024, and February 7, 2025, 406 adults were screened, and 230 participants underwent randomization across 38 sites in the US. Site locations are listed in Supplementary Table 1 with the manuscript.
Outcomes	<p>Endpoints were pre-defined and guided by the FDA draft guidance "Obesity and Overweight: Developing Drugs and Biological Products for Weight Reduction."</p> <p>The primary endpoint (efficacy estimand) was the percent change in body weight from baseline to Week 36. The secondary endpoints were percentages of participants who achieved $\geq 5\%$, $\geq 10\%$, and $\geq 15\%$ reductions in body weight at Week 36, and changes in body weight (absolute), waist circumference, and BMI from baseline to Week 36. Additional secondary safety endpoints were TEAEs, SAEs, adverse events of special interest (AESI), laboratory parameters, electrocardiograms, and vital signs.</p> <p>The primary efficacy estimand, pre-defined in the statistical analysis plan, estimates the treatment effect of aleniglipron relative to placebo at Week 36 in participants who met the inclusion criteria and would have completed the treatment period. Data collected before the occurrence of any intercurrent events (ICE) (+2 days) were used for the analysis. ICE were defined as permanent discontinuation of study drug, initiation of other anti-obesity medication, or bariatric surgery; data subsequent to ICE were handled by the hypothetical strategy, regarded as invalid and set to missing. Missing data were imputed implicitly. The primary endpoint based on the efficacy estimand was analyzed using a mixed model for repeated measures (MMRM) with treatment group, randomization strata (baseline BMI and sex), visit, treatment-by-visit interaction, and baseline measurement as covariates. An unstructured covariance model was used. The continuous endpoints based on the 2 estimands were analyzed using an MMRM with treatment group, randomization strata (baseline BMI and sex), visit, treatment-by-visit interaction, and baseline measurement as covariates. An unstructured covariance model was used. Using the MMRM model, missing data was imputed implicitly. This analysis is deemed unbiased under the missing at random assumption. For the body weight categorical endpoints, logistic regression was used to analyze the data. Missing values at Week 36 were imputed according to the multiple-imputation approach, and values were combined using Rubin's rule.</p> <p>All tests of treatment effects were conducted at a 2-sided alpha level of 0.05, and 2-sided 95% CIs were calculated. Lipid parameters, fasting glucose, and hsCRP were log-transformed before fitting the MMRM as described in the supplementary material. Because of the exploratory nature of the OLE study, no estimand or model-based approach was planned. Change from double-blind baseline in body weight was summarized based on observed data. Summary descriptives (n, mean, median, std, min and max) were presented by visit and treatment group separately.</p>

Plants

Seed stocks

Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.

Novel plant genotypes

Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.

Authentication

Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosaicism, off-target gene editing) were examined.