# CLINICAL STUDY REPORT SYNOPSIS

**Sponsor:** Pfizer, Inc

**Investigational Product:** Danuglipron (PF-06882961)

**Clinical Study Report Synopsis:** Protocol C3421015

**Protocol Title:** An 8-Week Phase 1, Randomized, Double-Blind, Sponsor-Open, Placebo-Controlled, Parallel-Group Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Twice Daily PF-06882961 Administration in Japanese Adults With Type 2 Diabetes Mellitus

**Investigators:** Refer to Appendix 16.1.4.1 for a list of investigators involved in this study.

**Study Centers:** This study was conducted at 1 center in Japan. Refer to Appendix 16.1.4.1 for the details of site involved in this study.

**Publications Based on the Study:** None.

**Study Initiation Date:** 26 October 2020

**Study Completion Date:** 25 March 2021

**Report Date:** 12 November 2021

**Previous Report Dates:** Not Applicable.

**Phase of Development:** Phase 1

**Primary and Secondary Study Objectives and Endpoints:** The study objectives and endpoints are presented in Table S1.

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### Table S1. Study Objectives and Endpoints

| Types | Objectives | Endpoints |
|---|---|---|
| Primary | | |
| Safety | To evaluate the safety and tolerability of multiple, oral doses of danuglipron, administered to adult Japanese participants with T2DM | Incidence of treatment-emergent AEs (AEs and SAEs), clinical laboratory abnormalities, vital signs, and ECG parameters during the entire study |
| Secondary | | |
| PK | To characterize plasma PK of danuglipron following Day 1 and following multiple, oral doses administered to adult Japanese participants with T2DM | Danuglipron plasma PK parameters $AUC_{24}$, $C_{max}$, $T_{max}$, $t_{½}$ (as appropriate for the dosing paradigm) following Day 1, and multiple dose administration, as data permitted |

Abbreviations: AE=adverse event; $AUC_{24}$=area under the plasma concentration-time profile from time 0 to 24 hours; $C_{max}$=maximum plasma concentration observed from time 0 to 24 hours; ECG=electrocardiogram; PK=pharmacokinetic; SAE=serious adverse event; $t_{½}$=terminal half-life; T2DM=Type 2 diabetes mellitus; $T_{max}$=time for $C_{max}$.

## METHODS

**Study Design:** This was a Phase 1, randomized, double-blind (sponsor-open), placebo-controlled, 4-arm, parallel-group study of danuglipron in adult Japanese participants with Type 2 diabetes mellitus (T2DM) inadequately controlled on diet and exercise alone. The purpose of this study was to evaluate the safety, tolerability, and pharmacokinetic (PK) of multiple oral doses of danuglipron in adult Japanese participants with T2DM, who were not receiving any background anti-hyperglycemic medication.

Participants received oral doses of danuglipron or placebo in this study. Approximately 9 participants were planned to be enrolled in each arm, for a total of 36 (4 arms) participants to be randomized. The randomization ratio was 1:1:1:1 (1 of 3 active dosing regimens of danuglipron or placebo), and all 4 arms were enrolled in parallel. The study was conducted at a single clinical site in Japan.

Target dose levels, achieved after completion of titration, for the 4 arms of the study were placebo and danuglipron doses of 40 mg twice a day (BID), 80 mg BID, and 120 mg BID. Dose titration was incorporated to enhance tolerability to danuglipron. The titration was planned to start at danuglipron 10 mg BID (or matching placebo), then with increase in dose every week to reach the targeted dose level of 40 mg BID at the start of Week 3 for danuglipron 40, 80, and 120 mg BID dose groups, to reach the targeted dose level of 80 mg BID at the start of Week 5 for danuglipron 80 and 120 mg BID dose groups, and to reach the targeted dose level of 120 mg BID at the start of Week 7 for danuglipron 120 mg BID dose group. The maximum dose of danuglipron in this study did not exceed 120 mg BID.

Following the screening period to confirm eligibility (up to 4 weeks), the treatment period was for approximately 8 weeks, followed by an approximate 4-week follow-up. The total duration of participation in this study was approximately 12 weeks, after the screening period. Dosing occurred with food BID, and up to 2 weeks (for target dose level:

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40 mg BID), 4 weeks (for target dose level: 80 mg BID) or 6 weeks (for target dose level: 120 mg BID) of the 8-week dosing duration was used for dose titration to maximize tolerability of danuglipron.

**Diagnosis and Main Criteria for Inclusion:** Male and female participants of 20 to 70 years of age, inclusive, at the time of signing the informed consent document; with body mass index (BMI) of 22.5 to 45.4 kg/$m^2$ and a total body weight >50 kg (110 lb) that had been stable (<5% change) for 90 days prior to screening (Visit 1); hemoglobin A1c (HbA1c) ≥7% and ≤10.5% at screening; who were being treated with diet and exercise but were not taking antidiabetic medications for T2DM were included in the study.

Participants with evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing), had a history of myocardial infarction, unstable angina, arterial revascularization, stroke, New York Heart Association Functional Class II - IV heart failure, or transient ischemic attack within 6 months of screening, who had a diagnosis of type 1 diabetes mellitus or secondary forms of diabetes, or a history of ketoacidosis, had a personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome Type 2, or participants with suspected MTC per the investigator's judgment, or had a known intolerance or hypersensitivity to glucagon-like peptide-1 receptor (GLP-1R) agonists, fasting blood glucose >270 mg/dL (15.0 mmol/L) at screening, or fingerstick blood glucose on Day -2 of >270 mg/dL (15.0 mmol/L) were excluded from the study.

**Study Treatment:**

Danuglipron 10 mg, 40 mg, and 100 mg and matching placebo tablets were supplied centrally by the sponsor to the site as packaged blister cards.

Participants took 3 tablets of danuglipron or matching placebo in the morning at approximately 0800 hours with food and 3 tablets in the evening at approximately 1800 hours with food, approximately 10-12 hours apart and at approximately the same time each day. Participants took a total of 6 tablets of danuglipron or matching placebo daily. The treatment period was for approximately 8 weeks.

Participants swallowed the study drug whole, and did not crush, chew, break, or dissolve the study drug prior to swallowing. Downward titration or dosing was not permitted during the study; participants who could not tolerate the titration scheme and/or assigned dose were required to discontinue dosing of the study drug.

Investigational product description is provided in Table S2.

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### Table S2. Investigational Product Description

| Investigational Product Description | Vendor Lot Number | Pfizer Lot Number | Strength /Potency | Dosage Form |
|---|---|---|---|---|
| PF-06882961-82 10 mg oval white to off-white tablet | N/A | 18-003389 | 10 mg | Tablet |
| PF-06882961-82 40 mg oval white to off-white tablet | N/A | 18-003390 | 40 mg | Tablet |
| PF-06882961-82 100 mg oval white to off-white tablet | N/A | 18-003391 | 100 mg | Tablet |
| Placebo oval tablet (2:1, MCC:lactose) | B19053 | 19-002564 | 0 mg | Tablet |

Abbreviations: MCC=microcrystalline cellulose; N/A=not applicable.

**Efficacy Evaluations:** Not Applicable.

**Pharmacokinetic Evaluations:**

Blood samples of approximately 3 mL, to provide a minimum of 1 mL of plasma, were collected into appropriately labeled tubes containing dipotassium ethylenediaminetetraacetic acid for measurement of plasma concentrations of danuglipron at the following time points: Day 1 (0 hour [predose] and at 1, 2, 4, 6, 8, 10, 12, and 14 hours [postdose]), Day 2 (24 hours after AM dose on Day 1), Days 15, 29, and 43 (prior to AM dose and at 4 hours after AM dose), Day 50 (24 hours after AM dose on Day 49), Day 55 and Day 56 (0 hour [predose] and at 1, 2, 4, 6, 8, 10, 12, and 14 hours [postdose]), Day 57 (24 hours and 36 hours after AM dose on Day 56), Day 58 (48 hours after AM dose on Day 56), and at early termination visit. Samples collected for measurement of plasma concentrations of danuglipron were analyzed using a validated analytical method.

The following danuglipron PK parameters: area under the plasma concentration-time profile from time 0 to 24 hours ($AUC_{24}$), maximum plasma concentration observed from time 0 to 24 hours ($C_{max}$), time for $C_{max}$ ($T_{max}$), and terminal half-life ($t_{½}$) following Day 1, and multiple dose administration, were calculated for each participant and treatment, using non-compartmental analysis of plasma concentration-time data.

**Safety Evaluations:**

Safety assessments consisted of the collection of adverse events (AEs), serious adverse events (SAEs), clinical laboratory abnormalities, vital signs (blood pressure [BP] and pulse rate), and electrocardiogram (ECG) monitoring.

Safety was monitored at regular intervals throughout the study.

**Statistical Methods:**

Pharmacokinetic Analysis

The danuglipron PK concentration population was defined as all participants randomly assigned to the study drug who took at least 1 dose of danuglipron and in whom at least 1 plasma PK concentration value of danuglipron was reported.

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The danuglipron PK parameter analysis population was defined as all participants randomly assigned to the study drug who took at least 1 dose of danuglipron and who had at least 1 of the PK parameters of interest for danuglipron calculated.

PK samples from placebo group were not analyzed.

The PK parameters ($AUC_{24}$, $C_{max}$, $T_{max}$ and $t_{½}$) were summarized descriptively by treatment, dose and day (Day 1 and Day 56) for subjects in the PK parameter analysis set. Actual PK sampling times were used in the derivation of PK parameters.

Safety

The safety analysis set included all participants randomly assigned to study drug who took at least 1 dose of study drug. Participants were analyzed according to the product they actually received.

Safety data were summarized descriptively and reported in accordance with the sponsor reporting standards.

## RESULTS

### Subject Disposition and Demography:

Of 65 participants screened for entry into the study, 37 participants were randomized and assigned to receive the study drug. Ten participants received danuglipron 40 mg BID and 9 participants each received danuglipron 80 mg BID, danuglipron 120 mg BID, or placebo. All 37 randomized participants were included in the safety analysis set. All 28 participants treated with danuglipron (in active treatment groups) were included in the PK concentration and PK parameter analyses sets.

Of the 37 randomized participants, 8 participants discontinued the study drug and 29 participants completed the dosing regimen. The disposition events summary is presented in Table S3.

Of the 8 participants who discontinued the study drug, 6 participants (2, 3, and 1 participant in danuglipron 40, 80, and 120 mg BID groups, respectively) permanently discontinued from the study drug due to treatment-emergent adverse events (TEAEs). One participant in placebo group discontinued the study drug due to 'lack of efficacy'. One participant in danuglipron 40 mg BID group discontinued the study drug as the participant no longer met eligibility criteria.

Demographic characteristics were generally comparable across the treatment groups. The 37 treated participants consisted of 32 males (86.5%) and 5 females (13.5%). All 37 participants were Asian and Not Hispanic or Latino. The mean age of all participants was 55.8 years (range: 34 to 70 years).

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The mean weight and BMI were greater for all danuglipron dose groups compared to placebo. The mean weight for all participants was 78.6 kg (range: 58.9 to 102.6 kg), and the mean weight varied across treatment groups ranging from 73.3 kg to 81.5 kg. The mean BMI for all participants was 27.8 $kg/m^2$ (range: 22.9 to 36.8 $kg/m^2$), and the mean BMI varied across treatment groups ranging from 25.9 $kg/m^2$ to 28.6 $kg/m^2$.

The mean duration of diabetes for all participants was 5.748 years (range: 0.19 to 20.45 years). The mean duration of diabetes varied widely across treatment groups, ranging from 2.926 years to 9.107 years.

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**Table S3. Disposition Events Summary - Safety Analysis Set (Protocol C3421015)**

| Number (%) of Subjects | Placebo (N=9) n (%) | PF-06882961 40mg (N=10) n (%) | PF-06882961 80mg (N=9) n (%) | PF-06882961 120mg (N=9) n (%) |
|---|---|---|---|---|
| Disposition phase: Blinded Treatment | | | | |
| Subjects Entered: | 9 (100.0) | 10 (100.0) | 9 (100.0) | 9 (100.0) |
| Discontinued from Study | 0 | 0 | 0 | 0 |
| Reason for discontinuation | | | | |
| Adverse Event | 0 | 0 | 0 | 0 |
| Lack of Efficacy | 0 | 0 | 0 | 0 |
| No Longer Meets Eligibility Criteria | 0 | 0 | 0 | 0 |
| Discontinued from Study Intervention | 1 (11.1) | 3 (30.0) | 3 (33.3) | 1 (11.1) |
| Reason for discontinuation | | | | |
| Adverse Event | 0 | 2 (20.0) | 3 (33.3) | 1 (11.1) |
| Lack of Efficacy | 1 (11.1) | 0 | 0 | 0 |
| No Longer Meets Eligibility Criteria | 0 | 1 (10.0) | 0 | 0 |
| Completed | 8 (88.9) | 7 (70.0) | 6 (66.7) | 8 (88.9) |
| Disposition phase: Follow-Up | | | | |
| Subjects Entered: | 9 (100.0) | 10 (100.0) | 9 (100.0) | 9 (100.0) |
| Discontinued from Study | 0 | 0 | 0 | 0 |
| Reason for discontinuation | | | | |
| Adverse Event | 0 | 0 | 0 | 0 |
| Lack of Efficacy | 0 | 0 | 0 | 0 |
| No Longer Meets Eligibility Criteria | 0 | 0 | 0 | 0 |
| Completed | 9 (100.0) | 10 (100.0) | 9 (100.0) | 9 (100.0) |

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Table 14.1.1.2.2 PF-06882961 is for Pfizer internal use.

**Efficacy Results:** There were no efficacy evaluations done in this study.

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**Pharmacokinetic Results:**

Danuglipron Pharmacokinetics

Following single and multiple dosing of danuglipron in adult Japanese participants with T2DM starting at a 10 mg BID dose on Day 1 and titrating up to 40 mg, 80 mg, and 120 mg BID doses on Day 56, maximum plasma concentrations ($C_{max}$, maximum plasma concentration during the dosing interval tau1 [0 to 10 hours] [$C_{max1}$] and maximum plasma concentration during the dosing interval tau2 [10 to 24 hours] [$C_{max2}$]) were observed within a median $T_{max}$, time for $C_{max1}$ ($T_{max1}$) and time for $C_{max2}$ ($T_{max2}$) of approximately 2 hours to 6 hours post each dose administered on Day 56.

Following multiple dosing, exposure appeared to increase in a dose-proportional manner for doses titrated up to 40 mg, 80 mg, and 120 mg BID, with dose-proportional increases in geometric mean $AUC_{24,}$ area under the plasma concentration-time profile from time 0 to time tau1 (0 to 10 hours) ($AUC_{tau1}$), area under the plasma concentration-time profile from time 0 to time tau2 (10 to 24 hours) ($AUC_{tau2}$), $C_{max}$, $C_{max1}$ and $C_{max2}$ values.

Lower median danuglipron concentrations were observed for the 120 mg BID dose group compared to the 80 mg BID dose group at the 24, 36, and 48 hours postdose on Day 56; the high inter-participant variability at these time points and the small number of participants per cohort most likely contributed to this observation.

Mean $t_{½}$ ranged from 5.300 hours to 6.373 hours across the doses administered. Inter-participant variability for danuglipron exposure was based on geometric mean $AUC_{24}$ and $C_{max}$ values, with percent coefficient of variation (%CV) values ranging between 58% to 73% for $AUC_{24}$, 52% to 80% for $C_{max}$, and 43% to 87% for $C_{max1}$ on Day 1; and 45% to 148% for $AUC_{24}$, 54% to 153% for $C_{max}$, and 51% to 153% for $C_{max1}$ on Day 56 across all dose groups. The 120 mg BID dose group had the largest variability in exposure on Day 56, with geometric %CVs of 148% for $AUC_{24}$ and 153% for $C_{max}$ and $C_{max1}$.

**Safety Results:**

Adverse Events

Incidence of all-causalities and treatment-related TEAEs are presented by system organ class (SOC) and preferred term (PT) in Table S4 and Table S5, respectively.

A total of 70 all-causalities TEAEs were reported by 28 participants (75.7%) in the study, of which 54 (54/70: 77.14%) TEAEs reported by 24 participants (64.9%) were considered treatment-related. The number of participants with AEs (both all-causalities and treatment-related) were observed to be higher in the active treatment groups compared with the placebo group.

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The most frequently reported (in ≥10% of participants) all-causalities TEAEs by SOC were Gastrointestinal Disorders (67.6%) and Nervous System Disorders (13.5%). The most frequently reported (in ≥10% of participants) treatment-related TEAE by SOC was Gastrointestinal Disorders (64.9%).

The most frequently reported (in ≥10% of participants) all-causalities TEAEs by PT were nausea (48.6%), vomiting (43.2%), abdominal discomfort (35.1%), diarrhea (10.8%), and headache (10.8%). All TEAEs of nausea (48.6%), vomiting (43.2%), abdominal discomfort (35.1%), and diarrhea (10.8%) were considered as treatment-related in all dose groups. The incidence of all-causalities TEAEs in the Gastrointestinal Disorders SOC in each danuglipron dose groups were higher than the incidence in the placebo group (11.1%).

All but one of all-causalities TEAEs were mild or moderate in severity. One TEAE was reported as severe and was not considered treatment-related.

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**Table S4. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (All Causalities) - Safety Analysis Set (Protocol C3421015)**

| Number of Subjects Evaluable for AEs | Placebo (N=9) | PF-06882961 40mg (N=10) | PF-06882961 80mg (N=9) | PF-06882961 120mg (N=9) | Total (N=37) |
|---|---|---|---|---|---|
| **Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| With Any adverse event | 3 (33.3) | 7 (70.0) | 9 (100.0) | 9 (100.0) | 28 (75.7) |
| GASTROINTESTINAL DISORDERS | 1 (11.1) | 7 (70.0) | 9 (100) | 8 (88.9) | 25 (67.6) |
| Abdominal discomfort | 0 | 4 (40.0) | 4 (44.4) | 5 (55.6) | 13 (35.1) |
| Abdominal pain upper | 0 | 0 | 1 (11.1) | 0 | 1 (2.7) |
| Dental caries | 1 (11.1) | 0 | 0 | 1 (11.1) | 2 (5.4) |
| Diarrhoea | 0 | 1 (10.0) | 2 (22.2) | 1 (11.1) | 4 (10.8) |
| Nausea | 0 | 6 (60.0) | 8 (88.9) | 4 (44.4) | 18 (48.6) |
| Stomatitis | 0 | 0 | 1 (11.1) | 0 | 1 (2.7) |
| Vomiting | 0 | 5 (50.0) | 6 (66.7) | 5 (55.6) | 16 (43.2) |
| INFECTIONS AND INFESTATIONS | 0 | 2 (20.0) | 0 | 1 (11.1) | 3 (8.1) |
| Gastroenteritis | 0 | 1 (10.0) | 0 | 0 | 1 (2.7) |
| Hordeolum | 0 | 1 (10.0) | 0 | 0 | 1 (2.7) |
| Influenza | 0 | 0 | 0 | 1 (11.1) | 1 (2.7) |
| INVESTIGATIONS | 1 (11.1) | 1 (10.0) | 0 | 0 | 2 (5.4) |
| Alanine aminotransferase increased | 0 | 1 (10.0) | 0 | 0 | 1 (2.7) |
| Aspartate aminotransferase increased | 0 | 1 (10.0) | 0 | 0 | 1 (2.7) |
| Lipase increased | 1 (11.1) | 0 | 0 | 0 | 1 (2.7) |
| METABOLISM AND NUTRITION DISORDERS | 0 | 1 (10.0) | 1 (11.1) | 1 (11.1) | 3 (8.1) |
| Decreased appetite | 0 | 0 | 1 (11.1) | 1 (11.1) | 2 (5.4) |

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**Table S4. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (All Causalities) - Safety Analysis Set (Protocol C3421015)**

| Number of Subjects Evaluable for AEs | Placebo (N=9) | PF-06882961 40mg (N=10) | PF-06882961 80mg (N=9) | PF-06882961 120mg (N=9) | Total (N=37) |
|---|---|---|---|---|---|
| **Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| Hypoglycaemia | 0 | 1 (10.0) | 0 | 0 | 1 (2.7) |
| NERVOUS SYSTEM DISORDERS | 1 (11.1) | 2 (20.0) | 1 (11.1) | 1 (11.1) | 5 (13.5) |
| Headache | 1 (11.1) | 2 (20.0) | 1 (11.1) | 0 | 4 (10.8) |
| Presyncope | 0 | 0 | 0 | 1 (11.1) | 1 (2.7) |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | 0 | 0 | 1 (11.1) | 0 | 1 (2.7) |
| Dermatitis psoriasiform | 0 | 0 | 1 (11.1) | 0 | 1 (2.7) |

Subjects are only counted once per treatment per event.
Totals for the No. of Subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report two or more different adverse events within the higher level category.
Includes data up to lag days after last dose of study drug.
MedDRA v23.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 28APR2021 (05:21) Source Data: adae Table Generation: 09JUN2021 (11:47)
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Table 14.3.1.2.4 PF-06882961 is for Pfizer internal use.

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**Table S5. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Treatment Related) - Safety Analysis Set (Protocol C3421015)**

| Number of Subjects Evaluable for AEs | Placebo (N=9) | PF-06882961 40mg (N=10) | PF-06882961 80mg (N=9) | PF-06882961 120mg (N=9) | Total (N=37) |
|---|---|---|---|---|---|
| **Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| With Any adverse event | 0 | 7 (70.0) | 9 (100.0) | 8 (88.9) | 24 (64.9) |
| GASTROINTESTINAL DISORDERS | 0 | 7 (70.0) | 9 (100) | 8 (88.9) | 24 (64.9) |
| Abdominal discomfort | 0 | 4 (40.0) | 4 (44.4) | 5 (55.6) | 13 (35.1) |
| Diarrhoea | 0 | 1 (10.0) | 2 (22.2) | 1 (11.1) | 4 (10.8) |
| Nausea | 0 | 6 (60.0) | 8 (88.9) | 4 (44.4) | 18 (48.6) |
| Vomiting | 0 | 5 (50.0) | 6 (66.7) | 5 (55.6) | 16 (43.2) |
| METABOLISM AND NUTRITION DISORDERS | 0 | 1 (10.0) | 1 (11.1) | 1 (11.1) | 3 (8.1) |
| Decreased appetite | 0 | 0 | 1 (11.1) | 1 (11.1) | 2 (5.4) |
| Hypoglycaemia | 0 | 1 (10.0) | 0 | 0 | 1 (2.7) |

Subjects are only counted once per treatment per event.
Totals for the No. of Subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report two or more different adverse events within the higher level category.
Includes data up to lag days after last dose of study drug.
MedDRA v23.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 28APR2021 (05:21) Source Data: adae Table Generation: 09JUN2021 (11:47)
(Snapshot date : 19APR2021) Output File: ./csr6/C3421015/adae_s0311_1
Table 14.3.1.3.4 PF-06882961 is for Pfizer internal use.

There were no deaths, SAEs, or permanent discontinuations from the study due to TEAEs reported in the study.

A total of 5 participants (13.5%) reported medication error events; none of which were associated with any AEs.

One participant (2.7%) experienced 1 severe TEAE of alanine aminotransferase increased (ALT) increased in the treatment period, which resolved on Day 36, and was not considered treatment-related; the study drug was temporarily interrupted due to this TEAE.

A total of 6 participants (16.2%) permanently discontinued from the study drug due to TEAEs and were moved to the early termination visit after discontinuation; subsequently

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followed by, Follow-up Visit 1 and Follow-up Visit 2. All 6 participants discontinued due to treatment-related TEAEs of abdominal discomfort, nausea, and vomiting (2 participants [5.4%] each). All except 1 TEAE of abdominal discomfort were moderate in severity while 1 TEAE of abdominal discomfort was mild in severity. The outcome of all 6 TEAEs, which resulted in discontinuations from study drug was reported as resolved.

Two participants (5.4%) temporarily discontinued the study drug due to TEAEs, of which 1 participant in 80 mg BID group discontinued the study drug due to treatment-related TEAE of nausea and another participant in 40 mg BID group discontinued the study drug due to TEAEs of ALT increased and aspartate aminotransferase increased (AST) increased, which were not considered to be treatment-related. The TEAEs of nausea and AST increased were moderate in severity and the TEAE of ALT increased was severe. The outcome of all 3 TEAEs that resulted in temporary discontinuation of the study drug was reported as resolved.

Hypoglycemic Adverse Events

One participant in the 40 mg BID dose group experienced a probable symptomatic hypoglycemia (as the blood glucose was not measured) of mild severity, which was considered treatment-related. The participant had symptoms of dizziness, light headedness, and sweats, but required no assistance; and the symptoms resolved on the same day of onset when the participant was treated with oral carbohydrates.

Clinical Laboratory Evaluation

Without regard to baseline abnormality, 36 (97.3%) of the 37 participants evaluable for laboratory tests experienced laboratory abnormalities. Overall, the most common laboratory abnormality (in ≥50% of participants), without regard to baseline abnormality included, glucose (mmol/L) >1.5 × ULN (24 [64.9%] participants),
urine glucose ≥1 (21 [56.8%] participants), triglycerides (mmol/L) >1.3 × upper limit of normal (ULN) (20 [54.1%] participants), urine protein ≥1 (20 [54.1%] participants), granular casts >1 (2 [100.0%] participants), and hyaline casts >1 (2 [100.0%] participants). Of note, the glucose values were included for fasting status only at scheduled visits. There were no apparent dose-related increases in the incidence of laboratory test abnormalities.

Vital Signs

Two participants met pre-specified criteria for categorical analysis of supine systolic BP decrease ≥30 mm Hg, with 1 participant in the placebo group and 1 participant in the danuglipron 120 mg BID group meeting this criterion. Ten participants met the pre-specified criteria for categorical analysis of supine systolic BP increase ≥30 mm Hg, with 3 participants each in the placebo and danuglipron 80 mg BID dose groups and 2 participants each in the 40 mg and 120 mg BID dose groups. Nine participants met the pre-specified criteria for categorical analysis of supine diastolic BP increase ≥20 mm Hg, with 1 participant in the placebo group, 2 participants in the 40 mg BID group and 3 participants

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each in the 80 mg BID and 120 mg BID dose groups. None of the participants met the pre-specified criteria for pulse rate with values of <40 bpm or >120 bpm.

On Day 1, there was increases in the mean time-matched double differences in systolic BP over the course of the day for all the danuglipron BID dose groups, compared with placebo. However, on Day 56, danuglipron 40 mg BID dose group had a decrease in mean time-matched double differences in systolic BP similar to placebo, while the danuglipron 80 mg and 120 mg BID dose groups had a trend for increases in time-matched double differences in systolic BP over the course of the day. Mean systolic BP values for all dose groups were generally in the normal range.

On Day 1, there was a trend for increases in the mean time-matched double differences in diastolic BP over the course of the day for all the danuglipron BID dose groups, compared with placebo. However, on Day 56, danuglipron 40 mg BID dose group had a decrease in diastolic BP similar to placebo, while the danuglipron 80 mg and 120 mg BID dose groups had a trend for increases in time-matched double differences in diastolic BP over the course of the day. Mean diastolic BP values for all dose groups were generally in the normal range.

On Day 1, mean time-matched double differences in pulse rate was similar for the danuglipron BID dose groups, compared with placebo. However, on Day 56, all danuglipron BID dose groups had a trend for increases in mean time-matched double differences in pulse rate compared to placebo, over the course of the day. Also, the increase was greater in danuglipron 120 mg BID dose group compared with other groups. Mean pulse rate values for all dose groups were generally in the normal range.

Electrocardiogram

A total of 3 (8.1%) participants reported post-baseline ECG data meeting pre-specified categorical analysis criteria of corrected QT using Fridericia's formula (QTcF) interval >450 and ≤480 msec, of which 1 (11.1%) participant each were in the placebo, danuglipron 80 mg, and danuglipron 120 mg groups. No data met the criteria of PR interval ≥300 msec or QRS duration ≥140 msec. There were no apparent dose-related increases in the frequency of ECG abnormalities by categorical analysis.

No apparent clinically adverse trends were noted for PR, QRS, QT, and QTcF intervals. The mean time-matched double differences in ECG heart rate for the danuglipron 120 mg BID dose group on Day 56 was higher than the placebo and danuglipron 40 mg and 80 mg dose groups.

## CLINICAL STUDY REPORT SYNOPSIS

**Conclusions:**

Safety

- Ascending, multiple, oral doses of danuglipron were generally safe in adult Japanese participants with T2DM. The most commonly reported all-causalities TEAEs were nausea, vomiting, abdominal discomfort, diarrhea, and headache.

- There were no apparent dose-related increases in the frequency of laboratory, vital sign or ECG abnormalities by categorical analysis. A trend for increases in time-matched double differences in systolic and diastolic BP was observed on Day 56 with danuglipron doses of 80 mg and 120 mg BID, relative to placebo and danuglipron 40 mg BID, with mean systolic and diastolic BP values in the normal range.

- Only 1 hypoglycemic adverse event of mild severity was reported as a probable symptomatic hypoglycemia in the danuglipron 40 mg BID dose group.

PK

- Dose-proportional increases in danuglipron geometric mean $AUC_{24,}$ $AUC_{tau1}$, $AUC_{tau2}$, $C_{max}$, $C_{max1}$ and $C_{max2}$ values were observed on Day 56 following titration up to 40, 80, or 120 mg BID.

- Peak concentrations ($C_{max,}$ $C_{max1}$ and $C_{max2}$) were observed within a median $T_{max}$,$T_{max1}$ and $T_{max2}$ of approximately 2 hours to 6 hours post each dose administered.

- Mean $t_{½}$ ranged from 5.300 hours to 6.373 hours across the doses administered.