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Efficacy and safety of danuglipron (PF-06882961) in adults with obesity: A randomized, placebo-controlled, dose-ranging phase 2b study

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Abstract

Aims: This randomized, double-blind, placebo-controlled Phase 2b study aimed to assess the efficacy, safety, and tolerability of danuglipron (PF-06882961), an oral small-molecule glucagon-like peptide-1 (GLP-1) receptor agonist, in adults with obesity.

Materials and Methods: Eligible participants (aged 18–75 years; with obesity, without diabetes) were randomized to receive danuglipron or placebo twice daily (BID) for 26 or 32 weeks. Danuglipron was escalated to doses of 40–200 mg BID in 1-, 2-, or 4-week intervals. Assessments included body weight, waist circumference, and safety evaluations.

Results: Overall, 628 participants were randomized; of 626 receiving study treatment (placebo, $n = 90$; danuglipron, $n = 536$), 39.3% completed treatment. Approximately 38% of participants discontinued treatment because of adverse events (AEs) and 22% discontinued for other reasons. The primary endpoint was the change in weight from baseline to the end of treatment; all danuglipron groups demonstrated statistically significant reductions with least squares mean percentage decreases from baseline ranging from −5.0% (90% confidence interval [CI] −6.8%, −3.2%) to −12.9% (90% CI −16.1%, −9.5%) relative to placebo. Danuglipron was considered safe. Consistent with the mechanism, the most frequently reported events were nausea and vomiting, and increased rates of gastrointestinal AEs were generally observed at higher doses.

Most events were reported as mild, and no other dose-related trends were observed in safety endpoints.

Conclusions: In participants with obesity, danuglipron resulted in statistically significant and clinically meaningful reductions in body weight versus placebo over 26 or 32 weeks. The overall safety profile observed in this study was consistent with expectations for the mechanism, although discontinuation rates due to AEs were higher than anticipated across all treatment groups, including placebo.

ClinicalTrials.gov identifier: NCT04707313.

KEYWORDS

danuglipron, glucagon-like peptide-1 receptor agonist, obesity, phase 2b study

1 | INTRODUCTION

Peptidic glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are approved for the management of type 2 diabetes (T2D) and to reduce excess body weight.[1–4] In treating the disease of obesity, clinicians also have the opportunity to reduce the burden of obesity-related conditions including T2D, cardiovascular disease, and hyperlipidemia. Much interest remains in identifying effective, convenient, accessible treatments for patients. Danuglipron (PF-06882961) is an orally administered, potent, small-molecule GLP-1 RA that was under investigation for chronic weight management and as a potential therapy for adults with T2D.[1]

In two randomized, double-blind, placebo-controlled Phase 1 studies in patients with T2D (NCT03538743; NCT04552470), danuglipron demonstrated a safety and tolerability profile consistent with the mechanism, resulting in robust reductions in glycemic indices and body weight.[5,6] Similar findings were observed in a 12-week, Phase 2, randomized, double-blind, placebo-controlled study of patients with T2D or obesity (NCT04617275) and a 16-week, Phase 2, randomized, double-blind, placebo-controlled study in patients with T2D (NCT03985293).[7,8] Across Phase 1 and 2 studies, the most commonly reported AEs for danuglipron were gastrointestinal and mild in severity.[5–8] Here, we report results of a randomized, double-blind, placebo-controlled Phase 2b study to assess the efficacy, safety, and tolerability of multiple dose levels of danuglipron administered twice daily (BID) to adults with obesity and without diabetes. After completion of this Phase 2b study, additional studies with danuglipron were conducted, and in one of these subsequent studies, a single asymptomatic participant experienced potential drug-induced liver injury. After a review of all clinical trial data and recent input from regulators, Pfizer announced the discontinuation of clinical development of danuglipron.[9]

2 | MATERIALS AND METHODS

2.1 | Study design

This study (NCT04707313) was conducted across 42 sites in Canada, Japan, Taiwan, and the United States between 29 Jan 2021 and 11 Oct 2023. The protocol and amendments were approved by all relevant independent ethics committees and institutional review boards. All participants provided written informed consent. The study was conducted in accordance with consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and International Council for Harmonisation Good Clinical Practice guidelines, and all applicable laws and regulations.

Following initial eligibility assessment, screening continued with a single-blind, 2-week placebo run-in period; participants maintaining acceptable adherence were randomized on Day 1 into the double-blind treatment phase. Danuglipron was taken orally BID, and doses were escalated according to a fixed scheme (Figure 1), with delayed escalation or dose reduction not permitted per protocol. While danuglipron may be administered without regard to the timing of food, dosing in this study generally occurred with morning and evening meals, approximately 10–12 h apart. Three cohorts were enroled sequentially; Cohorts 2 and 3 were added based on protocol amendments. These amendments were added to characterize tolerability and efficacy over longer dose escalation intervals. Cohorts 1 and 2 had a 26-week double-blind treatment phase, with participants randomized to receive: placebo; danuglipron with target doses of 40, 80, 120, 160, or 200 mg BID with 1-week dose escalation intervals; or danuglipron with target doses of 120, 160, or 200 mg BID with 2-week dose escalation intervals. Cohort 3 had a 32-week double-blind treatment phase, with participants randomized to receive: placebo; or danuglipron with target doses of 80, 140, or 200 mg BID with 4-week dose escalation intervals. Further details of randomization and study treatments are provided in Data S1.

2.2 | Participants

Males or females aged 18–75 years, with obesity (body mass index [BMI] ≥30.0 kg/m^2), stable body weight before screening (<5 kg change for 90 days), and without diabetes were eligible. Females who were pregnant, breastfeeding, or planning to become pregnant while participating in the study were ineligible. Additional criteria are described in Data S1.

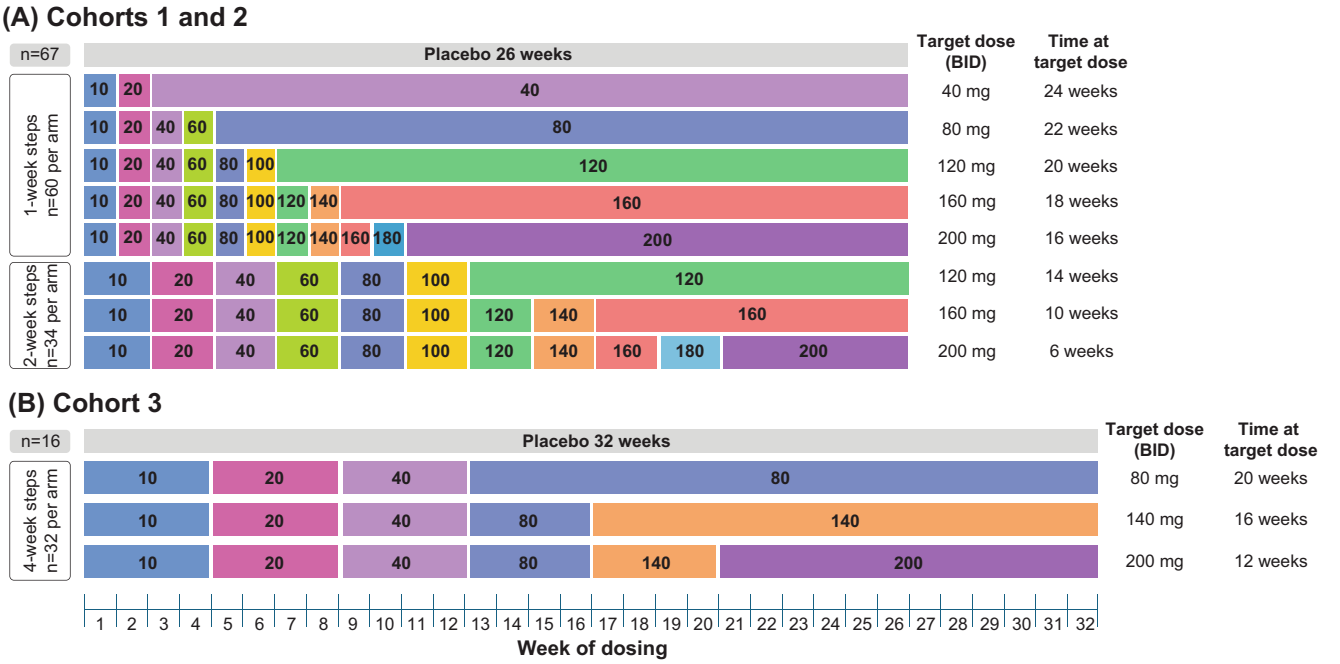

FIGURE 1 Study dose escalation scheme for (A) Cohort 1 (randomization across placebo, 1-week, and 2-week escalation arms for 26 weeks' dosing) and Cohort 2 (additional enrollment to placebo and 2-week escalation arms for 26 weeks' dosing), and (B) Cohort 3 (randomization across placebo and 4-week escalation arms for 32 weeks' dosing). BID, twice daily.

2.3 | Assessments

Body weight (in duplicate) and waist circumference (in triplicate) were measured during screening and at clinic visits every 2–4 weeks throughout the study. To ensure consistency, these measurements were taken in the fasted state after voiding urine and while wearing light clothing or a hospital gown. For all cohorts, adverse events (AEs) were monitored from screening to the end of follow-up (≥28 days after the last dose). Laboratory assessments, measurement of vital signs, and electrocardiograms (ECGs) were conducted at clinic visits. Based on product labelling for injectable GLP-1 RAs approved for obesity, the risk of suicidal ideation or behaviour (SIB) and depression were also evaluated at each visit.

2.4 | Endpoints

The primary efficacy endpoint was the percentage change in body weight from baseline to the end of treatment. Secondary efficacy endpoints included the proportions of participants with ≥5% reduction in body weight from baseline to the end of treatment, and absolute change in waist circumference from baseline to the end of treatment. Secondary pharmacodynamic endpoints included changes from baseline in glycated haemoglobin A1c (HbA1c) and fasting plasma glucose (FPG) over the treatment period. Secondary safety endpoints included the incidence of treatment-emergent AEs (TEAEs; including AEs and serious AEs [SAEs]); clinically significant abnormal laboratory, vital signs, and ECG parameters; and assessment of SIB and depression as determined by the Columbia-Suicide Severity Rating Scale (C-SSRS) and Patient Health Questionnaire-9 (PHQ-9).

2.5 | Statistical analyses

Sample sizes of 420, 49, and 112 participants were utilized for Cohorts 1, 2, and 3, respectively, to provide adequate power for the primary endpoint and to generate an adequately sized safety database in the target patient population.

Data from Cohorts 1 and 2 (26-week dosing durations) were combined and analysed together; data from Cohort 3 (32-week dosing duration) were analysed separately. Efficacy analyses included all participants who were randomized to and received ≥1 dose of study treatment, analysed according to the randomized treatment. For all analyses, data collected after discontinuation of study intervention were censored, representing an "on-treatment" estimand approach. Primary analysis of percentage change in body weight was conducted using mixed models for repeated measures (MMRM) fitted to change from baseline of $\log_e$-transformed values. Logistic regression was conducted to estimate the treatment effect for the secondary endpoint of proportions of patients with ≥5% reduction in body weight that were applied to multiple imputation (MI) datasets and combined using standard MI techniques. Absolute changes in waist circumference were analysed using an MMRM.

Safety data were summarized descriptively based on all participants randomized to and receiving ≥1 dose of study treatment and reported according to the treatment they received.

One-sided $p < 0.05$ was pre-specified as statistically significant for the primary and secondary efficacy endpoints, with no adjustments for multiple comparisons. For pharmacodynamics endpoints, two-sided $p < 0.1$ was pre-specified as statistically significant. All statistical analyses were conducted using SAS software Version 9.4 (Copyright© 2017 SAS Institute Inc).

Sample size determination and statistical analyses are further detailed in Data S1.

3 | RESULTS

3.1 | Disposition

Overall, 1220 participants were screened (Cohorts 1 and 2, $n = 926$; Cohort 3, $n = 294$) and 628 participants randomized (Cohorts 1 and 2, $n = 499$; Cohort 3, $n = 129$) (Figure 2). Dates of recruitment and follow-up for the study are reported in Data S1. Two participants in Cohorts 1 and 2 discontinued the study prior to the first dose of study treatment; therefore, efficacy and safety analyses in Cohorts 1 and 2 included 497 participants. In Cohort 3, all randomized participants received ≥1 dose of study treatment; therefore, efficacy and safety analyses included all 129 participants.

Of 626 participants randomized and treated, 246 (39.3%) completed the double-blind treatment phase on study treatment. Participants who discontinued treatment may have continued in the study off-treatment. Data provided here summarize discontinuations from study treatment, regardless of whether participants continued in the study or not. In Cohorts 1 and 2, 196 (39.4%) participants completed treatment and 301 (60.6%) discontinued treatment; in Cohort 3, 50 (38.8%) participants completed treatment and 79 (61.2%) discontinued treatment. For Cohorts 1 and 2, discontinuation rates ranged from 52% to 78% across danuglipron groups, versus 38% for placebo. In Cohort 3, discontinuation rates ranged from 59% to 69% across danuglipron groups, versus 42% for placebo.

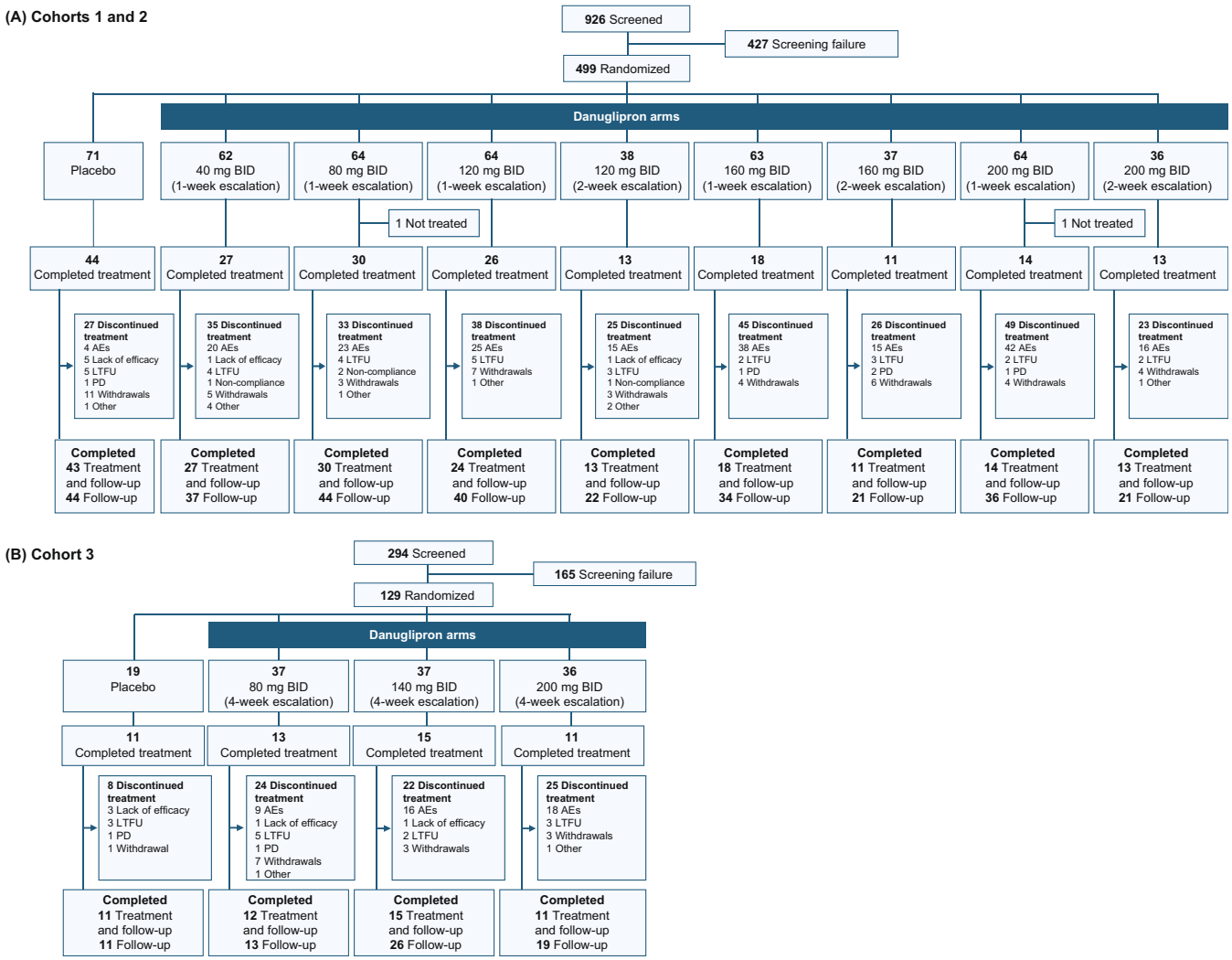

FIGURE 2 Disposition of study participants for (A) Cohorts 1 and 2 and (B) Cohort 3. AE, adverse event; BID, twice daily; LTFU, lost to follow-up; PD, protocol deviation.

Across cohorts, the most common reason for discontinuation was AEs (38.5% [$n = 241$] for all-causality AEs; 31.6% [$n = 198$] for treatment-related AEs in the gastrointestinal system organ class [SOC]), with higher discontinuation rates due to AEs in the danuglipron treatment groups (ranging 32%–67% [Cohorts 1 and 2], and 24%–50% [Cohort 3]) than in the placebo groups (6% [Cohorts 1 and 2] and 0% [Cohort 3]). The discontinuation rate from study treatment for reasons other than AEs was 22% overall and did not appear to be meaningfully different between placebo (Cohorts 1 and 2: 32% and Cohort 3: 42%) and danuglipron (11%–41%) treatment groups.

3.2 | Demographics and characteristics

The study was conducted across four regions, with participants in the safety analysis set located in the United States (70.6% [$n = 442$]), Canada (20.6% [$n = 129$]), Japan (8.1% [$n = 51$]), and Taiwan (0.6% [$n = 4$]). All four regions contributed to Cohort 1; Cohorts 2 and 3 were conducted at a subset of US sites only.

Demographics and baseline characteristics were generally consistent across treatment groups (Table 1). Median (range) age was 49.0 (18–74) years, 63.4% of participants were female, and 75.6% were White. Mean (range) weight at baseline was 110.1 (66.7–200.3) kg overall, 108.6 (66.7–200.3) kg in Cohorts 1 and 2, and 115.7 (74.3–195.6) kg in Cohort 3. Overall, mean (range) BMI was 38.9 (30–72) kg/m^2 and mean (range) waist circumference was 117.4 (80–193) cm.

3.3 | Primary efficacy outcome

At the end of treatment, all danuglipron groups demonstrated statistically significant (one-sided $p < 0.05$) reductions from baseline in body weight relative to placebo (Figure 3A). In Cohorts 1 and 2, placebo-adjusted modelled mean (90% CI) changes from baseline at Week 26 ranged from −5.0% (−6.8%, −3.2%) with danuglipron 80 mg BID (1-week dose escalation) to −9.5% (−11.4%, −7.6%) with danuglipron 160 mg BID (1-week dose escalation); in Cohort 3, changes at Week 32 ranged from −8.2% (−11.7%, −4.6%) with danuglipron 80 mg BID (4-week dose escalation) to −12.9% (−16.2%, −9.5%) with danuglipron 200 mg BID (4-week dose escalation) (Table S1). In all danuglipron groups, reductions in body weight were observed within the first few weeks of treatment and generally did not plateau; placebo groups exhibited a flat response or a slight increase in body weight from baseline (Figure 3B; Figure S1). While the rate of decline in body weight during the initial weeks of treatment appeared to be slightly slower with 4-week dose escalation intervals than in groups with 1- or 2-week dose escalation intervals, the overall weight loss trajectory across danuglipron groups was similar across all three cohorts.

3.4 | Secondary efficacy outcomes

Compared with placebo, all danuglipron groups had greater proportions of participants achieving ≥5% reductions in body weight from baseline to the end of treatment (Figure 3C). In Cohorts 1 and 2, proportions of participants with ≥5% reductions in body weight at Week 26 ranged from 48% (danuglipron 80 mg BID [1-week dose escalation]) to 80% (danuglipron 160 mg BID [1-week dose escalation]) versus 13% for placebo; in Cohort 3, proportions achieving the same reduction at Week 32 ranged from 64% (danuglipron 80 mg BID [4-week dose escalation]) to 88% (danuglipron 200 mg BID [4-week dose escalation]) versus 4% for placebo. Logistic regression-modelled odds ratios indicated favorability for danuglipron, with statistically significant differences for all treatment groups over placebo (data not presented).

There were statistically significant declines in waist circumference from baseline to the end of treatment for all danuglipron groups relative to placebo (one-sided $p < 0.05$). In Cohorts 1 and 2, modelled mean (90% CI) change in waist circumference from baseline to Week 26 was −1.3 (−2.6, 0.1) cm for placebo; across danuglipron groups, mean (90% CI) differences relative to placebo ranged from −4.5 (−6.6, −2.4) cm (80 mg BID [1-week dose escalation]) to −7.8 (−10.2, −5.4) cm (160 mg BID [1-week dose escalation]) (Figure S2). In Cohort 3, modelled mean (90% CI) change in waist circumference from baseline to Week 32 was 0.2 (−3.1, 3.5) cm for placebo; for danuglipron, mean (90% CI) differences relative to placebo ranged from −6.5 (−10.7, −2.2) cm (80 mg BID [4-week dose escalation]) to −11.6 (−16.0, −7.3) cm (200 mg BID [4-week dose escalation]). As waist and hip circumference decreased at similar rates over time, the waist-to-hip ratio was generally consistent over the duration of treatment (data not presented).

3.5 | Pharmacodynamic outcomes

All danuglipron groups apart from 80 mg BID (4-week dose escalation) demonstrated statistically significant but modest declines from baseline in HbA1c at the end of treatment relative to placebo (least squares means ranging from −0.1% to −0.4%). At the end of treatment, least squares mean changes from baseline in FPG were statistically significant for all danuglipron groups in Cohorts 1 and 2 (ranging from −6.7 to −9.9 mg/dL) versus placebo, but no significant changes were observed in Cohort 3.

3.6 | Safety and tolerability

Of 626 participants in the safety analysis set, 85.6% ($n = 536$) reported ≥1 all-causality TEAE, including 70.0% ($n = 63$) of those assigned to placebo and 88.2% ($n = 473$) of those taking danuglipron (Table 2). Total numbers of TEAEs reported were 194 with placebo (90 evaluable participants) and 1817 with danuglipron (536 evaluable

TABLE 1 Demographics and baseline characteristics.

Dose escalation interval Treatment duration	Cohorts 1 and 2 placebo 1 or 2 weeks 26 weeks	Cohort 3 placebo 4 weeks 32 weeks	Cohorts 1 and 2 danuglipron (mg BID) 40 1 week 26 weeks	 80 1 week 26 weeks	 120 1 week 26 weeks	 120 2 weeks 26 weeks	 160 1 week 26 weeks	 160 2 weeks 26 weeks	 200 1 week 26 weeks	 200 2 weeks 26 weeks	Cohort 3 danuglipron (mg BID) 80 4 weeks 32 weeks	 140 4 weeks 32 weeks	 200 4 weeks 32 weeks	Total
n	71	19	62	63	64	38	63	37	63	36	37	37	36	626
Age, year, median (range)	49 (23–71)	48 (22–68)	47 (26–73)	47 (18–74)	52 (21–70)	50 (20–74)	48 (19–71)	45 (20–63)	48 (21–72)	52 (26–74)	49 (26–66)	51 (23–64)	48 (25–72)	49 (18–74)
Female, *n* (%)	45 (63)	12 (63)	40 (65)	41 (65)	42 (66)	22 (58)	41 (65)	22 (59)	41 (65)	23 (64)	23 (62)	23 (62)	22 (61)	397 (63)
Race, *n* (%)														
White	55 (77)	16 (84)	48 (77)	42 (67)	45 (70)	31 (82)	42 (67)	30 (81)	45 (71)	31 (86)	29 (78)	31 (84)	28 (78)	473 (76)
Black or African American	4 (6)	3 (16)	4 (6)	10 (16)	11 (17)	4 (11)	8 (13)	5 (14)	5 (8)	3 (8)	8 (22)	6 (16)	5 (14)	76 (12)
Asian	11 (15)	0	8 (13)	10 (16)	8 (13)	3 (8)	10 (16)	2 (5)	13 (21)	2 (6)	0	0	0	67 (11)
Other/Not reported	1 (1)	0	2 (3)	1 (2)	0	0	3 (5)	0	0	0	0	0	3 (8)	10 (2)
Ethnicity, *n* (%)														
Hispanic or Latino	6 (8)	0	7 (11)	8 (13)	7 (11)	3 (8)	2 (3)	4 (11)	2 (3)	5 (14)	2 (5)	3 (8)	2 (6)	51 (8)
Not Hispanic or Latino	65 (92)	19 (100)	55 (89)	54 (86)	56 (88)	34 (89)	61 (97)	33 (89)	60 (95)	30 (83)	34 (92)	34 (92)	34 (94)	569 (91)
Not reported	0	0	0	1 (2)	1 (2)	1 (3)	0	0	1 (2)	1 (3)	1 (3)	0	0	6 (1)
Weight, kg, mean (SD)	109.1 (20.8)	119.2 (29.8)	109.6 (24.0)	107.6 (22.2)	103.8 (16.4)	113.2 (22.9)	106.0 (20.1)	113.4 (26.8)	106.9 (18.8)	114.6 (28.5)	112.5 (19.5)	115.1 (28.3)	117.6 (20.2)	110.1 (22.5)
BMI, kg/m^2, mean (SD)	38.7 (5.7)	40.9 (7.8)	38.7 (7.0)	38.8 (5.9)	37.5 (5.1)	39.4 (6.5)	38.4 (5.8)	38.6 (8.1)	38.2 (6.4)	40.1 (7.0)	39.2 (4.7)	39.9 (9.3)	40.5 (6.4)	38.9 (6.5)
Waist circumference, cm, mean (SD)	116.1 (13.4)	122.1 (16.9)	114.4 (15.7)	115.9 (13.3)	112.3 (12.5)	120.3 (13.8)	114.7 (13.3)	116.7 (16.0)	116.1 (14.5)	119.0 (17.9)	121.9 (15.2)	122.2 (20.6)	124.3 (16.3)	117.2 (15.2)
HbA_{1c}, %, mean (SD)	5.5 (0.4)	5.5 (0.3)	5.5 (0.3)	5.5 (0.4)	5.5 (0.4)	5.5 (0.3)	5.5 (0.4)	5.4 (0.4)	5.5 (0.5)	5.6 (0.4)	5.5 (0.4)	5.4 (0.4)	5.4 (0.4)	5.5 (0.4)
Fasting glucose, mg/dL, mean (SD)	99.1 (10.6)	94.5 (9.9)	98.8 (10.4)	97.8 (10.0)	97.6 (8.4)	100.5 (10.5)	97.2 (10.1)	98.8 (11.6)	98.4 (12.2)	100.6 (9.3)	98.8 (16.0)	95.3 (8.5)	98.8 (9.9)	98.3 (10.6)
Systolic BP, mmHg, mean (SD)	125.5 (11.9)	126.1 (11.8)	126.3 (10.9)	125.2 (10.8)	126.5 (14.7)	126.5 (10.3)	124.0 (12.8)	123.5 (12.2)	126.9 (10.8)	126.4 (10.4)	125.6 (12.7)	128.6 (12.4)	127.7 (12.9)	126.0 (11.9)
Diastolic BP, mmHg, mean (SD)	78.8 (9.1)	81.4 (7.0)	79.0 (9.0)	78.1 (7.3)	79.1 (8.5)	80.6 (7.2)	78.0 (8.4)	80.4 (6.7)	79.0 (7.6)	79.6 (7.9)	81.5 (6.9)	81.2 (7.1)	80.4 (7.5)	79.4 (7.9)

Note: Demographics and BMI collected at screening; all other characteristics were collected at baseline.
Abbreviations: BID, twice daily; BMI, body mass index; BP, blood pressure; HbA_{1c}, glycated haemoglobin A_{1c}; SD, standard deviation.

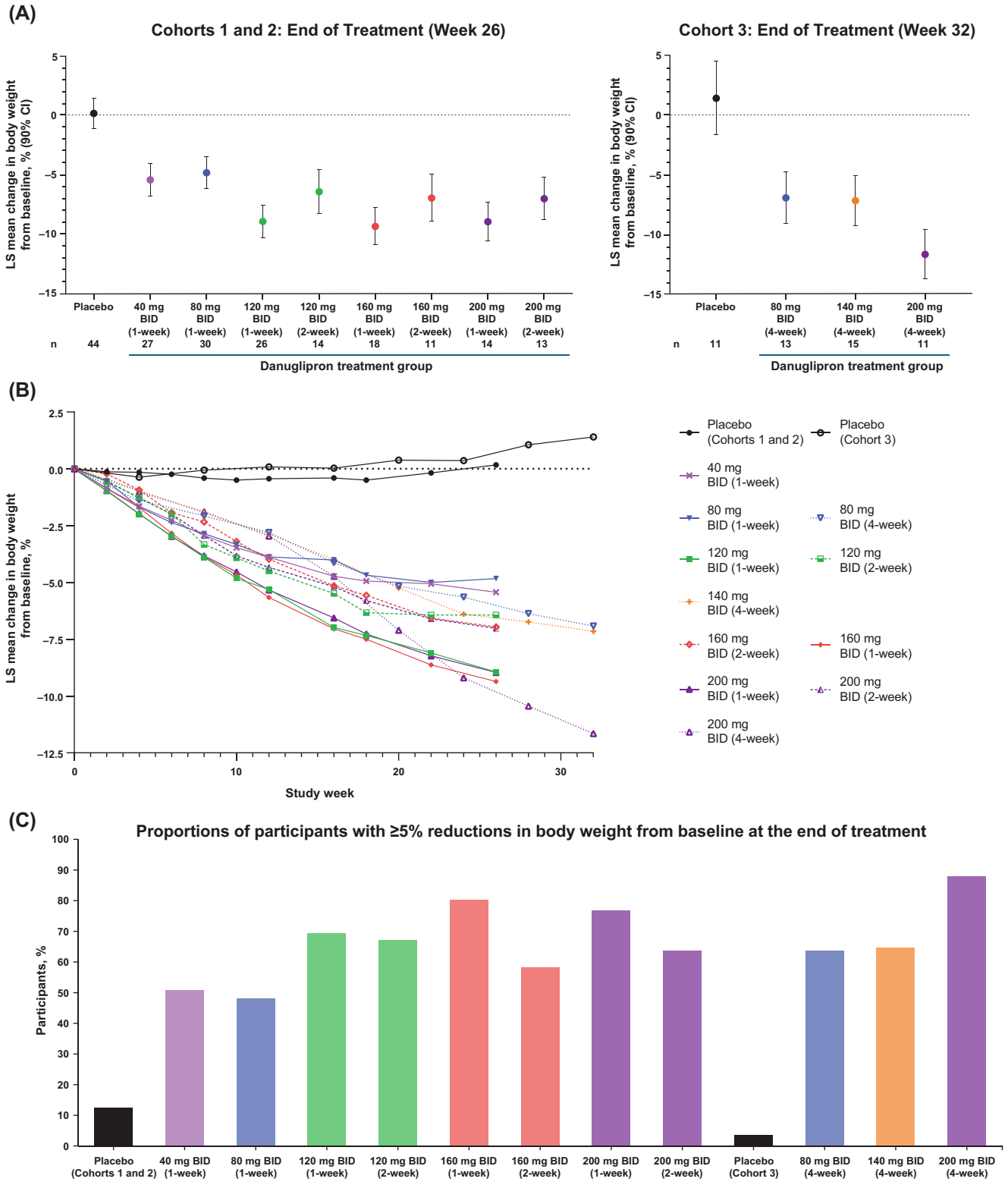

FIGURE 3 Changes in body weight for danuglipron treatment groups and placebo. (A) Least squares mean percentage changes from baseline at the end of treatment. (B) Least squares mean percentage changes over the duration of treatment.† (C) Proportions of participants with ≥5% reductions in body weight from baseline at the end of treatment. End of treatment was Week 26 for Cohorts 1 and 2 and Week 32 for Cohort 3, and measurements collected after discontinuation of study treatment were censored, representing an "on-treatment" estimand approach for all 3 panels. A mixed model for repeated measures (MMRM) approach was used for Panels A and B, and Panel C incorporated multiple imputation. †Separate plots showing error bars (90% CIs) are presented for the individual dose groups in Figure S1. BID, twice daily; CI, confidence interval; LS, least squares.

TABLE 2 Summary of treatment-emergent adverse events.

Dose escalation interval Treatment duration	Cohorts 1 and 2 placebo 1 or 2 weeks 26 weeks	Cohort 3 placebo 4 weeks 32 weeks	Cohorts 1 and 2 danuglipron (mg BID) 40 1 week 26 weeks	 80 1 week 26 weeks	 120 1 week 26 weeks	 120 2 weeks 26 weeks	 160 1 week 26 weeks	 160 2 weeks 26 weeks	 200 1 week 26 weeks	 200 2 weeks 26 weeks	Cohort 3 danuglipron (mg BID) 80 4 weeks 32 weeks	 140 4 weeks 32 weeks	 200 4 weeks 32 weeks	Total
n	**71**	**19**	**62**	**63**	**64**	**38**	**63**	**37**	**63**	**36**	**37**	**37**	**36**	**626**
All causality														
AEs, *n*	148	46	183	237	212	137	214	100	229	114	108	148	135	2011
Participants with TEAEs, *n* (%)														
Any TEAE	50 (70)	13 (68)	52 (84)	59 (94)	54 (84)	32 (84)	59 (94)	30 (81)	59 (94)	30 (83)	30 (81)	34 (92)	34 (94)	536 (86)
Serious TEAEs	1 (1)	0	2 (3)	1 (2)	0	1 (3)	1 (2)	0	5 (8)	1 (3)	2 (5)	2 (5)	3 (8)	19 (3)
Severe TEAEs	1 (1)	0	4 (6)	5 (8)	3 (5)	2 (5)	4 (6)	0	6 (10)	0	4 (11)	2 (5)	3 (8)	34 (5)
Temporary dose reduction or interruption due to TEAEs	9 (13)	3 (16)	10 (16)	17 (27)	16 (25)	9 (24)	16 (25)	13 (35)	20 (32)	11 (31)	10 (27)	11 (30)	10 (28)	155 (25)
Discontinuation of study treatment due to TEAEs	4 (6)	0	20 (32)	23 (37)	25 (39)	15 (39)	38 (60)	15 (41)	42 (67)	16 (44)	9 (24)	16 (43)	18 (50)	241 (38)
Gastrointestinal TEAEs	21 (30)	6 (32)	40 (65)	49 (78)	45 (70)	31 (82)	54 (86)	28 (76)	56 (89)	25 (69)	24 (65)	31 (84)	32 (89)	442 (71)
Participants with TEAEs (≥10% and ≥5 participants in any group), *n* (%)														
Nausea	11 (15)	2 (11)	28 (45)	39 (62)	41 (64)	22 (58)	36 (57)	25 (68)	34 (54)	18 (50)	14 (38)	27 (73)	25 (69)	322 (51)
Vomiting	2 (3)	1 (5)	10 (16)	24 (38)	26 (41)	16 (42)	27 (43)	11 (30)	29 (46)	16 (44)	3 (8)	14 (38)	17 (47)	196 (31)
Diarrhoea	7 (10)	1 (5)	5 (8)	17 (27)	12 (19)	9 (24)	13 (21)	3 (8)	11 (17)	6 (17)	8 (22)	8 (22)	9 (25)	109 (17)
Headache	8 (11)	3 (16)	6 (10)	11 (17)	11 (17)	3 (8)	11 (17)	6 (16)	7 (11)	6 (17)	5 (14)	3 (8)	4 (11)	84 (13)
Constipation	3 (4)	2 (11)	8 (13)	10 (16)	7 (11)	5 (13)	12 (19)	4 (11)	9 (14)	6 (17)	7 (19)	2 (5)	5 (14)	80 (13)
Dyspepsia	1 (1)	1 (5)	6 (10)	11 (17)	5 (8)	5 (13)	13 (21)	2 (5)	13 (21)	4 (11)	5 (14)	3 (8)	7 (19)	76 (12)
Gastroesophageal reflux disease	0	1 (5)	7 (11)	8 (13)	8 (13)	10 (26)	3 (5)	4 (11)	10 (16)	6 (17)	2 (5)	2 (5)	8 (22)	69 (11)
Fatigue	5 (7)	1 (5)	3 (5)	4 (6)	7 (11)	0	6 (10)	5 (14)	7 (11)	2 (6)	5 (14)	1 (3)	1 (3)	47 (8)
Urinary tract infection	3 (4)	0	4 (6)	9 (14)	4 (6)	1 (3)	3 (5)	0	4 (6)	2 (6)	4 (11)	3 (8)	5 (14)	42 (7)
Abdominal distension	1 (1)	1 (5)	3 (5)	3 (5)	3 (5)	5 (13)	2 (3)	3 (8)	2 (3)	0	2 (5)	1 (3)	1 (3)	27 (4)
Treatment related														
AEs, *n*	35	8	82	151	141	84	149	69	144	62	54	78	81	1138
Participants with TEAEs, *n* (%)														
Any TEAE	20 (28)	4 (21)	36 (58)	50 (79)	48 (75)	30 (79)	55 (87)	28 (76)	55 (87)	26 (72)	23 (62)	30 (81)	30 (83)	435 (69)
Serious TEAEs	0	0	0	0	0	0	0	0	0	0	0	0	1 (3)	1 (0.2)
Severe TEAEs	0	0	3 (5)	4 (6)	2 (3)	1 (3)	3 (5)	0	2 (3)	0	2 (5)	0	2 (6)	19 (3)
Temporary dose reduction or interruption due to TEAEs	0	1 (5)	8 (13)	16 (25)	13 (20)	6 (16)	12 (19)	13 (35)	18 (29)	9 (25)	7 (19)	8 (22)	5 (14)	116 (19)

TABLE 2 (Continued)

	Cohorts 1 and 2 placebo	Cohort 3 placebo	Cohorts 1 and 2 danuglipron (mg BID)								Cohort 3 danuglipron (mg BID)			Total
Dose escalation interval	1 or 2 weeks	4 weeks	40	80	120	120	160	160	200	200	80	140	200	
Treatment duration	26 weeks	32 weeks	1 week 26 weeks	1 week 26 weeks	1 week 26 weeks	2 weeks 26 weeks	1 week 26 weeks	2 weeks 26 weeks	1 week 26 weeks	2 weeks 26 weeks	4 weeks 32 weeks	4 weeks 32 weeks	4 weeks 32 weeks	
n	71	19	62	63	64	38	63	37	63	36	37	37	36	626
Discontinuation of study treatment due to TEAEs	1 (1)	0	15 (24)	20 (32)	22 (34)	13 (34)	34 (54)	15 (41)	40 (63)	13 (36)	7 (19)	14 (38)	14 (39)	208 (33)
Gastrointestinal TEAEs	16 (23)	3 (16)	34 (55)	48 (76)	44 (69)	30 (79)	51 (81)	28 (76)	54 (86)	23 (64)	22 (59)	28 (76)	29 (81)	410 (65)

Abbreviations: AE, adverse event; BID, twice daily; TEAE, treatment-emergent AE.

participants). Of all reported TEAEs, 56.6% were judged to be related to study treatment.

Most all-causality TEAEs were mild in severity (63.1%), 35.1% were moderate, and 1.8% severe. SAEs were reported in 19 (3.0%) participants (Table 2). One participant in the danuglipron 200 mg BID (4-week dose escalation) group had SAEs of nausea and bilious vomiting that were considered related to study treatment; no other SAEs were reported as treatment related. No deaths were reported during the study.

Across all three study cohorts, TEAEs in the gastrointestinal disorders SOC were reported in 30.0% ($n = 27$) of participants on placebo and in 77.4% ($n = 415$) of participants in the danuglipron treatment groups. The most frequently reported TEAEs were nausea (51.4% [$n = 322$]) and vomiting (31.3% [$n = 196$]). Proportions of participants reporting nausea and vomiting were higher across danuglipron groups than placebo groups (Table 2). During danuglipron dose escalation, first instances of nausea and vomiting generally occurred earlier in treatment groups with 1-week escalation intervals versus those with 2- or 4-week intervals at corresponding target doses (Figure S3). Proportions of participants with first occurrences of nausea or vomiting at dose steps up to and including 80 mg BID were generally below 10% each week, and few participants per week (generally <5%) reported first events of nausea and vomiting after reaching target doses of 40 mg or 80 mg BID.

Overall, 38.5% ($n = 241$) of participants discontinued study treatment due to all-causality TEAEs, and 33.2% ($n = 208$) discontinued due to treatment-related TEAEs (Table 2). Across danuglipron groups, discontinuations due to AEs were highest with the 200 mg BID (1-week dose escalation) group and lowest with the 80 mg BID (4-week dose escalation). Four (4.4%) participants on placebo discontinued due to AEs. Preferred terms reported as the reason for discontinuation in ≥2% of participants were nausea, vomiting, dyspepsia, and diarrhoea. Nausea and vomiting, respectively, were reported as reasons for discontinuation in 21.1% ($n = 113$) and 13.1% ($n = 70$) of participants on danuglipron, compared with 1.1% ($n = 1$) and 0% on placebo (Table S2).

There were no dose-related increases in the frequency of vital signs or ECG values meeting pre-specified categorical criteria, and no pulse rate value exceeded the pre-specified threshold of 120 beats per minute (bpm) in any treatment group. Isolated numerical differences in ECG parameter values outside of reference ranges were observed; however, no dose-related adverse trends across treatment groups were apparent. No clear dose-related differences from placebo were observed in pulse rate at the end of treatment with least squares mean changes from baseline ranging from −0.2 to 3.4 bpm (at 0 h) and 5.2–13.2 bpm (at 2 h) in danuglipron groups, and 0.0–3.0 bpm (at 0 h) and 4.8–11.8 bpm (at 2 h) in placebo groups.

No dose-related trends in laboratory test abnormalities, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), amylase, or lipase, were observed. No participants experienced ALT values >5 times the upper limit of normal (ULN); one participant in the placebo group had AST levels >5 times the ULN (Table S3). There

were no dose-related trends in the frequency of TEAEs of hypoglycaemia, and no cases of severe hypoglycaemia were reported.

No participants were withdrawn from study treatment due to concerns from SIB or depression assessments. Summary data from SIB and depression questionnaires did not indicate any imbalance in responses or trends relating to SIB or depression across treatment groups.

4 | DISCUSSION

In this randomized, double-blind, placebo-controlled Phase 2b study of danuglipron in adult patients with obesity and without diabetes, the primary efficacy endpoint was met, with all danuglipron treatment groups demonstrating statistically significant reductions from baseline body weight ranging from −5.0% to −12.9% with 26 or 32 weeks of dosing, relative to placebo. As these are generally consistent with the magnitude of reductions reported as being clinically meaningful for other GLP1 RAs, and did not appear to plateau over the treatment period, body weight reductions achieved with longer-term dosing of danuglipron may be expected to result in clinical benefits.[2,3,10] Secondary efficacy assessments also indicated favourable outcomes for danuglipron over placebo. Statistically significantly greater proportions of participants achieving ≥5% reductions in body weight were observed in all danuglipron groups versus placebo, and participants receiving danuglipron also demonstrated statistically significantly greater declines in waist circumference from baseline relative to placebo.

Across the range of doses tested, 40–200 mg BID, danuglipron treatment was generally safe, and no unexpected signals were identified. Most TEAEs were mild in intensity; the most common events were gastrointestinal, with nausea and vomiting being the most frequently reported TEAEs in participants randomized to danuglipron and the TEAEs most frequently reported as reasons for discontinuation. The types of TEAEs reported (preferred terms and SOCs) were generally consistent with those previously reported for danuglipron[5,7,8] and other GLP-1 RAs,[4,11] including in Phase 2 and 3 studies of other small- and large-molecule GLP-1 RAs in adults with obesity or overweight.[12–15] Differences in rates of TEAEs emerged between danuglipron treatment groups, in which lower target doses, and in some cases longer dose escalation intervals, were generally associated with lower rates of TEAEs. For example, the 80 mg BID 1-week group reported nausea and vomiting rates at 62% and 38%, respectively, whereas rates of 38% and 8% were observed with 4-week dose escalation intervals to the same target dose. Similarly, discontinuations due to all-causality TEAEs were reported with higher frequency in groups with shorter dose escalation intervals and higher target doses. In the 16-week Phase 2 trial of danuglipron in T2D, the proportion of participants discontinuing study treatment because of TEAEs was also dose-responsive across danuglipron groups (3%–34% compared with 8% for placebo).[8] In a separate 12-week Phase 2 study in participants with T2D or obesity without T2D assessing 1- and 2-week escalation steps to higher target doses of danuglipron, discontinuation from treatment due to TEAEs occurred in 18%–38% (danuglipron) compared with 6% (placebo) in participants with T2D and 55% (danuglipron) compared with 0% (placebo) in the obesity cohort, which received only the highest target dose of 200 mg BID (or placebo) with 1-week escalation steps.[7] In danuglipron groups, discontinuations from study treatment were most commonly due to gastrointestinal TEAEs. In the current Phase 2 study in obesity, for Cohorts 1 and 2 with more rapid dose escalation, discontinuations due to gastrointestinal AEs occurred earlier compared with danuglipron groups with 4-week dose escalation intervals in Cohort 3, where such discontinuations due to gastrointestinal AEs were less than 10% through to Week 12 for all groups (data not presented). Gastrointestinal AEs generally improved over time in most treatment groups. Otherwise, there were no observed imbalances across danuglipron and placebo arms in the rates of abnormal safety measurements (including vital signs, ECG values, laboratory tests, and SIB and depression assessments) or rates of AEs, aside from those anticipated with this mechanism.

When this study was initiated, participants in Cohorts 1 and 2 were randomized to groups with 1- and 2-week dose escalation intervals similar to those being assessed in the Phase 2 trials of danuglipron in T2D being conducted at the same time.[7,8] These administration schedules were selected as, given the half-life of danuglipron,[6,16] exposure would be expected to reach steady-state in this timeframe. Cohort 3 was added via a protocol amendment to assess the potential impact of slower (monthly) dose escalation and the data gathered in this group, along with those available for injectable GLP-1 RAs, indicate that a more gradual dose-escalation approach may result in improved tolerability relative to more rapid dose escalation.

In all cohorts, a fixed dose escalation scheme was used with the aim of assessing safety and efficacy at a range of target doses and dose escalation steps, without the potentially confounding heterogeneity introduced by flexible dosing. Strategies that could mitigate AEs and potentially improve adherence and study retention in later stage studies (e.g. additional time at a given dose level, or reduction to a previously tolerated dose) were not permitted in this Phase 2 assessment. The rate of discontinuation due to AEs was higher than anticipated in the danuglipron groups, particularly given that most AEs were reported as being of mild intensity. This was most notable in participants randomized to the once-weekly dose escalation schedule. Participants in the placebo groups also had higher than expected discontinuation rates which could suggest that, across treatment groups, other factors in addition to the mild AEs reported may have contributed to the decision to discontinue treatment.

The proportion of participants in the current study who discontinued treatment for any reason was 61% overall, including placebo (39%) and danuglipron (64%) groups. The discontinuation rate observed in the placebo groups was higher than generally reported in other Phase 2 trials of similar duration (ranging from 8%–29%).[12,17–19] The proportion of discontinuations from study treatment for reasons other than AEs was also high (22% overall) and did not appear to be meaningfully different between placebo (Cohorts 1 and 2: 32%; Cohort 3: 42%) and danuglipron (11%–41%) treatment groups.

High rates of discontinuation have been observed in studies in participants with obesity, including in the Phase 3b Light study, which reported 1-year retention rates of 26.3% and 37.5% in placebo and naltrexone-bupropion arms, respectively.[20] It has been reported that overall rates of discontinuation from treatment with GLP-1 RAs may be higher in patients with obesity than in those with T2D.[21] In some cases, higher doses of GLP-1 RAs in studies of patients with obesity, relative to those in patients with T2D, may contribute to an increased risk of AEs and subsequently higher discontinuation rates.[13,22] For approved GLP-1 RAs such as semaglutide, rates of discontinuations due to AEs, particularly gastrointestinal AEs, were higher in Phase 2 studies than in Phase 3 studies, for which target doses and escalation schemes were selected based on Phase 2 outcomes.[23,24] It could be hypothesized that incorporating some flexibility in dose escalation may have given the opportunity for gastrointestinal AEs to improve or resolve, such that the rate of retention would have been improved.

Specific challenges may have contributed to discontinuation rates in the current study. The therapeutic landscape for obesity has been evolving rapidly since study initiation in January 2021, for example, with the FDA approval of semaglutide for chronic weight management in the United States in June 2021.[3] The increasing availability of approved treatment options may influence participants' willingness to remain in a research study, and their expectations on rate and extent of weight loss. This may impact retention, particularly in placebo arms, if participants perceive little therapeutic benefit (although less than 25% of discontinuations from placebo groups in this study were explicitly reported as being due to lack of efficacy). Additionally, permitting flexibility in dose escalation, as seen in other comparable studies in this population, may improve adherence and retention.

Potential limitations of this study include the high rates of discontinuations reported across treatment groups, including among participants receiving placebo. This resulted in missing data at the later time points in which the modelling assumption of "missing at random" may not be entirely valid; however, observed and modelled mean results were similar (Table S1). Since Cohorts 2 and 3 were added to the study based on protocol amendments, treatment periods occurred at different times for each cohort; in addition, Cohort 3 used a longer treatment duration than Cohorts 1 and 2. Lastly, there were minor variations in body weight at baseline, potentially due to differences in geographic locations where participants were recruited for each cohort. Strengths of this study, compared with previous Phase 1 and 2 studies with danuglipron, include the longer treatment period (26 or 32 weeks versus 12 or 16 weeks) and enrollment of only participants with obesity and without T2D. The range of dosage levels and escalation periods allowed for a broader comparison of efficacy, safety, and tolerability across treatment cohorts in patients with obesity.

The safety profile observed in this study was consistent with previous studies of danuglipron and with the known profiles of other GLP-1 RAs. There were no clinically significant adverse trends in safety measurements, including laboratory tests, vital signs, and ECG assessments. There were no danuglipron-treated participants with significantly elevated liver enzyme levels. The types of TEAEs reported were generally in line with expectations, and most TEAEs were mild in severity. Discontinuation rates due to AEs were higher than anticipated, indicating opportunities for improvement in tolerability profile and study retention. Overall, the outcomes of this Phase 2b study demonstrate the efficacy of danuglipron at target doses of 40–200 mg BID in participants with obesity, relative to placebo, with statistically significant and clinically meaningful reductions from baseline in body weight. After completion of this Phase 2b study, additional studies with danuglipron were conducted. In one of these subsequent studies, a single asymptomatic participant experienced potential drug-induced liver injury. While the overall frequency of liver enzyme elevations across all danuglipron studies was in line with approved agents in the class, after a review of the totality of information and recent input from regulators, Pfizer announced discontinuation of the clinical development of danuglipron.[9]

AUTHOR CONTRIBUTIONS

Clare Buckeridge: design; conduct; analysis; writing manuscript. **Sonia Cobain:** design; conduct; analysis; writing manuscript. **Harold E. Bays:** conduct/data collection; writing manuscript. **Osamu Matsuoka:** conduct/data collection; writing manuscript. **Yasushi Fukushima:** conduct/data collection; writing manuscript. **Patricia Halstead:** design; conduct; analysis; writing manuscript. **Nikolaos Tsamandouras:** design; conduct; analysis; writing manuscript. **Nicole Sherry:** analysis; writing manuscript. **Donal N. Gorman:** design; conduct; analysis; writing manuscript. **Aditi R. Saxena:** design; conduct; analysis; writing manuscript.

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PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.16534.

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 deidentified 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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