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SYNOPSIS

Study Title: A Phase 2b, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Dose-Ranging Study to Evaluate the Efficacy and Safety of PF-06882961 Administration in Adults With Obesity

Study Number: C3421019

Regulatory Agency or Public Disclosure Identifier Number:

ClinicalTrials.gov ID: NCT04707313

EudraCT ID: 2020-001312-19

Study Phase: Phase 2b

Name of Study Intervention: Danuglipron (PF-06882961)

Name of Sponsor/Company: Pfizer Inc.

CSR Version and Report Date:

Document Version	Report Date
Final CSR (primary completion date:13SEP2023) Version 1.0	01 April 2024

Number of Study Center(s) and Investigator(s):

This study was conducted at 42 sites in Canada, Japan, Taiwan and the United States with 1220 participants screened (Cohorts 1 and 2: 926 and Cohort 3: 294) and 628 participants randomized (Cohorts 1 and 2: 499 and Cohort 3: 129).

A list of study centers and investigators involved in this study is provided in Appendix 16.1.4.1.

Publications: None

Study Period:

Study Initiation Date: 29 January 2021

Primary Completion Date: 13 September 2023

Study Completion Date: 11 October 2023

This study was neither discontinued nor interrupted.

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Rationale:

Glucagon-like peptide-1 (GLP-1) is a neuroendocrine hormone that is predominantly released from the small intestine in response to food intake. GLP-1 activation of the glucagon-like peptide-1 receptor (GLP-1R) stimulates insulin release, inhibits glucagon secretion in a glucose-dependent manner, and delays gastric emptying. In addition, GLP-1 has been shown to increase satiety and suppress food intake. Danuglipron (PF-06882961) is an orally administered, small molecule GLP-1R agonist that is currently being investigated as an adjunct to diet and exercise for chronic weight management in adults who are overweight with co-morbidities or who have obesity, and as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).

This study assessed the efficacy, safety, tolerability and pharmacokinetics (PK) of danuglipron in adults with obesity.

Objectives, Endpoints, and Statistical Methods:

The study objectives, endpoints and estimands are listed in Table S1.

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Table S1. Study Objectives, Estimands and Endpoints

Objective	Estimands	Endpoints
Primary		
• To compare the effect of multiple dose levels of danuglipron versus placebo on body weight in participants with obesity	• Estimand 1: This estimand is intended to provide a population level estimate of the mean treatment effect (danuglipron versus placebo) on a continuous endpoint in all evaluable participants while on treatment.	• Percent change from baseline (CFB) in body weight at end of treatment (EoT).[a]
Secondary		
• To characterize the safety and tolerability of multiple dose levels of danuglipron administered to participants with obesity.	• There are no defined estimands for these endpoints and they will be analyzed using Pfizer data standards as applicable.	• Incidence of treatment emergent adverse events (TEAEs) (adverse events [AEs] and serious adverse events [SAEs]), and clinically significant abnormal laboratory, vital signs and electrocardiogram (ECG) parameters. • Assessment of mental health as determined by Columbia-Suicide Severity Rating Scale (C-SSRS) and Patient Health Questionnaire-9 (PHQ-9).
• To compare the effect of multiple dose levels of danuglipron versus placebo on additional parameters of body weight in participants with obesity.	• Estimand 2: This estimand is intended to provide a population level estimate of the odds ratio treatment effect (danuglipron versus placebo) on a binary endpoint in all evaluable participants while on treatment.	• Response as defined by a body weight loss of ≥5% from baseline at EoT.[a]
	• Estimand 1 as above.	• **Cohorts 1 and 2**: Percent CFB in body weight at Weeks 2, 4, 6, 8, 10, 12, 16, 18 and 22. • **Cohort 3**: Percent CFB in body weight at Weeks 4, 8, 12, 16, 20, 24 and 28.
	• Estimand 3: This estimand is intended to provide a population level estimate of the mean treatment effect (danuglipron versus placebo) on a continuous endpoint in all evaluable participants while on treatment.	• Absolute CFB in waist circumference at EoT.[a]
	• Estimand 4: This estimand is similar to 3 above.	• Absolute CFB in waist-to-hip ratio at EoT.[a]
• To compare the effect of multiple dose levels of danuglipron versus	• Estimand 5: This estimand is similar to 3 above.	• **Cohorts 1 and 2**: Absolute CFB in hemoglobin A1c (HbA1c) at Weeks 16 and 26. • **Cohort 3**: Absolute CFB in HbA1c at Weeks 16, 24 and 32.

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Table S1. Study Objectives, Estimands and Endpoints

Objective	Estimands	Endpoints
placebo on glycemic parameters in participants with obesity.	• Estimand 6: This estimand is similar to 3 above.	• Absolute CFB in fasting plasma glucose (FPG) at each planned in-clinic study visit up through the EoT visit.[b]

Note: For all endpoints, baseline is defined as the result closest prior to dosing at V3 (Day 1).
a. End of Treatment defined as Week 26 for Cohorts 1 and 2, and as Week 32 for Cohort 3.
b. For Cohorts 1 and 2, this includes Weeks 2, 4, 6, 8, 10, 12, 16, 18, 22 and 26; for Cohort 3, this includes Weeks 4, 8, 12, 16, 20, 24, 28 and 32.

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Statistical methods used in this study are as follows:

The primary estimand (Estimand 1) was the population average treatment effect on the percent CFB in body weight at EoT of danuglipron compared to placebo in all evaluable participants while on treatment.

For Cohorts 1 and 2, EoT was defined as Week 26. For Cohort 3, EoT was defined as Week 32. Measurements after discontinuation of study intervention were censored and treated as missing data.

A secondary estimand was the population odds ratio of the treatment effect of achieving a body weight loss ≥5% from baseline at EoT of danuglipron compared to placebo in all evaluable participants while on treatment. All other key secondary continuous clinical endpoints were analyzed using a similar estimand to the primary estimand described above.

The primary analysis of the primary endpoint was conducted using a mixed model repeated measures (MMRM) analysis of the CFB in body weight through EoT, and Cohorts 1 and 2 were analyzed separately to Cohort 3. MMRM models were fitted to the CFB of $\log_e$-transformed values. The model for Cohorts 1 and 2 included Weeks 2, 4, 6, 8, 10, 12, 16, 18, 22 and 26. The model for Cohort 3 included Weeks 4, 8, 12, 16, 20, 24, 28 and 32.

The primary analysis included all participants randomly assigned to study intervention and who took at least 1 dose of randomized study intervention. The MMRM models included treatment, time, strata (females versus males) and treatment-by-time interaction as fixed effects, baseline as a covariate and the baseline-by-time interaction with time fitted as a repeated effect and participant as a random effect. Baseline body weight was included on the $\log_e$ scale. An unstructured correlation matrix was used, and the Kenward-Roger approximation was used for estimating degrees of freedom for the model parameters. Missing values was imputed as part of the MMRM model assumptions and no adjustments were made for multiplicity. The modelled mean $\log_e$-differences and 90% CIs for the $\log_e$-differences at EoT were extracted from the model and exponentiated to provide estimates of the relative difference in each danuglipron treatment arm reported separately, compared to placebo.

AEs (Tier 1, 2 and 3 AEs) were summarized by treatment group and overall and in accordance with sponsor reporting standards using the safety analysis set.

Methodology:

This was a Phase 2b, multicenter, randomized, double-blind, placebo controlled, parallel group, study to assess the efficacy, safety, tolerability and PK of twice daily oral administration of danuglipron in adult participants with obesity. There were 3 Cohorts included in the study: Cohort 1 under the original protocol, Cohort 2 added under Amendment 1, and Cohort 3 added under Amendment 2. The 3 Cohorts were enrolled sequentially.

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For all cohorts, following the initial screening period to confirm eligibility (up to 4 weeks), screening continued with a 2-week placebo run-in period which was single-blinded (participant). Eligible participants who maintained acceptable compliance during the 2-week placebo-run in-period were randomized on Day 1 to double-blinded study intervention. The dose of danuglipron was titrated according to a fixed titration scheme (ie, no down titration was permitted per protocol) in 1-, 2- or 4-week steps to a target dose, followed by a stable dosing period. The double-blind treatment phase was followed by an approximate 4-week follow-up period.

Cohorts 1 and 2 (dosing duration 26 weeks)

Participants were randomized into 1 of 9 study arms:

- placebo
- 5 danuglipron arms with target doses of 40, 80, 120, 160 and 200 mg twice daily (BID) and 1-week titration steps
- 3 danuglipron arms with target doses of 120, 160 and 200 mg BID and 2-week titration steps.

Cohort 3 (dosing duration 32 weeks)

Participants were randomized to 1 of 4 additional study arms:

- placebo
- 3 danuglipron arms with target doses of 80, 140 and 200 mg BID and 4-week titration steps.

Number of Participants (planned and analyzed):

Cohorts 1 and 2

Combining Cohorts 1 and 2, the planned number of participants to be randomized was 469 (67 in the placebo, 60 in each of the 5 danuglipron arms with 1-week titration steps and 34 in each of the 3 danuglipron arms with 2-week titration steps). A total of 499 participants were randomized to receive the study intervention (danuglipron or placebo). Two of the 499 randomized participants did not receive either placebo or danuglipron as they discontinued the study prior to the first dose. All 497 participants who received at least 1 dose of danuglipron or placebo in Cohorts 1 and 2 were included in the Safety Analysis Set and Estimand Set 1 (efficacy analyses for primary endpoint were based on Estimand Set 1).

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Cohort 3

The planned number of participants to be randomized was 112 (16 in the placebo and 32 in each of 3 danuglipron arms with 4-week titration steps). A total of 129 participants were randomized to receive the study intervention and all were treated. All 129 participants who received at least 1 dose of danuglipron or placebo in Cohort 3 were included in the Safety Analysis Set and Estimand Set 1 (efficacy analyses for primary endpoint were based on Estimand Set 1).

Diagnosis and Main Criteria for Inclusion and Exclusion:

Enrolled in this study were male or female participants between the ages of 18 and 75 years with obesity (body mass index [BMI] ≥30.0 kg/m^2), without diabetes and stable body weight (<5 kg change for 90 days) before Screening.

Study Interventions, Dose, Mode of Administration, and Batch Number(s):

For the purposes of this synopsis, study intervention refers to danuglipron and matching placebo. Blinded study intervention was provided as tablets for oral administration, with the placebo run-in being single blinded (participant only) and the randomized treatment period being double-blinded. Study intervention was provided in blister packs in Cohorts 1 and 2 and in bottles in Cohort 3. Participants in Cohorts 1 and 2 were instructed to take 4 tablets of study intervention in the morning with food and 4 tablets of study intervention in the evening with food, for a total of 8 tablets daily. Participants in Cohort 3 were instructed to take 2 tablets of study intervention in the morning with food and 2 tablets of study intervention in the evening with food, for a total of 4 tablets daily. The morning and evening doses were to be taken approximately 10-12 hours apart and at approximately the same time each day.

Information for study intervention administered is provided in Table S2.

Table S2. Study Intervention(s) Administered

Investigational Product Description	Vendor Lot No.	Pfizer Lot No.	Strength / Potency	Dosage Form
PF-06882961-82 10 mg Oval White to Off-White Tablet	19-DP-00037	19-002058	10 mg	Tablet
PF-06882961-82 10 mg Oval White to Off-White Tablet	19-DP-00079	19-003955	10 mg	Tablet
PF-06882961-82 10 mg Oval White to Off-White Tablet	20-DP-00124	20-000624	10 mg	Tablet
PF-06882961-82 10 mg Oval White to Off-White Tablet	20-DP-00125	20-000625	10 mg	Tablet
PF-06882961-82 10 mg Oval White to Off-White Tablet	20-DP-00126	20-000626	10 mg	Tablet
PF-06882961-82 10 mg Oval White to Off-White Tablet	20-DP-00127	20-000627	10 mg	Tablet
PF-06882961-82 10 mg Oval White to Off-White Tablet	20-004009	20-DP-00275	10 mg	Tablet

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Table S2. Study Intervention(s) Administered

Investigational Product Description	Vendor Lot No.	Pfizer Lot No.	Strength / Potency	Dosage Form
PF-06882961-82 10 mg Oval White to Off-White Tablet	N/A	22-DP-00944	10 mg	Tablet
PF-06882961-82 100 mg Oval White to Off-White Tablet	19-DP-00081	19-003957	100 mg	Tablet
PF-06882961-82 100 mg Oval White to Off-White Tablet	20-DP-00139	20-001096	100 mg	Tablet
PF-06882961-82 100 mg Oval White to Off-White Tablet	20-DP-00190	20-002208	100 mg	Tablet
PF-06882961-82 100 mg Oval White to Off-White Tablet	20-DP-00191	20-002209	100 mg	Tablet
PF-06882961-82 100 mg Oval White to Off-White Tablet	20-004044	20-DP-00287	100 mg	Tablet
PF-06882961-82 100 mg Oval White to Off-White Tablet	20-004045	20-DP-00288	100 mg	Tablet
PF-06882961-82 40 mg Oval White to Off-White Tablet	19-DP-00035	19-001766	40 mg	Tablet
PF-06882961-82 40 mg Oval White to Off-White Tablet	19-DP-00080	19-003956	40 mg	Tablet
PF-06882961-82 40 mg Oval White to Off-White Tablet	20-DP-00130	20-001097	40 mg	Tablet
PF-06882961-82 40 mg Oval White to Off-White Tablet	20-DP-00131	20-001098	40 mg	Tablet
PF-06882961-82 40 mg Oval White to Off-White Tablet	20-DP-00189	20-002207	40 mg	Tablet
PF-06882961-82 40 mg Oval White to Off-White Tablet	20-DP-00273	20-003894	40 mg	Tablet
PF-06882961-82 40 mg Oval White to Off-White Tablet	N/A	21-DP-00638	40 mg	Tablet
PF-06882961-82 40 mg Oval White to Off-White Tablet	N/A	22-DP-00945	40 mg	Tablet
Placebo Oval Tablet (2:1, MCC:Lactose)	N/A	18-003038	0 mg	Tablet
Placebo Oval Tablet (2:1, MCC:Lactose)	19-DP-00020	19-001253	0 mg	Tablet
Placebo Oval Tablet (2:1, MCC:Lactose)	B19053	19-002564	0 mg	Tablet
Placebo Oval Tablet (2:1, MCC:Lactose)	B20001	20-000160	0 mg	Tablet
Placebo Oval Tablet (2:1, MCC:Lactose)	B20050	20-001719	0 mg	Tablet

Duration of Study Intervention:

For Cohorts 1 and 2, the planned double-blind treatment phase was 26 weeks (182 days). For the 1-week titration arms in Cohort 1, up to 10 weeks of the dosing duration were used for

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titration. For the 2-week titration arms in Cohorts 1 and 2, up to 20 weeks were used for dose titration.

For Cohort 3, the planned double-blind treatment phase was 32 weeks (224 days). For Cohort 3, up to 20 weeks of the dosing duration were used for titration.

Summary of Results:

Demographic and Other Baseline Characteristics:

The demographic characteristics of all 626 participants in the safety analysis set (Cohorts 1, 2 and 3) were generally similar across treatment groups for most parameters. More than half of the participants were female (397 participants, 63.4%), with a similar proportion of male and female participants in each treatment group. Across all the treatment groups, the mean (standard deviation [SD]) age was 48.2 (12.02) years and mean (SD) BMI at Screening was 38.9 (6.47) kg/m^2. At baseline, the mean weight was higher in Cohort 3 (115.4 kg) compared to Cohorts 1 and 2 (108.5 kg).

Exposure:

For Cohorts 1 and 2, the observed median (range) duration of study intervention was 113 (1 – 204) days. Compliance was calculated from first dose until EoT or discontinuation from study intervention. The overall mean reported compliance was similar across the treatment groups with the range from 91.4% to 96.4%.

For Cohort 3, the observed median (range) duration of study intervention was 147 (1 – 231) days. The overall mean reported compliance was similar across the treatment groups with the range from 92.1% to 96.4%.

Efficacy Results:

Percent CFB in body weight:

Cohorts 1 and 2

The primary efficacy endpoint was percent CFB in body weight at EoT (Week 26) and was analyzed using Estimand Set 1. At Week 26, the least square (LS) mean and placebo-adjusted modelled mean percent CFB ranged from -4.83% to -9.36% and -5.00% to -9.52%, respectively across all danuglipron treatment groups. The modelled LS mean percent CFB for placebo was +0.17% at Week 26. All danuglipron treatment groups demonstrated statistically significant (2-sided p-value <0.1) reductions in the LS mean percent CFB in body weight at Week 26, relative to placebo.

The percent CFB in body weight over the treatment period (assessed at each planned in-clinic study visit from week 2 to 22) was a secondary efficacy endpoint and was analyzed using an MMRM model based on Estimand Set 1. In danuglipron treatment groups, weight loss was observed early with statistically significant decreases from baseline, compared to placebo,

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observed in some danuglipron treatment groups at Week 2 and all danuglipron treatment groups from Week 4 onwards. Most danuglipron arms did not appear to reach a plateau over the dosing duration. In contrast, for placebo the response was flat or with a slight increase from baseline over the dosing duration. Generally, greater weight loss over time was observed in the danuglipron arms and, generally, greater weight loss was observed at higher target doses of danuglipron relative to lower target doses.

Cohort 3

The primary efficacy endpoint was percent CFB in body weight at EoT (Week 32) and was analyzed using Estimand Set 1. At Week 32, the LS mean and placebo-adjusted modelled mean percent CFB ranged from – 6.92% to -11.65% and -8.21% to -12.87%, respectively across all danuglipron treatment groups. The modelled LS mean percent CFB for placebo was +1.40% at Week 32. All danuglipron treatment groups demonstrated statistically significant (2-sided p-value <0.1) reductions in the LS mean percent CFB in body weight at Week 32, relative to placebo.

The percent CFB in body weight over the treatment period (assessed at each planned in-clinic study visit from week 4 to 28) was a secondary efficacy endpoint and was analyzed using an MMRM model based on Estimand Set 1. In danuglipron treatment groups, weight loss was observed early with statistically significant decreases from baseline compared to placebo observed in all danuglipron treatment groups from Week 4 onwards. Most danuglipron arms did not appear to reach a plateau over the dosing duration. In contrast, for placebo the response was flat or with slight increase from baseline over the dosing duration. Generally, greater weight loss over time was observed in the danuglipron arms and, generally, greater weight loss was observed at higher target doses of danuglipron relative to lower target doses.

Response as defined by body weight loss of a ≥5% from baseline at EoT

Response as defined by body weight loss of a ≥5% from baseline at EoT was a secondary endpoint and was analyzed using Estimand Set 1.

Cohorts 1 and 2

Greater proportions of participants in the danuglipron dose groups achieved a change in body weight loss of ≥5% at 26 weeks, compared with placebo with all danuglipron groups statistically significant (2-sided p-value <0.1). The proportion of participants with a body weight loss of ≥5% (based on statistical analyses using multiple imputation) within the danuglipron groups ranged from 48.0% to 80.2% compared to 12.6% within the placebo group.

Cohort 3

Greater proportions of participants in the danuglipron dose groups achieved a change in body weight loss of ≥5% at 32 weeks, compared with placebo with all danuglipron groups

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statistically significant (2-sided p-value <0.1). The proportion of participants with a body weight loss of ≥5% (based on statistical analyses using multiple imputation) within the danuglipron groups ranged from 63.8% to 87.9% compared to 3.5% within the placebo group.

Absolute CFB in waist circumference

Cohorts 1 and 2

The Absolute CFB in waist circumference at Week 26 was a secondary endpoint and was analyzed using Estimand Set 1. At Week 26, there were statistically significant (2-sided p-value <0.1) declines in waist circumference for all danuglipron treatment groups relative to placebo. The LS mean CFB and modelled mean differences from placebo at Week 26 of danuglipron treatment ranged from -5.75 cm to -9.05 cm and -4.50 cm to -7.80 cm, respectively. The modelled CFB in the placebo group at Week 26 was -1.25 cm.

Cohort 3

Absolute CFB in waist circumference at Week 32 was a secondary endpoint and was analyzed using Estimand Set 1. At Week 32, there were statistically significant (2-sided p-value <0.1) declines in waist circumference for all danuglipron treatment groups relative to placebo. The LS mean CFB and modelled mean differences from placebo at Week 32 of danuglipron treatment ranged from - 6.27 cm to -11.43 cm and -6.46 cm to -11.62 cm, respectively. The modelled CFB in the placebo group at Week 32 was +0.19 cm. Generally, greater decreases in waist circumference were observed at higher target doses of danuglipron relative to lower target doses.

Absolute CFB in waist-to-hip ratio

Cohorts 1 and 2

Absolute CFB in waist-to-hip ratio at Week 26 was a secondary endpoint and was analyzed using Estimand Set 1. The LS mean CFB and modelled mean differences from placebo at Week 26 of danuglipron treatment ranged from -0.02 to 0.00 and -0.02 to 0.01, respectively. The modelled CFB in the placebo group at Week 26 was -0.002. At Week 26, statistically significant (2-sided p-value <0.1) differences in changes in waist-to-hip ratio was only observed in the danuglipron 40 mg BID (1-week titration) group relative to placebo.

Cohort 3

Absolute CFB in waist-to-hip ratio at Week 26 was a secondary endpoint and was analyzed using Estimand Set 1. The LS mean CFB and modelled mean differences from placebo at Week 32 of danuglipron treatment ranged from -0.01 to -0.02 and -0.02 to -0.03, respectively. The modelled CFB in the placebo group at Week 32 was +0.01. At Week 32, no

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statistically significant (2-sided p-value <0.1) differences in changes in waist-to-hip ratio was observed in any danuglipron treatment group relative to placebo.

Safety Results:

Overall, 85.6% of the 626 evaluable participants reported at least 1 all causality TEAE in the study, including 70% of participants assigned to placebo and 88% of participants assigned to danuglipron. Of the TEAEs reported during the study, 57% were judged to be related to study intervention.

The majority (63.1%) of TEAEs reported were mild in severity, with 35.1% reported as moderate and 1.8% as severe. There were 23 treatment-emergent SAEs reported in 19 participants. Of these, 1 participant in the danuglipron 200 mg BID (4-week titration) treatment group had SAEs of nausea and bilious vomiting that were reported by the investigator as related to study intervention; no other SAEs were reported as related to study intervention for this or other participants. There were no deaths reported during the study.

Across all 3 study cohorts, all-causality TEAEs in the gastrointestinal disorders System Organ Class (SOC) were reported by the highest proportion of participants (70.6% of participants in the study overall), where nausea, vomiting and diarrhoea occurred in 51.4%, 31.3% and 17.4% of participants, respectively.

Of all TEAEs reported in this study overall, 57% were reported as treatment related. The SOC with treatment-related TEAEs reported by the largest proportion of participants was Gastrointestinal disorders (65.5%); this was followed by Nervous system disorders (11.5%). Of all TEAEs reported in the Gastrointestinal disorder SOC, a majority (approximately 93%) were treatment-related.

For all 3 cohorts, the 3 TEAEs of interest were: diarrhoea, nausea and vomiting. Across all 3 study cohorts, Preferred terms (PTs) of nausea, vomiting, and diarrhoea occurred in 51.4%, 31.3% and 17.4% of participants, respectively. The rates of PTs of nausea and vomiting in the danuglipron treatment groups ranged from 37.8% to 73.0% and from 8.1% to 47.2%, respectively, compared to 10.5% to 15.5% and 2.8% to 5.3% in placebo, respectively. Among all danuglipron treatment groups, the lowest rates of nausea and of vomiting were observed in the 40 mg BID (1-week titration) and 80 mg BID (4-week titration) groups. The rates of nausea and vomiting reported in the 40 mg BID group (1-week titration) were 45.2% and 16.1%, respectively. The 80 mg BID 1-week titration treatment group reported nausea and vomiting at 61.9% and 38.1%, while rates of 37.8% and 8.1% were observed for the 80 mg BID group (4-week titration). The rates of PTs of diarrhoea in the danuglipron treatment groups ranged from 8.1% to 27.0%, compared to 8.9% in placebo. The proportion of participants reporting diarrhoea did not appear to have a clear relationship with danuglipron dose level.

Overall, there was no evidence of higher rates of hypoglycemia with increasing target dose of danuglipron and there were no events of severe hypoglycemia reported.

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The all-causality AEs most frequently reported as having led to study intervention discontinuation were in the Gastrointestinal disorders SOC (33% of participants). Nausea and vomiting were noted as the reason for discontinuation in 21% and 12% of participants, respectively within the danuglipron groups, and 0.2% and 0% of participants, respectively within the placebo groups. The discontinuation rate from study intervention for any reason was high across all treatment groups (61% overall), including placebo (39%) and danuglipron (64%) arms. The overall rate of discontinuation from study intervention due to all-causality AEs was 39%. For danuglipron treatment groups, the highest rate of discontinuation due to AE was observed at the 200 mg dose with rapid (1 week) titration steps (67%), and the lowest rate at the 80 mg dose with 4-week titration steps (24%). Discontinuation due to nausea and vomiting were generally observed more in the 1-week and 2-week titration groups compared with the 4-week titration groups. Discontinuation due to nausea and vomiting generally increased with higher target dose and was generally lower with slower titration, at the same target dose.

For all 3 cohorts, no clear clinically significant adverse dose-related trends were observed in any laboratory parameter, including gamma-glutamyl transferase (GGT), amylase, lipase, triglycerides, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), bile acid, calcitonin, thyrotropin, free thyroxine, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol (direct), total bilirubin, and glomerular filtration rate Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), and there was no clear imbalance in incidence of the laboratory abnormalities across all the treatment groups.

Across all 3 cohorts, a total of 11 participants had values of ALT and/or AST >3 × upper limit of normal (ULN). The proportion of participants experiencing ALT or AST >3 × ULN was lower in the danuglipron arms (ALT: 1.0%, AST: 0.6%) compared with placebo arms (ALT: 2.3%, AST: 2.3%), with no apparent imbalance across danuglipron dose levels. There were no ALT values exceeding 5 × ULN; 1 participant in the placebo treatment group had AST >5 × ULN (maximum reported value of 228 U/L [5.7 × ULN]). Of the 11 participants with AST/ALT >3 × ULN, 1 participant had moderate AEs of Alanine aminotransferase increased (investigator term: elevated ALT) and Aspartate aminotransferase increased (investigator term: elevated AST). Both AEs were reported as not related to the study intervention and resulted in permanent discontinuation of the study intervention.

There were no apparent dose-related increases in the frequency of vital sign or ECG values meeting pre-specified categorical criteria of potential clinical concern. While there were isolated numerical differences in ECG parameter values outside reference ranges, there were no apparent dose related, adverse trends noted across treatment groups.

Across all 3 cohorts, no participants were withdrawn from study intervention due to mental health concerns. The summary data did not suggest any imbalance in responses or notable trend (suicidal ideation or behavior) across the treatment groups.

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Pharmacodynamic Results:

Absolute CFB in HbA1c

Cohorts 1 and 2

The mean baseline HbA1c ranged from 5.4% to 5.6% across the treatment groups. All danuglipron treatment groups had a CFB decrease in HbA1c at Weeks 16 and 26 with mean CFB ranging from -0.17% to -0.28% and -0.10% to -0.31%, respectively, compared to placebo (0% for both Weeks 16 and 26). All danuglipron treatment groups demonstrated statistically significant (2-sided p-value <0.1) declines in the LS mean changes from baseline in HbA1c at Weeks 16 and 26, relative to placebo. The LS mean differences to placebo in HbA1c at Week 16 and Week 26 ranged from -0.18% to -0.29% and -0.14% to -0.32%, respectively.

Cohort 3

The mean baseline HbA1c ranged from 5.36% to 5.47% across the treatment groups. All danuglipron treatment groups had a CFB decrease in HbA1c at Weeks 16, 24 and 32 with mean CFB ranging from -0.17% to -0.27%, -0.15% to -0.32% and -0.11% to -0.43%, respectively, compared to placebo (-0.03%, 0.06% and 0.00%, respectively). All danuglipron treatment groups demonstrated statistically significant declines in the LS mean CFB in HbA1c at Weeks 16 and 32, relative to placebo, except danuglipron 80 mg BID (4-week titration) (2-sided p-value >0.1). The LS mean differences to placebo in HbA1c at Weeks 16, 24 and 32 ranged from -0.11% to -0.24%; -0.18% to -0.36%; and -0.10% to -0.40%, respectively.

Absolute CFB in FPG at each planned in-clinic study visit up to through the EoT

Cohorts 1 and 2

The mean baseline FPG ranged from 97.2 mg/dL to 100.6 mg/dL across the treatment groups. At Week 26, all danuglipron treatment groups demonstrated statistically significant (2-sided p-value <0.1) declines in the LS mean changes from baseline in FPG, relative to placebo. At Week 26, the LS mean differences to placebo in FPG ranged from -6.71 mg/dL to -9.94 mg/dL.

Cohort 3

The mean baseline FPG ranged from 94.5 mg/dL to 98.8 mg/dL across the treatment groups. There were no statistically significant (2-sided p-value >0.1) changes in the LS mean CFB in FPG for danuglipron treatment groups at Week 32, relative to placebo. At Week 32, the LS mean differences to placebo in FPG ranged from 0.08 mg/dL to 3.09 mg/dL.

CLINICAL STUDY REPORT SYNOPSIS

Conclusions:

Efficacy

- In participants with obesity, without diabetes, all danuglipron treatment groups demonstrated statistically significant reductions in percent CFB in body weight, with placebo-adjusted modelled mean changes from baseline ranging from -5.00% to -9.52% at Week 26 for Cohorts 1 and 2 (40 mg to 200 mg BID) and from -8.21% to -12.87% at Week 32 for Cohort 3 (80 to 200 mg BID).

- In participants with obesity, without diabetes, all danuglipron treatment groups demonstrated statistically significant reductions from baseline in waist circumference with placebo-adjusted modelled mean changes from baseline ranging from -4.50 cm to -7.80 cm at Week 26 for Cohorts 1 and 2 and from -6.46 cm to -11.62 cm at Week 32 for Cohort 3.

Safety

- Danuglipron was considered safe at target doses of 40 mg BID to 200 mg BID with no new safety findings observed.

- There were no apparent dose-related, adverse trends in laboratory, ECG or vital sign parameters.

    - In general, the proportion of participants with laboratory abnormalities was similar across the treatment groups, including placebo. The proportion of participants with liver function test abnormalities (ALT or AST) was lower in the danuglipron arms compared with placebo, with no apparent imbalance across danuglipron dose levels.
    - There were no apparent dose-related increases in the frequency of vital sign or ECG values meeting pre-specified categorical criteria of potential clinical concern. While declines from baseline in systolic BP were noted in most danuglipron dose groups across the dosing interval, no clear dose-related differences from placebo were observed in systolic or diastolic BP at the EoT. Modest increases from baseline in pulse rate were noted, however no clear dose-related differences from placebo were observed at the EoT, and no participant had a reported pulse rate >120 bpm.

- The majority (63.1%) of TEAEs reported were mild in severity, with 35.1% reported as moderate and 1.8% as severe. All-causality TEAEs in the Gastrointestinal disorders SOC were reported by the highest proportion of participants (70.6% of participants in the study overall), where PTs of nausea, vomiting and diarrhoea occurred in 51.4%, 31.3% and 17.4% of participants, respectively.

CLINICAL STUDY REPORT SYNOPSIS

- The discontinuation rate from study intervention for any reason was high across all treatment groups, including placebo (39%) and danuglipron (64%) arms. The overall rate of discontinuation from study intervention due to all-causality AEs was 39%. For danuglipron groups, the highest rate of discontinuation was observed at the 200 mg BID dose with rapid (1-week) titration steps (67%), and the lowest rate at the 80 mg BID dose with 4-week titration steps (24%), while the rate in the placebo group was 4%. The most common reason for discontinuation from danuglipron arms was due to GI adverse events (mainly nausea and vomiting).

PD

As anticipated for this population of participants without diabetes, the effect of danuglipron on glycemic parameters was modest.

- All danuglipron dose levels (40 mg to 200 mg BID) demonstrated statistically significant but modest declines in the LS mean CFB in HbA1c at EoT, relative to placebo.

- All danuglipron treatment groups in Cohorts 1 and 2 demonstrated statistically significant but modest declines in the LS mean changes from baseline in FPG, relative to placebo (ranging from -6.71 mg/dL to -9.94 mg/dL) at Week 26. There were no statistically significant changes in the LS mean CFB in FPG for danuglipron treatment groups in Cohort 3 at Week 32, relative to placebo.