CLINICAL STUDY REPORT SYNOPSIS

SYNOPSIS

Study Title: A Phase 2, Randomized, Double-Blind, Placebo Controlled, Dose Ranging, Dose Finding, Parallel Group Study to Assess Efficacy and Safety of PF-07081532, and Open Label Oral Semaglutide, in Adults With Type 2 Diabetes Mellitus (T2DM) Inadequately Controlled on Metformin, and Separately PF-07081532 Compared to Matching Placebo in Adults With Obesity but Without T2DM

Study Number: C3991004

Regulatory Agency or Public Disclosure Identifier Number:

ClinicalTrials.gov ID: NCT05579977

EudraCT Number: 2022-002834-15

Study Phase: 2

Name of Study Intervention: PF-07081532 (lotiglipron)

Name of Sponsor/Company: Pfizer Inc.

CSR Version and Report Date: Final CSR Version 1.0, 26 January 2024

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

This study was conducted at 78 sites in 7 countries (Bulgaria, Canada, Czech Republic, Hungary, Japan, Poland, United States [including sites in Puerto Rico]). 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 (First Participant First Visit [FPFV]): 27 October 2022

Early Study Termination Date: 22 September 2023

The study started with FPFV on 27 October 2022 and First Participant First Dose (FPFD) on 29 November 2022. On 25 June 2023, based on emerging pharmacokinetic (PK) data from Phase 1 Drug-Drug Interaction (DDI) studies (C3991040 [NCT05671653] and C3991047 [NCT05788328]), clinical observations of elevated transaminases in these studies as well as in this outpatient Phase 2 study, the decision was made to stop dosing in Study C3991004 and terminate the clinical development of PF-07081532.

Following the premature termination decision, on 26 June 2023, an urgent safety measure communication was made to all Health Authorities; study sites were informed to instruct all

CLINICAL STUDY REPORT SYNOPSIS

ongoing participants to immediately discontinue study drug and to complete early termination visits as soon as possible. Additional guidance on the follow-up of treatment-emergent adverse events (TEAEs) and laboratory abnormalities was provided to sites on 30 June 2023 and this additional safety follow-up for all participants was completed on 22 September 2023 (last participant last visit [LPLV]).

Rationale:

Study C3991004 was the first study in the clinical program with PF-07081532 powered to evaluate the efficacy of a range of PF-07081532 doses compared to matching placebo in adults with type 2 diabetes mellitus (T2DM) inadequately controlled on metformin and separately adults with obesity but without T2DM via outpatient dosing, employing 4-week dose-escalation intervals for up to 20 weeks (and up to 5 steps), and evaluating once-daily doses from 20 mg to 260 mg.

Objectives, Endpoints, and Statistical Methods:

The study objectives and endpoints defined by protocol (version date: 13 September 2022) and statistical analysis plan (SAP, version date: 27 September 2023) are presented in the Table S1.

Table S1. Study Objectives, Endpoints and Estimands

Objectives	Endpoints	Estimands
Primary:		
To evaluate the efficacy of a range of PF-07081532 doses compared to placebo, ***in participants with T2DM inadequately controlled on metformin***	Placebo-adjusted, change from baseline in ***HbA1c*** at Week 32	**Population:** All treated participants with T2DM inadequately controlled on metformin **Variable:** Placebo-adjusted, change from baseline in **HbA1c** at Week 32 **Intercurrent events:** • An On Treatment strategy was used: Measurements after initiation of glycemic rescue medication or discontinuation of study intervention were considered as intercurrent events, which were censored and treated as missing data. The missing data due to censoring, study withdrawal or other reasons (eg, laboratory failure) had data imputed based on a MAR assumption. Participants with inadequate compliance had their HbA1c values used as-is in the analysis. **Population-level summary measure:** The population-based treatment effect was the difference in the mean change from baseline in each PF-07081532 arm compared to placebo.
To evaluate the efficacy of a range of PF-07081532 doses compared to placebo, ***in participants with obesity but without T2DM***	Placebo-adjusted, percent change from baseline in ***body weight*** at Week 32	**Population:** All treated participants with obesity but without T2DM **Variable**: Placebo-adjusted, percent change from baseline in body weight at Week 32 **Intercurrent events:**

CLINICAL STUDY REPORT SYNOPSIS

Table S1. Study Objectives, Endpoints and Estimands

Objectives	Endpoints	Estimands
		• An On Treatment strategy was used: Measurements after discontinuation of study intervention were considered as intercurrent events, which were censored and treated as missing data. The missing data due to censoring, study withdrawal or other reasons (eg, equipment failure) had data imputed based on a MAR assumption. Participants with inadequate compliance had their body weight values used as-is in the analysis. **Population-level summary measure:** The population-based treatment effect was the difference in the mean percent change from baseline in each PF-07081532 arm compared to placebo.
Secondary:		
To assess the effect of a range of PF-07081532 doses compared to placebo on various parameters, ***in participants with T2DM inadequately controlled on metformin***	Proportion of participants who achieve ***HbA1c*** <7% (<53 mmol/mol) at Week 32[a]	**Population:** All treated participants with T2DM inadequately controlled on metformin **Variable**: Proportion of participants who achieve HbA1c <7% (<53 mmol/mol) at Week 32 **Intercurrent events:** • An On Treatment strategy was used: Measurements after initiation of glycemic rescue medication or discontinuation of study intervention were considered as intercurrent events which were censored and treated as missing data. Missing data were not imputed. Participants with inadequate compliance had their HbA1c values used as-is in the analysis. **Population-level summary measure:** The population-based treatment effect was the odds ratio of achieving HbA1c <7% in a PF-07081532 arm relative to placebo.
	Placebo-adjusted, change from baseline in ***FPG*** at Week 32	The estimand for placebo-adjusted, change from baseline in ***FPG*** at Week 32 endpoint was constructed in a similar manner as placebo-adjusted, change from baseline in ***HbA1c*** at Week 32
	Placebo-adjusted, percent change from baseline in ***body weight*** at Week 32	The estimand for the placebo-adjusted, percent change from baseline in ***body weight*** at Week 32 endpoint was constructed in a similar manner as placebo-adjusted, change from baseline in ***HbA1c*** at Week 32
To compare the efficacy of PF-07081532 and Rybelsus® relative to placebo, ***in participants with T2DM inadequately controlled on metformin***	Placebo-adjusted, change from baseline in ***HbA1c*** at Week 32	**Population:** All treated participants with T2DM inadequately controlled on metformin **Variable:** Placebo-adjusted, change from baseline in **HbA1c** at Week 32 **Intercurrent events:** • An On Treatment strategy was used: Measurements after initiation of glycemic rescue medication or discontinuation of study intervention were considered as intercurrent events, which were censored and treated as missing data. The missing data due to

CLINICAL STUDY REPORT SYNOPSIS

Table S1. Study Objectives, Endpoints and Estimands

Objectives	Endpoints	Estimands
		censoring, study withdrawal or other reasons (eg, laboratory failure) had data imputed based on a MAR assumption. Participants with inadequate compliance had their HbA1c values used as-is in the analysis. **Population-level summary measure:** The population-based treatment effect was the difference in the mean change from baseline in each PF-07081532 arm and Rybelsus arm compared to placebo.
To assess the effect of a range of PF-07081532 doses compared to placebo on various parameters ***in participants with obesity but without T2DM***	• Proportion of participants achieving ≥5%, ≥10%, and ≥15% ***body weight loss*** at Week 32 relative to baseline[a] • Placebo-adjusted, ***absolute*** change from baseline in ***waist circumference*** at Week 32 • Placebo-adjusted, ***absolute*** change from baseline in ***waist-to-hip ratio*** at Week 32 • Placebo-adjusted, change from baseline in ***HOMA-IR*** at Week 32 • Placebo-adjusted, change from baseline in ***HOMA-S*** at Week 32	**Population:** All treated participants with obesity but without T2DM **Variables:** Proportion of participants achieving ≥5%, ≥10%, and ≥15% body weight loss at Week 32 relative to baseline **Intercurrent events:** • An On Treatment strategy was used: Measurements after initiation of glycemic rescue medication or discontinuation of study intervention were considered as intercurrent events, which were censored and treated as missing data. Missing data were not imputed. Participants with inadequate compliance had their body weight values used as-is in the analysis. **Population-level summary measure:** The population-based treatment effect was the odds ratio of PF-07081532 arm relative to placebo. The estimand for each of the continuous endpoints was constructed in a similar manner as the primary endpoint placebo-adjusted, percent change from baseline in **body weight** at Week 32.

To assess the safety and tolerability with a range of PF-07081532 doses compared to placebo, ***in participants with T2DM inadequately controlled on metformin*** and separately ***participants with obesity but without T2DM***	In ***each*** population randomized,
	• Number (and percent) of participants with:
	  • TEAEs
	  • SAEs
	  • AE leading to permanent discontinuation from study intervention or study
	  • Hypoglycemia
	  • AESIs
	  • Clinical laboratory abnormalities
	  • Vital sign abnormalities
	  • 12-lead ECG abnormalities
	• And TEAEs, presented in descending order of frequency	

To assess the safety and tolerability with a range of PF-07081532 doses compared to placebo, ***in***	Assessment of mental health as determined by: • C-SSRS	

CLINICAL STUDY REPORT SYNOPSIS

Table S1. Study Objectives, Endpoints and Estimands

Objectives	Endpoints	Estimands
participants with obesity but without T2DM		
Tertiary:		
To assess the effect of a range of PF-07081532 doses compared to placebo on various parameters ***in participants with T2DM inadequately controlled on metformin***	• Placebo-adjusted, ***absolute*** change from baseline in ***HbA1c, FPG, FPI, HOMA-IR, HOMA-S over time*** to Week 32 • Placebo-adjusted, ***absolute*** change from baseline in ***waist circumference*** at Week 32[a] • Placebo-adjusted, ***absolute*** change from baseline in ***waist-to-hip ratio*** at Week 32[a]	• The estimand for each of the continuous endpoints was constructed in a similar manner as placebo-adjusted, change from baseline in ***HbA1c*** at Week 32
To assess the effect of a range of PF-07081532 doses compared to placebo on various parameters ***in participants with obesity but without T2DM***	• Placebo-adjusted, ***absolute*** change from baseline in **HbA1c**[a]**, *FPI, HOMA-IR, HOMA-S over time*** to Week 32	• The estimand for each of the continuous endpoints was constructed in a similar manner as the primary endpoint placebo-adjusted, percent change from baseline in ***body weight*** at Week 32
To explore effect of a range of PF-07081532 doses compared to placebo, ***in participants with T2DM inadequately controlled on metformin*** and separately ***participants with obesity but without T2DM***	In ***each*** population randomized, • Shift from baseline in glycemic category (euglycemia, pre-diabetes, T2DM) at Week 32[a] • Placebo-adjusted, ***absolute*** change from baseline in ***SBP, DBP, PR and HR over time*** to Week 32 • Placebo-adjusted, ***percent*** change from baseline in ***fasting serum lipid parameters (HDL-C, direct LDL-C, TG, total cholesterol) over time*** to Week 32	• ***For Cohort 1***, the estimand for each of the continuous endpoints was constructed in a similar manner as placebo-adjusted, change from baseline in ***HbA1c*** at Week 32 • ***For Cohort 2***, the estimand for each of the continuous endpoints was constructed in a similar manner as the primary endpoint placebo-adjusted, percent change from baseline in ***body weight*** at Week 32
To characterize PK of: • PF-07081532, ***in participants with T2DM inadequately controlled on metformin*** and separately ***participants with obesity but without T2DM*** • Rybelsus, ***in participants with T2DM inadequately***	In ***each*** population randomized, descriptive summary of trough concentrations of PF-07081532 and Rybelsus	

CLINICAL STUDY REPORT SYNOPSIS

Table S1. Study Objectives, Endpoints and Estimands

Objectives	Endpoints	Estimands
controlled on metformin		
To explore effect of a range of PF-07081532 doses compared to placebo, on endogenous biomarker of CYP3A activity ***in the entire population randomized***	Placebo-adjusted, ***percent*** change from baseline in ***4-β-hydroxycholesterol to cholesterol*** **ratio** ***over time*** to Week 32	
To explore the effect on PCOAs with a range of PF-07081532 doses compared to placebo, ***in participants with obesity but without T2DM***	Change from baseline at Week 20 and Week 32, on the following endpoints: • PGI-S (6 items)[a] • PROMIS® Fatigue Custom 9-item Version[a] • PROMIS® Physical Function Custom 13-item Version[a] • IWQOL-Lite-CT©[a] • SF-36v2®[a] PGI-C (6 items)[a] at Week 20 and Week 32	

Abbreviations: AE=adverse event; AESI= adverse event of special interest; C-SSRS=Columbia Suicide Severity Rating Scale; CYP=cytochrome P450; DBP=diastolic blood pressure; ECG= electrocardiogram; FPG=fasting plasma glucose; FPI=fasting plasma insulin; HbA1c=glycated hemoglobin; HDL-C=high-density lipoprotein-cholesterol; HOMA-IR=Homeostatic Model Assessment for Insulin Resistance; HOMA-S=Homeostatic Model Assessment for Insulin Sensitivity; HR=heart rate; IWQOL-Lite-CT=Impact of Weight on Quality of Life-Lite Clinical Trials Version; LDL-C=low-density lipoprotein-cholesterol; MAR=missing at random; PCOA=Patient Centered Outcome Assessments; PGI-C=Patient's Global Impression of Change; PGI-S=Patient's Global Impression of Severity; PK=pharmacokinetic(s); PR=pulse rate; PROMIS=Patient-Reported Outcomes Measurement Information System; SAE=serious adverse event; SBP=systolic blood pressure; SF-36=36-item Short Form Health Survey; T2DM=type 2 diabetes mellitus; TEAE=treatment-emergent adverse event; TG= triglyceride

a. Analysis was not performed for this endpoint due to termination of the PF-07081532 program and premature termination of the Study C3991004.

Due to termination of the clinical development of PF-07081532 and premature termination of study C3991004, planned analyses for the endpoints were modified and reduced. Statistical analyses were limited to visits with sufficient data, and therefore, study result interpretation may be limited.

Methodology:

This was a multisite, multinational, randomized, double-blind, double-dummy, placebo-controlled, dose-ranging, dose-finding, parallel-group study to assess efficacy and safety/tolerability of PF-07081532 and open-label Rybelsus® in adults with T2DM inadequately controlled on metformin (Stratum 1) compared to matching placebo, and separately PF-07081532 compared to matching placebo in adults with obesity but without T2DM (Stratum 2).

CLINICAL STUDY REPORT SYNOPSIS

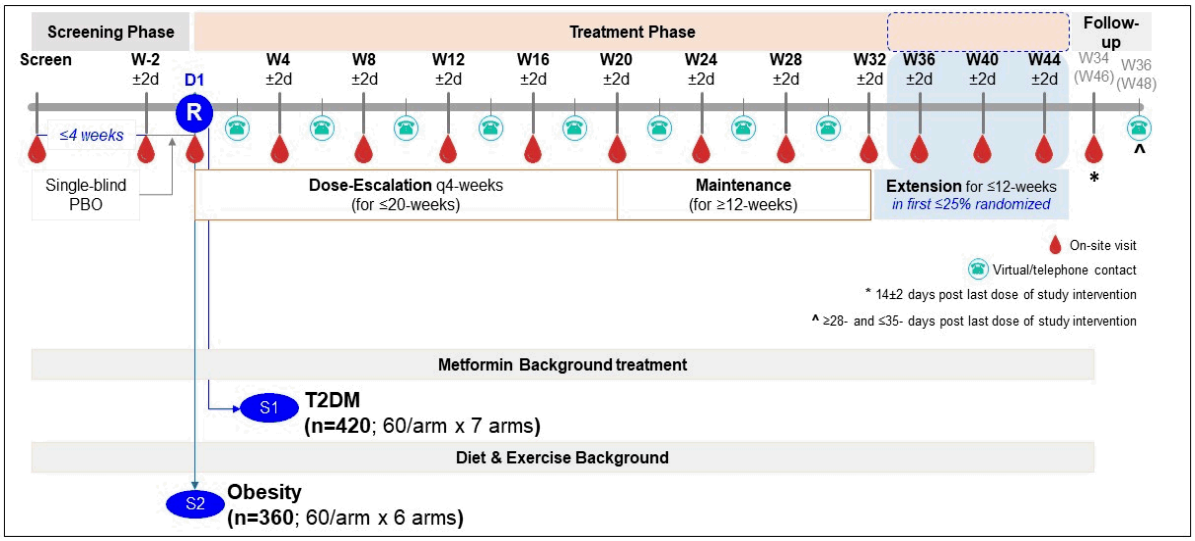
- In **Stratum 1**, 3 interventions, PF-07081532, its matching placebo, and open-label Rybelsus, were to be evaluated across 7 arms in participants with T2DM on a background of metformin.

- In **Stratum 2**, 2 interventions, PF-07081532 and its matching placebo, were to be evaluated across 6 arms in participants with obesity and without T2DM.

- Across all 12 treatment arms of PF-07081532/placebo, each dose consisted of 3 tablets per dose once daily (QD), using dispensation of 3 bottles (1 tablet per bottle).

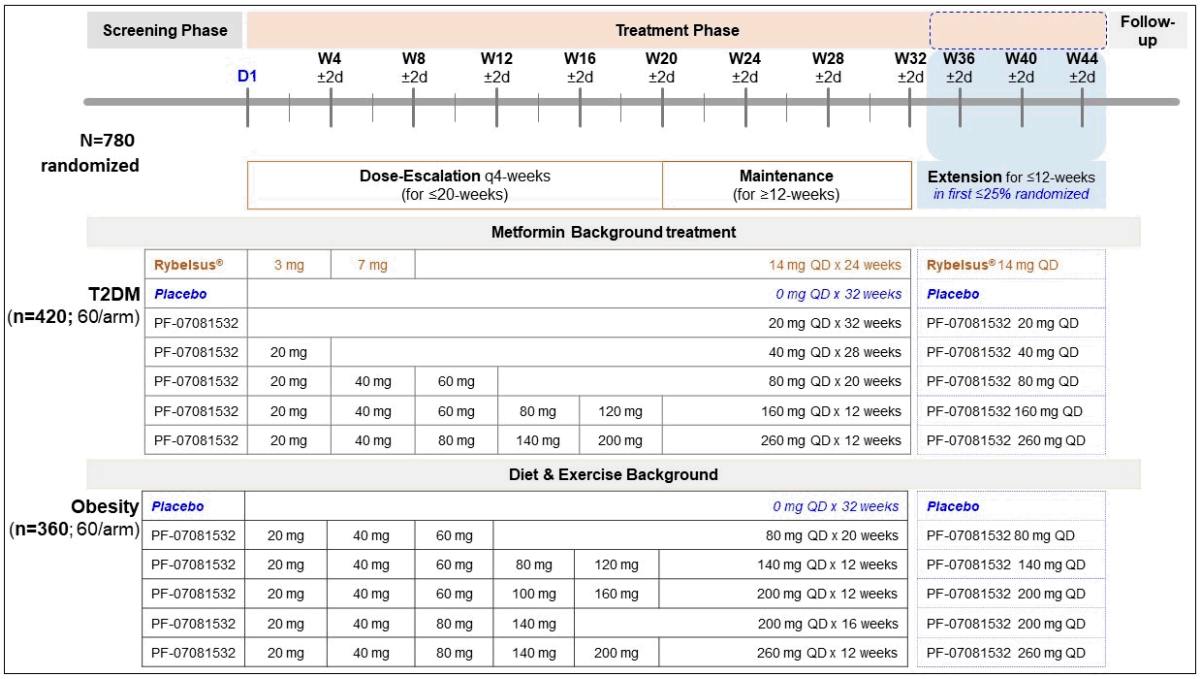
Schematics of the study design and the study treatment outline are presented in Figure S1 and Figure S2.

Figure S1. Study Design Schema



CLINICAL STUDY REPORT SYNOPSIS

Figure S2. Dose-Escalation Scheme



Number of Participants (Planned and Analyzed):

Approximately 780 participants (60 per arm) were to be enrolled and randomized in the study to ensure approximately 650 participants (51 per arm) offer evaluable data for the primary endpoint. Across each of the 2 populations, approximately 420 participants (60 per arm) with T2DM inadequately controlled on metformin plus approximately 360 (60 per arm) with obesity but without T2DM, were to be enrolled.

During the study, a total of 1532 participants were screened, 973 completed the Screening Phase and 902 were randomized after completion of the Run-In Phase. Of these, 513 had T2DM inadequately controlled on metformin (Stratum 1, hereafter referred as 'participants with T2DM') and 389 had obesity but without T2DM (Stratum 2, hereafter referred as 'participants with obesity'). Stratum 1 randomized 22% (n=93) more than the target of 420 participants while Stratum 2 randomized 8% (n=29) more than the target of 360 participants.

- A total of 901 participants, 512 with T2DM (Stratum 1) and 389 with obesity (Stratum 2), who were randomly assigned and took at least 1 dose of study intervention (placebo, PF-07081532 [in Strata 1 and 2] or Rybelsus [Stratum 1 only]) were included in the evaluable set and safety analysis set.

- Excluding the 139 participants treated with placebo, a total of 762 participants, 437 with T2DM (Stratum 1) and 325 with obesity (Stratum 2), who were treated with at least

CLINICAL STUDY REPORT SYNOPSIS

1 dose of PF-07081532 or Rybelsus and had at least 1 concentration value reported were included in the PK concentration set.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Enrolled in this study were adult participants with T2DM inadequately controlled with metformin at doses ≥500 mg/day (for Stratum 1), and participants with obesity (defined by body mass index [BMI] ≥30.0 kg/m^2) but without T2DM (for Stratum 2).

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

Study interventions in this study included:

- PF-07081532
- Placebo, matching PF-07081532
- Open-label Rybelsus (ie, oral semaglutide) - in Stratum 1 (T2DM) only

The study interventions administered for each study arm are listed in Figure S2. The manufacturing lot numbers for the study interventions dispensed in this study are provided in Table S2.

Table S2. Study Intervention(s) Administered

Investigational Product Description	Vendor Lot No.	Pfizer Lot No.	Strength / Potency	Dosage Form
Placebo Oval Tablet (2:1, MCC:Lactose)	B20050	20-001719	0 mg	Tablet
PF-07081532-82 20 mg Tablet	N/A	21-DP-00907	20 mg	Tablet
PF-07081532-82 20 mg Tablet	N/A	22-DP-01000	20 mg	Tablet
PF-07081532-82 60 mg Tablet	N/A	21-DP-00908	60 mg	Tablet
PF-07081532-82 60 mg Tablet	N/A	22-DP-01001	60 mg	Tablet
PF-07081532-82 100 mg Tablet	N/A	21-DP-00909	100 mg	Tablet
PF-07081532-82 100 mg Tablet	N/A	22-DP-01004	100 mg	Tablet
PF-07081532-82 100 mg Tablet	N/A	22-DP-01005	100 mg	Tablet
Semaglutide (Rybelsus) 3 mg Tablet	MA41369	22-AE-00515	3 mg	Commercial product
Semaglutide (Rybelsus) 3 mg Tablet	MS6FX13	22-AE-00581	3 mg	Commercial product
Semaglutide (Rybelsus) 3 mg Tablet	MA41441	22-AE-00657	3 mg	Commercial product
Semaglutide (Rybelsus) 3 mg Tablet	MS6GA40	22-AE-00658	3 mg	Commercial product
Semaglutide (Rybelsus) 7 mg Tablet	LA41212	22-AE-00516	7 mg	Commercial product
Semaglutide (Rybelsus) 7 mg Tablet	MS6FY28	22-AE-00582	7 mg	Commercial product
Semaglutide (Rybelsus) 7 mg Tablet	MA41507	22-AE-00677	7 mg	Commercial product
Semaglutide (Rybelsus) 14 mg Tablet	MA41465	22-AE-00517	14 mg	Commercial product
Semaglutide (Rybelsus) 14 mg Tablet	MS6FY17	22-AE-00595	14 mg	Commercial product
Semaglutide (Rybelsus) 14 mg Tablet	MA41495	22-AE-00656	14 mg	Commercial product

PF-07081532 and PF-07081532-82 are used interchangeably throughout the report.

CLINICAL STUDY REPORT SYNOPSIS

Duration of Study Intervention:

The treatment duration in this study was planned to be 32 weeks for most participants; though in the first set of up to 25% randomized participants, treatment interval was designed to be extended for an additional up to 12 weeks (for a total duration of up to 44 weeks).

This study was terminated prior to observation of Week 32, and prior to reaching a maintenance dose in most participants, see Exposure section.

Summary of Results:

Demographic and Other Baseline Characteristics:

In participants with T2DM (Stratum 1), 54.7% of participants were males and 45.3% were females. The majority of participant were White (75.2%). The median (range) age was 59.0 (28, 76) years. The mean (standard deviation [SD]) BMI was 33.695 (6.8868) kg/m^2. The median (range) duration of T2DM was 7.50 (0.2, 31.1) years. The median (range) duration of metformin use was 3.10 (0.2, 29.2) years. The mean (SD) HbA1c was 7.97% (0.915%). The median (range) HbA1c was 7.80% (5.4%, 11.4%).

In participants with obesity (Stratum 2), 39.1% of participants were males and 60.9% were females. The majority of participant were White (81.7%). The median (range) age was 50.0 (18, 76) years. The mean (SD) BMI was 37.751 (6.1963) kg/m^2. The mean (SD) body weight was 107.280 (22.1703) kg. The median (range) body weight was 104.420 (66.40, 227.25) kg. The median (range) waist circumference was 113.530 (82.87, 183.0) cm, and median (range) waist-to-hip ratio was 0.940 (0.59, 1.24).

Exposure:

By the time of early termination of the study by the sponsor, no participant reached the planned duration of study treatment of 32 weeks. The longest exposure was reached by 2 participants with T2DM and 2 participants with obesity, who each completed their Week 28 Visit in this study.

In participants with T2DM (Stratum 1),

- In PF-07081532 20 mg, 40 mg, 80 mg groups and Rybelsus 14 mg group, most participants (≥84.9%) completed dose titration and reached maintenance phase.
- In PF-07081532 160 mg and 260 mg groups, 9.7% and 8.1% of the participants completed dose titration (Weeks 16-20) and reached maintenance phase, respectively.

In participants with obesity (Stratum 2),

- In PF-07081532 80 mg group, most participants (80.3%) completed dose titration and reached maintenance phase.

CLINICAL STUDY REPORT SYNOPSIS

- In PF-07081532 140 mg, 200 mg (5 steps), 200 mg (4 steps) and 260 mg groups, 57.8%, 58.5%, 65.2% and 43.8% of the participants completed dose titration (Weeks 16-20) and reached maintenance phase, respectively.

Efficacy Results:

Change From Baseline in HbA1c at Week 32 in Participants With T2DM

Due to the scarcity of data at later visits, mixed model repeated measures (MMRM) estimates for the change from baseline (CFB) in HbA1c in participants with T2DM (Stratum 1) were limited to Week 16.

PF-07081532:

At Week 16, statistically significant reductions vs placebo ($p < 0.0001$) in CFB in HbA1c were observed with all PF-07081532 doses (20 mg, 40 mg, 80 mg, 160 mg, and 260 mg). Interpretation of the dose-response relationship is challenging at Week 16 due to the titration of the higher doses of 160 mg and 260 mg only reaching 80 mg and 140 mg, respectively.

Statistically significant reductions vs placebo ($p < 0.0001$) with all PF-07081532 doses were observed as early at Week 4 and progressively increased through Week 16. At Week 16, based on placebo-adjusted least square (LS) mean CFB, the starting, lowest dose of 20 mg of PF-07081532 appeared less effective (-0.95%) than the higher dose groups (-1.26 to -1.37%).

Rybelsus:

At Week 16, statistically significant reduction vs placebo ($p < 0.0001$) in CFB in HbA1c was observed in the Rybelsus 14 mg group. Statistically significant reduction vs placebo ($p = 0.03$) was observed as early at Week 4 in the Rybelsus 14 mg group and progressively increased through Week 16.

The placebo-adjusted mean CFB in HbA1c at Week 16 was -0.86% in the Rybelsus 14 mg group, which was generally consistent with what reported in PIONEER 4 (-1.1% at Week 26 and about -1% by graph at Week 14).

Percent Change From Baseline in Body Weight at Week 32 in Participants With Obesity

Due to the scarcity of data at later visits, MMRM estimates for the percent CFB in body weight in participants with obesity (Stratum 2) were limited to Week 20.

At Week 20, statistically significant reductions vs placebo ($p < 0.01$) in percent CFB in body weight were observed with all PF-07081532 doses (80 mg, 140 mg, 200 mg [5 steps], 200 mg [4 steps] and 260 mg). However, based on the placebo-adjusted LS mean percent CFB, the lowest dose of 80 mg of PF-07081532 (-2.44%) appeared to be less effective than the higher PF-07081532 doses (-4.37% to -5.63%). Of note, the statistically significant

CLINICAL STUDY REPORT SYNOPSIS

reduction (p = 0.0028) in body weight (LS mean = -1.84%) compared to baseline observed in the placebo group may be attributable to dietary counseling provided to all participants throughout the study. Interpretation of the dose-response relationship is challenging at Week 20 due to the titration of the higher doses of 140 mg, 200 mg (5 steps), and 260 mg only reaching 120 mg, 160 mg, and 200 mg, respectively.

Statistically significant reductions vs placebo (p <0.01) were observed with all PF-07081532 doses as early at Week 8 and continued to further decline through Week 20.

Change From Baseline in FPG at Week 32 in Participants With T2DM

Due to the early termination of the study, few participants with T2DM (Stratum 1) reached a duration of treatment of 20 weeks and beyond (≤11 participants per group).

In participants with T2DM (Stratum 1), mean FPG at baseline was numerically higher in the PF-07081532 20 mg group (180.7 mg/dL), while being similar across the placebo, the Rybelsus 14 mg group and other PF-07081532 treatment groups (ranged from 166.8 mg/dL to 173.7 mg/dL).

On-treatment reductions from baseline in FPG were observed in all PF-07081532 treatment groups through Week 16, with a mean CFB at Week 16 ranging from -48.9 mg/dL to -31.0 mg/dL, vs -9.3 mg/dL in the placebo group. On-treatment reductions from baseline in FPG were also observed in the Rybelsus 14 mg group through Week 16, with a mean CFB of -28.6 mg/dL at Week 16.

Percent Change From Baseline in Body Weight at Week 32 in Participants With T2DM

Due to the scarcity of data at later visits, MMRM estimates for percent CFB in body weight in participants with T2DM (Stratum 1) were limited to Week 16.

At Week 16, statistically significant reductions vs placebo (p <0.001) in percent CFB in body weight were observed with all PF-07081532 doses except the lowest dose of 20 mg. However, based on the placebo-adjusted LS mean percent CFB, the lowest dose of 20 mg of PF-07081532 (-0.91 %) appeared to be less effective than the higher PF-07081532 doses (-2.72% to -3.74%). Of note, the statistically significant reduction (p = 0.0342) in body weight (LS mean = -1.05%) compared to baseline observed in the placebo group may be attributable to dietary counseling provided to all participants throughout the study. Starting at Week 8, statistically significant reductions vs placebo (p <0.01) were observed with all PF-07081532 doses except the lowest dose of 20 mg. The mean weight loss observed in the Rybelsus group is generally consistent with the approximately 3 kg weight loss observed at Week 14 in PIONEER 4.

CLINICAL STUDY REPORT SYNOPSIS

Change From Baseline in Waist Circumference at Week 32 in Participants With Obesity

Due to the early termination of the study, no participant reached a duration of study treatment of 32 weeks. All available data for the CFB in waist circumference (at Weeks 12 and 24) are descriptively summarized for participants with obesity (Stratum 2). Of note, few participants with obesity (≤12 participants per group) reached Week 24.

In participants with obesity (Stratum 2), mean waist circumference at baseline ranged from 113.138 cm to 117.312 cm across the placebo and the PF-07081532 treatment groups. At Week 12, on-treatment mean reductions from baseline in waist circumference were observed in all PF-07081532 treatment groups (ranged from -3.559 cm to -1.079 cm), as well as in the placebo group (-2.702 cm).

Change From Baseline in Waist-to-Hip Ratio at Week 32 in Participants With Obesity

Due to the early termination of the study, no participant reached a duration of study treatment of 32 weeks. All available data for the CFB in waist-to-hip ratio (at Weeks 12 and 24) are descriptively summarized for participants with obesity (Stratum 2). Of note, few participants with obesity (≤12 participants per group) reached Week 24.

In participants with obesity (Stratum 2), mean waist-to-hip ratio at baseline was similar across the placebo and PF-07081532 treatment groups, ranging from 0.927 to 0.955. At Week 12, on-treatment mean CFB in waist-to-hip ratio was -0.013 in the placebo group and ranged from -0.010 to 0.015 in the PF-07081532 treatment groups.

Change From Baseline in HOMA-IR Over Time

Due to the early termination of the study, no participants reached a duration of treatment of 32 weeks. All available data for the absolute value and CFB in HOMA-IR (at baseline and at Week 16) are descriptively summarized.

In participants with T2DM (Stratum 1), at baseline, mean HOMA-IR ranged from 4.702 to 6.308 across the placebo group, the PF-07081532 treatment groups and the Rybelsus 14 mg group. At Week 16, mean CFB in HOMA-IR was -1.027 in the placebo group, ranged from -1.774 to 0.522 in the PF-07081532 treatment groups, and -1.150 in the Rybelsus 14 mg group.

In participants with obesity (Stratum 2), at baseline, mean HOMA-IR ranged from 2.799 to 3.483 across the placebo and PF-07081532 treatment groups. At Week 16, mean CFB in HOMA-IR was 0.630 in the placebo group and ranged from -1.172 to 0.984 in the PF-07081532 treatment groups.

CLINICAL STUDY REPORT SYNOPSIS

Change From Baseline in HOMA-S Over Time

Due to the early termination of the study, no participants reached a duration of treatment of 32 weeks. All available data for the absolute value and CFB in HOMA-S (at baseline and at Week 16) are descriptively summarized.

In participants with T2DM (Stratum 1), at baseline, mean HOMA-S ranged from 29.392% to 36.153% across the placebo group, the PF-07081532 treatment groups and the Rybelsus 14 mg group. At Week 16, mean CFB in HOMA-S was 5.963% in the placebo group, 8.849% in the Rybelsus 14 mg group, and ranged from 7.705% to 26.372% in the PF-07081532 treatment groups.

In participants with obesity (Stratum 2), at baseline, mean HOMA-S ranged from 44.123% to 55.297% across the placebo and PF-07081532 treatment groups. At Week 16, mean CFB in HOMA-S was -2.419% in the placebo group and ranged from -7.085% to 7.807% in the PF-07081532 treatment groups.

Safety Results:

Adverse Events:

In participants with T2DM (Stratum 1),

- A total of 707 all-causality TEAEs were reported in 303 (59.2%) participants with T2DM (Stratum 1). The incidence of all-causality TEAEs was 46.7% in the placebo group, 50.7%-75.7% in the PF-07081532 treatment groups, and 49.3% in the Rybelsus 14 mg group. The majority of the all-causality TEAEs were mild or moderate in severity.

- All-causality TEAEs were most frequently reported in the system organ class (SOC) of Gastrointestinal (GI) disorders (38.9%), those that occurred in ≥5% of participants were nausea (18.6%), diarrhoea (8.6%), vomiting (8.2%) and constipation (5.3%). No clear increase in incidence with increasing PF-07081532 dose was observed for any of the GI AEs of interest. For GI-related TEAE of nausea, the PF-07081532 starting dose of 20 mg dose showed higher incidence than placebo and Rybelsus starting dose of 3 mg during the timeframe of Day 1 to Week 4.

- All-causality SAEs were reported in 11 (2.1%) participants: 1 (1.3%) in the placebo group, 3 (approximately 4%) each in the PF-07081532 40 mg and 80 mg groups, 0, 1 (1.4%) and 2 (2.7%) in the PF-07081532 20 mg, 160 mg, and 260 mg groups, respectively, and 1 (1.4%) in the Rybelsus 14 mg group. One death due to non-treatment-related AE of cardiac arrest was reported in a participant randomized to placebo.

- Study intervention discontinuations due to all-causality TEAE were reported in 51 (10%) participants, most of them were receiving PF-07081532 doses of 40 mg, 80 mg and 260 mg (11 [15.3%], 10 [13.7%] and 17 [23.0%] participants, respectively), vs 0 in

CLINICAL STUDY REPORT SYNOPSIS

the placebo group. The most common AEs (≥2% of participants) that resulted in permanent discontinuation from study intervention included nausea (15 [2.9%] participants) and vomiting (10 [2.0%] participants).

In participants with obesity (Stratum 2),

- A total of 1258 all-causality TEAEs were reported in 317 (81.5%) participants with obesity (Stratum 2). The incidence of all-causality TEAEs was 68.8% in the placebo group, 78.1%-90.9% in the PF-07081532 treatment groups. The majority of the all-causality TEAEs were mild or moderate in severity.

- All-causality TEAEs were most frequently reported in the SOC of GI disorders (67.4%), those that occurred in ≥5% of participants were nausea (46.8%), constipation (22.9%), diarrhoea (21.1%), vomiting (20.6%), gastrooesophageal reflux disease (10.5%), headache (9.5%), decreased appetite (9.3%), fatigue (8.5%), dyspepsia (8.0%), abdominal pain (7.5%) and urinary tract infection (5.1%). There appeared to be a dose-dependent trend for the incidence of vomiting. No apparent dose trend was observed for any of the GI AEs of interest. GI AE of vomiting was associated primarily with doses of PF-07081532 80 mg and higher. GI AE of constipation showed a numerically decreasing incidence over time across most PF-07081532 doses. The titration of PF-07081532 dose of 140 mg to 200 mg which happened at Week 16 was associated with high incidence of nausea and vomiting in participants with obesity (in the PF-07081532 200 mg [4 steps] and 260 mg groups). However, the same transition in participants with T2DM (in PF-07081532 260 mg group) did not show the same pattern.

- All-causality SAEs were reported in 10 (2.6%) participants: 1 (1.6%) in the placebo group, 1 (1.5%) in the PF-07081532 200 mg (5 steps) group, and 2 (≤3.1%) in the other PF-07081532 groups. No deaths were reported.

- Study intervention discontinuations due to all-causality TEAEs were reported in 97 (24.9%) participants, most frequently in the PF-07081532 140 mg, 200 mg (4 steps), 200 mg (5 steps) and 260 mg groups (23.1%-36.4%, vs 7.8% in the placebo group, and 18.2% in the PF-07081532 80 mg group). There appeared to be a dose-related increase in discontinuations of study intervention. The more rapid titration for the PF-07081532 200 mg group (4 steps) showed a higher discontinuation rate of 36.4% compared to the slower titration for the same dose (5 steps) with 23.1% discontinuations. More rapid titration for PF-07081532 showed a higher discontinuation rate compared to slower titration. The most common AEs (≥2% of participants) that resulted in permanent discontinuation from the study intervention in the 97 participants included nausea (48 [12.3%] participants), vomiting (29 [7.5%] participants), diarrhoea (14 [3.6%] participants) and constipation (8 [2.1%] participants).

- Exposure during pregnancy (with SAE of spontaneous abortion) was reported in 1 participant with obesity (Stratum 2) randomized to PF-07081532 140 mg dose. The estimated day of conception was Study Day 94, with the last dose of PF-07081532

CLINICAL STUDY REPORT SYNOPSIS

(80 mg) self-administered on Study Day 107. The outcome of this pregnancy was spontaneous abortion on Study Day 157.

Clinical Laboratory Results:

Overall, 84.3% of the participants with T2DM (Stratum 1) had at least 1 laboratory test abnormality reported: 89.3% in the placebo group, 79.2%-87.7% across PF-07081532 treatment groups, and 87.7% in the Rybelsus 14 mg group. The most frequently occurring laboratory test abnormalities (in ≥10% of participants) were glucose (fasting) >1.5 × upper limit of normal (ULN) (57.2%), urine glucose ≥1 (26.9%), leukocyte esterase ≥1 (24.6%), HbA1c >1.3 × ULN (19.6%), gamma-glutamyl transferase (GGT) >3.0 × ULN (12.5%), HDL Cholesterol (fasting) <0.8 × lower limit of normal (LLN) (11.7%).

Overall, 60.3% of the participants with obesity (Stratum 2) had at least 1 laboratory test abnormality reported: 56.3% in the placebo group, 49.2%-72.7% across PF-07081532 treatment groups. The most frequently occurring laboratory test abnormalities (in ≥10% of participants) were leukocyte esterase ≥1 (27.4%), GGT >3.0 × ULN (26.7%), urine hemoglobin ≥1 (17.0%), LDL direct (fasting) >1.2 × ULN (10.9%), thyrotropin <0.8 × LLN (10.0%).

Alanine aminotransferase (ALT):

Due to the scarcity of data at later visits, discussion of the analysis for the CFB in ALT was limited to Week 16 for participants with T2DM (Stratum 1), and Week 20 for participants with obesity (Stratum 2). Of note, less than 50% of the participants with T2DM had ALT data reported at Week 16.

In participants with T2DM (Stratum 1),

- Mean and median baseline values for ALT were similar across the placebo, the PF-07081532 treatment groups, and the Rybelsus 14 mg group (mean: 27.1 U/L-31.4 U/L, median: 22.5 U/L-27.0 U/L).

- At Weeks 8 and 12, ALT median CFB across all PF-07081532 treatment groups was in tight range from -3.0 U/L (20 mg group at Week 12) to 1.0 U/L (80 mg group at Week 8). However, ALT mean CFB was higher in the PF-07081532 40 mg, 80 mg, 160 mg and 260 mg groups at Weeks 8 and 12 (ranging from 1.9 U/L to 24.2 U/L, both in 80 mg group at Weeks 12 and 8, respectively), reflecting the impact of ALT spikes in individual participants.

- At Week 16, ALT median CFB remained in a narrow range (-1.5 U/L [80 mg group] to 1.0 U/L [260 mg group]) across all PF-07081532 treatment groups and ALT mean CFB returned to baseline (or below) in the PF-07081532 20 mg, 40 mg, 80 mg and 160 mg groups (mean CFB: ≤0.5 U/L), while remaining modestly elevated in the PF-07081532 260 mg group (mean CFB: 9.9 U/L). No increase from baseline in ALT value was

CLINICAL STUDY REPORT SYNOPSIS

observed in the placebo, PF-07081532 20 mg or Rybelsus 14 mg groups through Week 16.

- Post-baseline ALT >3.0 × ULN was reported in 23 (4.5%) participants: 5 (6.9%), 6 (8.3%), 4 (5.6%) and 8 (11.0%) in the PF-07081532 40 mg, 80 mg, 160 mg and 260 mg groups, respectively; no elevations of ALT >3.0 × ULN were observed in the placebo, PF-07081532 20 mg or Rybelsus groups. Thirteen (2.6%) participants experienced ALT >5.0 × ULN: 3 (4.2%), 4 (5.6%), 2 (2.8%) and 4 (5.5%) in the PF-07081532 40 mg, 80 mg, 160 mg and 260 mg groups, respectively. Nine (1.8%) participants experienced ALT >8.0 × ULN: 1 (1.4%), 3 (4.2%), 2 (2.8%) and 3 (4.1%) in the PF-07081532 40 mg, 80 mg, 160 mg and 260 mg groups, respectively.

In participants with obesity (Stratum 2),

- Mean and median baseline values for ALT were similar across the placebo, the PF-07081532 80 mg, 140 mg, 200 mg (5 steps), and 200 mg (4 steps) groups (mean ranging from 26.8 U/L-28.4 U/L, median: 21.0 U/L-23.0 U/L), and numerically lower in the PF-07081532 260 mg group (mean: 23.5 U/L, median 19.0 U/L).

- Through Week 20, the median CFB remained in a very tight range for all PF-07081532 treatment groups from -3.0 U/L to -1.0 U/L except for the 140 mg group at Week 20 (-5.0 U/L). Among the PF-07081532 80 mg and 200 mg (4 steps) groups, small mean increases from baseline in ALT were observed (CFB ≤8.5 U/L, 200 mg [4 steps] group at Week 8) as individual participant elevations had impact on the mean results.

- Post-baseline ALT >3.0 × ULN was reported in 20 (5.2%) participants, with each group having at least one: 1 (1.6%), 2 (3.2%), 6 (9.5%), 2 (3.2%), 8 (12.1%) and 1 (1.6%) in the placebo, PF-07081532 80 mg, 140 mg, 200 mg (5 steps), 200 mg (4 steps) and 260 mg groups, respectively. Four (1.0%) participants experienced ALT >5.0 × ULN: 1 (1.6%), 1 (1.6%) and 2 (3.0%) in the PF-07081532 80 mg, 140 mg, and 200 mg (4 steps) groups, respectively. Two (0.5%) participants experienced ALT >8.0 × ULN: 1 each (approximately 1.5%) in the PF-07081532 80 mg and 200 mg (4 steps) groups.

Aspartate aminotransferase (AST)

Due to the scarcity of data at later visits, discussion of the analysis for the CFB in AST was limited to Week 16 for participants with T2DM (Stratum 1), and Week 20 for participants with obesity (Stratum 2). Of note, less than 50% of the participants with T2DM had AST data reported at Week 16.

In participants with T2DM (Stratum 1),

- Mean and median baseline value for AST ranged from 21.9 U/L to 26.5 U/L and 19.0 U/L to 22.0 U/L, respectively, across the placebo, the PF-07081532 treatment groups, and the Rybelsus 14 mg group. At Weeks 8 and 12, AST median CFB remained

CLINICAL STUDY REPORT SYNOPSIS

within a narrow range (-1.0 U/L to 1.0 U/L) across all treatment groups. At Weeks 8 and 12, mean CFB gently increased in the PF-07081532 40 mg, 80 mg, 160 mg and 260 mg groups (ranged from 0.2 U/L [40 mg group at Week 12] to 11.5 U/L [80 mg group at Week 8]), suggesting mean values were impacted by individual participants with AST elevations.

- At Week 16, AST median CFB remained constrained within a tight range (-1.0 U/L to 1.0 U/L) in the PF-07081532 40 mg, 80 mg, 160 mg and 260 mg groups. Mean CFB returned to baseline (or below) in the PF-07081532 20 mg, 40 mg, 80 mg and 160 mg groups (mean CFB: ≤-0.2 U/L), while remaining modestly elevated in the PF-07081532 260 mg group (mean CFB: 6.4 U/L). No increase from baseline in the mean AST values were observed in the placebo, PF-07081532 20 mg or Rybelsus 14 mg groups through Week 16.

- Post-baseline AST >3.0 × ULN was reported in 12 (2.4%) participants: 3 (approximately 4%) each in the PF-07081532 40 mg, 80 mg, 160 mg and 260 mg groups.
  Eight (1.6%) participants experienced AST >5.0 × ULN: 1 (1.4%), 3 (4.2%), 2 (2.8%) and 2 (2.7%) in the PF-07081532 40 mg, 80 mg, 160 mg and 260 mg groups, respectively. Three (0.6%) participants experienced AST >8.0 × ULN: 1 (1.4%) each in the PF-07081532 80 mg, 160 mg and 260 mg groups, respectively.

In participants with obesity (Stratum 2),

- Mean and median baseline value for AST was similar across the placebo and the PF-07081532 treatment groups (mean: 20.4 U/L-23.2 U/L, median: 18.5 U/L-21.5 U/L). Through Week 20, AST median CFB were tightly constrained, ranging from -2.0 U/L to 0.0 U/L across the PF-07081532 treatment groups.

- Small increase from baseline in mean AST was observed in the PF-07081532 200 mg (4 steps) group at Week 8 (4.0 U/L), and in the 80 mg group at Week 12 (3.3 U/L) as impacted by individual participants with elevations. At weeks 16 and 20, AST mean CFB were constrained within the range of -2.0 U/L to 2.0 U/L across the PF-07081532 treatment groups.

- Post-baseline AST >3.0 × ULN was reported in 6 (1.6%) participants. Three (0.8%) participants experienced AST >5.0 × ULN: 1 (1.6%) and 2 (3.0%) in the PF-07081532 80 mg and 200 mg (4 steps) groups, respectively. One (0.3%) participant experienced AST >8.0 × ULN (PF-07081532 80 mg group).

Drug-Induced Liver Injury (Hy's Law) Case

No on-treatment Hy's law case was reported in either participants with T2DM (Stratum 1) or participants with obesity (Stratum 2).

CLINICAL STUDY REPORT SYNOPSIS

One potential on-study Hy's law case was reported in a participant with obesity (Stratum 2): One female participant in the PF-07081532 200 mg (4 steps) group experienced lab test abnormality of ALT >3.0 × ULN accompanied with total bilirubin >2.0 × ULN 46 days after last dose of study treatment and 2 days after onset of an SAE of epistaxis. The participant was also noted to have elevated ALP >2 × ULN.

Other Safety Evaluations

Vital Signs:

SBP

In participants with T2DM (Stratum 1), 2 participants experienced post-baseline SBP <90 mmHg: 1 (1.4%) each in the PF-07081532 80 mg and 160 mg groups.

In participants with obesity (Stratum 2), 6 participants experienced post-baseline SBP <90 mmHg: 3 (4.5%), 2 (3.1%) and 1 (1.6%) in the PF-07081532 80 mg, 200 mg (5 steps) and 260 mg groups, respectively.

DBP

In participants with T2DM (Stratum 1), 13 participants experienced post-baseline DBP >100 mmHg: 4 (5.5%) in the PF-07081532 20 mg group; 2 (approximately 3%) each in the PF-07081532 40 mg, 80 mg and 160 mg, and Rybelsus 14 mg groups; 1 (1.4%) in the PF-07081532 260 mg group.

In participants with obesity (Stratum 2), 17 participants experienced post-baseline DBP >100 mmHg: 4 (approximately 6%) in the placebo, PF-07081532 80 mg and 140 mg groups, 3 (4.7%) in the PF-07081532 260 mg group and 2 (3.0%) in the PF-07081532 200 mg (4 steps) group.

PR

In participants with T2DM (Stratum 1), 3 participants experienced post-baseline PR >110 bpm: 1 (1.4%) each in the PF-07081532 20 mg, 40 mg and 260 mg groups.

In participants with obesity (Stratum 2), no participants experienced post-baseline PR abnormalities meeting pre-defined category of >110 bpm.

ECGs:

The most commonly reported ECG abnormalities meeting pre-specified categorical criteria were 30 msec≤ change in QTcF interval ≤60 msec, and 450 msec< QTcF interval ≤480 msec.

CLINICAL STUDY REPORT SYNOPSIS

In participants with T2DM (Stratum 1):

- Change in QTcF interval ≥30 msec and ≤60 msec: 4.0% in the placebo group, 4.2%-13.5% in the PF-07081532 treatment groups, and 11.0% in the Rybelsus 14 mg group.

- QTcF interval >450 msec and ≤480 msec: 6.7% in the placebo group, 2.7%-9.6% in the PF-07081532 treatment groups, and 6.8% in the Rybelsus 14 mg group.

In participants with Obesity (Stratum 2):

- Change in QTcF interval ≥30 msec and ≤60 msec: 4.7% in the placebo group, 4.7%-12.1% in the PF-07081532 treatment groups.

- QTcF interval >450 msec and ≤480 msec: 14.1% in the placebo group, 3.1%-10.9% in the PF-07081532 treatment groups.

C-SSRS in Participants with Obesity

C-SSRS results collected during the study were mapped to Columbia Classification Algorithm of Suicide Assessment (C-CASA). At baseline, all 389 participants with obesity (Stratum 2) were assessed, among whom 1 in the PF-07081532 260 mg group was assessed to have suicidal ideation without intent to act.

Post-baseline results were collected in 383 out of the 389 participants with obesity (Stratum 2):

- In the placebo group: 1 participant was assessed to have self-injurious behavior without suicidal intent.

- In the PF-07081532 260 mg group: 1 participant was assessed to have suicidal ideation without intent to act (the same participant who reported ideation at baseline).

PK Results:

PF-07081532 PK:

Across both participant populations, plasma PF-07081532 trough concentrations generally increased with increasing dose and were in accordance with the employed dosing scheme in each treatment group.

It was apparent that participants who had (any time after Day 1) ALT or AST measurements >3 × ULN exhibited on average higher PF-07081532 dose-normalized trough concentrations compared to participants who did not meet this criterion. Separation in trough PF-07081532 concentrations across the 2 groups (with non-overlapping confidence intervals [CIs]) was evident as early as Week 4 (the first trough PK sample collected) and continued at

CLINICAL STUDY REPORT SYNOPSIS

Week 8 and Week 12. Beyond Week 12, participants in the ALT/AST >3 × ULN group continued to exhibit on average higher concentrations but with overlapping CIs across the 2 groups, likely due to the decrease in the number of participants with available PK data in the ALT/AST >3 × ULN group (reflecting treatment discontinuation; N decreased from 32 at Week 12 to 16 and 12 at Weeks 16 and 20, respectively). The largest difference in trough concentrations between the 2 groups was observed at Week 8, aligning with the timing at which the majority of ALT/AST elevations were generally observed. In addition, dose-normalized trough concentrations of the participants in the ALT/AST >3 × ULN group were substantially increased on average at Week 8 compared to Week 4, indicating greater than dose-proportional increases in exposure in these participants.

Similar to what was observed with trough concentrations, participants in the ALT/AST >3 × ULN group exhibited on average higher PF-07081532 dose-normalized post-dose concentrations, with the largest difference between the 2 groups observed at Week 8. Separation in the post-dose concentration levels across the 2 groups (with non-overlapping CIs) started as early as Week 0 (the first post-dose PK sample collected in the study, on Day 1).

It was observed that several participants with ALT/AST elevations (ALT/AST >3 × ULN group) had individual PF-07081532 concentrations multiple-fold higher than the median concentration levels observed in participants without such elevations within the same treatment arm. This trend was clearly more evident in the T2DM compared to the obesity population, aligning with the observation that the magnitude of ALT/AST elevations was also generally larger in the T2DM population.

Semaglutide (Rybelsus) PK:

Plasma semaglutide trough concentrations generally increased with increasing dose in accordance with the employed dosing scheme.

Biomarkers:

Percent Change From Baseline in 4-β-Hydroxycholesterol to Cholesterol Ratio Over Time

In participants with T2DM (Stratum 1):

- Median baseline 4-β-hydroxycholesterol to cholesterol ratio ranged from 10.255×10^{-6} to 11.410×10^{-6} across the placebo, the PF-07081532 treatment groups and the Rybelsus 14 mg group.

- At Week 8, increase from baseline in 4-β-hydroxycholesterol to cholesterol ratio was observed in all PF-07081532 treatment groups (median percent CFB: 8.150%-13.678%) vs 2.637% in the Rybelsus 14 mg group, and 0.703% in the placebo group. At Week 16, the ratio continued to increase in the PF-07081532 80 mg, 160 mg and 260 mg groups

CLINICAL STUDY REPORT SYNOPSIS

(median percent CFB: 23.159%-31.229%), vs 5.668% in the Rybelsus 14 mg group, and 4.176% in the placebo group.

In participants with obesity (Stratum 2):

- Median baseline 4-β-hydroxycholesterol to cholesterol ratio ranged from 11.950×10^{-6} to 13.810×10^{-6} across the placebo and the PF-07081532 treatment groups.

- At Week 8, increase from baseline in 4-β-hydroxycholesterol to cholesterol ratio was observed in all PF-07081532 treatment groups (median percent CFB: 9.549%-15.648%) vs -1.875% in the placebo group. At Week 16, the ratio continued to increase in all PF-07081532 treatment groups (median percent CFB: 19.196%-31.928%), vs 3.518% in the placebo group.

Conclusions:

The clinical development of lotiglipron (PF-07081532) was terminated on 25 Jun 2023 based on PK data from Phase 1 DDI studies (C3991040 and C3991047) and laboratory measurements of elevated transaminases in these Phase 1 studies as well as in this Phase 2 Study C3991004.

Efficacy:

Superiority to placebo was observed in the efficacy analyses through Week 16 for participants with T2DM (Stratum 1) and through Week 20 for participants with obesity (Stratum 2). The evaluation for protocol-defined primary efficacy endpoints (placebo-adjusted CFB in HbA1c at Week 32 for participants with T2DM, and placebo-adjusted percent CFB in body weight at Week 32 for participants with obesity) were not possible due to the premature termination of this study.

- At Week 16, in participants with T2DM (Stratum 1), a statistically significant reduction vs placebo in CFB in HbA1c was observed for all PF-07081532 doses (20 mg, 40 mg, 80 mg, 160 mg and 260 mg) as well as the Rybelsus 14 mg group with placebo-adjusted LS mean CFB ranging between -1.37% (PF-07081532 80 mg) and -0.86% (Rybelsus).

- At Week 20, in participants with obesity (Stratum 2), a statistically significant reduction vs placebo in percent CFB in body weight was observed for all PF-07081532 doses (80 mg, 140 mg, 200 mg [5 steps], 200 mg [4 steps], and 260 mg) with placebo-adjusted LS mean percent CFB ranging from -5.63% (200 mg [5 steps]) to -2.44% (80 mg).

Safety:

- Consistent with the primary pharmacology of glucagon-like peptide-1 receptor (GLP-1R) agonist, GI-related TEAEs were the most frequently reported TEAEs as well as the most common cause for discontinuation of study drug, in the 2 populations enrolled in this

CLINICAL STUDY REPORT SYNOPSIS

study. Tolerability of PF-07081532 appeared to be higher in participants with T2DM (Stratum 1) compared to participants with obesity (Stratum 2).

- Slower titration for PF-07081532 showed better tolerability compared to a more rapid titration.

- While no on-treatment Hy's Law cases were observed in this study, repeated, oral administration of PF-07081532 at doses ≥40 mg QD was associated with incident transaminitis in 5% of the population randomized in this study with no clear traits identified in the population at risk of incident transaminitis.

PK:

- Across both T2DM and obesity populations, plasma PF-07081532 trough concentrations generally increased with increasing dose and were in accordance with the employed dosing scheme in each treatment group.

- Participants who had (any time after Day 1) ALT or AST measurements >3 × ULN exhibited on average higher PF-07081532 dose-normalized trough and post-dose plasma concentrations compared to participants who did not meet this criterion. Separation across the 2 groups (non-overlapping 90% CIs) was evident as early as Week 4 (for trough concentrations) and Week 0 (for post-dose concentrations), with maximum difference between the 2 groups observed at Week 8.

- Plasma semaglutide (Rybelsus) trough concentrations in participants with T2DM generally increased with increasing dose in accordance with the employed dosing scheme.

Biomarkers

- Increases in 4-β-hydroxycholesterol to cholesterol ratio were observed at Week 16 across all PF-07081532 treatment groups in both the T2DM and obesity populations (median percent CFB up to 31.2% and 31.9%, respectively, compared to 4.2% and 3.5% in placebo).