STATISTICAL ANALYSIS PLAN AMENDMENT

A PHASE 1 DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED, SINGLE- AND MULTIPLE-ASCENDING DOSE STUDY TO ASSESS THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF PF-06293620 IN SUBJECTS WITH TYPE 2 DIABETES MELLITUS

Compound:	PF-06293620 (RN909)
Compound Name:	Not Applicable
US IND Number:	118523
European Clinical Trial Database (EudraCT) Number:	N/A
Protocol Number:	B3501001
Phase:	Phase 1a

Protocol B3501001

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Statistical Analysis Plan Amendment (SAP)

Version: 2.0

Author: PPD (Clinical Statistician – PPD)

Date: 08NOV2016

List of Reviewers

Role Name	Reviewer's Name
Clinical Lead	PPD
Clinical Pharmacology Lead	PPD
Clinical Statistician	PPD
Regulatory Lead	PPD
Clinical Programming	PPD
COSTL	PPD

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ABBREVIATIONS

TERM	
ABPM	Ambulatory Blood pressure Monitoring
ADA	Anti-Drug Antibody
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BP	Blood Pressure
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DILI	Drug Induced Liver Injury
ECG	Electrocardiogram
FA	Fructosamine
HbA1c	Hemoglobin A1c
IV	Intravenous
LLN	Lower Limit of Normal
MAD	Multiple Ascending Dose
mL	Milliliter
MMRM	Mixed Model Repeated Measurements
MMTT	Mixed Meal Tolerance Test
MTD	Maximum Tolerated Dose
NOAEL	No Observed Adverse Effect Level
PD	Pharmacodynamics
PK	Pharmacokinetics
SAE	Serious Adverse Event
SC	Subcutaneous
T2D	Type 2 Diabetes Mellitus
TEAE	Treatment Emergent Adverse Event
TG	Triglycerides
ULN	Upper Limit of Normal

1. AMENDMENTS FROM PREVIOUS VERSION(S)

Statistical Analysis Plan Version 1, July 30, 2014.

2. INTRODUCTION

The purpose of this statistical analysis plan (SAP) amendment is to provide details of the analysis of protocol B3501001 Amendment 3 entitled, "A PHASE 1 DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED, SINGLE- AND MULTIPLE-ASCENDING DOSE STUDY TO ASSESS THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF PF-06293620 IN SUBJECTS WITH TYPE 2 DIABETES MELLITUS." The statistical methods described herein are based on the analyses proposed in the Final Protocol Amendment 3 dated 02October2015. This SAP supersedes the statistical considerations identified in the protocol and, where considerations are substantially different, they will be identified as such, and be amended in a future protocol amendment, if applicable. This SAP will be developed and finalized prior to database lock and unblinding of the clinical database.

The planned analyses identified in this SAP will be included in regulatory submissions and/or future manuscripts. Exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. Any post-hoc, or unplanned, analyses performed that are not specified in this SAP will be clearly identified in the clinical study report (CSR).

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E9 Guideline (Guidance for Industry: Statistical Principles for Clinical Trials) and on the ICH E3 Guideline (Guidance for Industry: Structure and Content of Clinical Study Reports).

3. STUDY DESIGN

This is a randomized, placebo-controlled, double-blind (sponsor unblinded; subjects and investigator blinded), single dose, and multiple-dose dose escalation study of PF-06293620The study was originally to be conducted in approximately 6 planned single-dose cohorts. Based on preliminary, unpublished, results from the first 4 SAD cohorts, the 1 mg/kg IV cohort will be evaluated but the 10 mg/kg IV cohort will not be conducted. Approximately 4 multiple dose cohorts are planned to seek a maximum tolerated dose (MTD) and evaluate different dosages for safety and tolerablity. The multiple-dose cohorts will be initiated based on a review of the preliminary, unpublished safety and PK results from the first three SAD dose cohorts. The subjects, investigators, CRO and site personnel (except site personnel responsible for drug preparation) will be blinded to treatment assignments. The Sponsor's clinical research team or designee (e.g. Medical Monitor) will be unblinded.

Single-Dose Cohorts:

The SAD portion will be conducted in approximately 5 planned cohorts with a total of up to approximately 40 subjects to seek a maximum tolerated dose (MTD). PF-06293620 will be administered subcutaneously(SC) at doses of 0.3, 1, 3, and 6 mg/kg. In addition, a 1 mg/kg

dose,will be given intravenously (IV). The screening period will last up to 28 days and the treatment period will last approximately 84 days. Progression to the next dose will occur if the last dose was well tolerated and after satisfactory review of the available safety data. The cohorts will be studied in a sequential ascending fashion with 15 day post-dose safety data from all of the subjects in the current cohort being reviewed by the Sponsor and Investigators prior to commencement of treatment in the next cohort. Subjects will be assigned to cohorts on the basis of their order of entry into the study. Within each cohort, approximately 8 subjects will be randomized to receive either PF-06293620 or placebo with a 3:1 ratio. The dosage and dose escalation scheme is shown in Table 1.

Table 1. Planned SAD Dosage Cohorts

Cohort	Dosage mg/kg	Route of Administration	Total n	Active	Placebo
1	0.3	SC	8	6	2
2	1	SC	8	6	2
3	3	SC	8	6	2
4	6	SC	8	6	2
5	1	IV	8	6	2

The Schedule of Activities table in the study protocol provides an overview of the protocol visits and procedures. Refer to the Study Procedures and Assessments sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

Multiple-Dose Cohorts:

The multiple ascending dose (MAD) portion will be conducted in approximately 4 planned cohorts, 75 mg, 150 mg, 250 mg, and a fourth cohort with dosage and regimen to be determined based on the review of the safety data from the previous cohort(s), with a total of up to approximately 40 subjects (8 PF-06293620: 2 placebo per cohort).

Subjects and the site personnel in the MAD cohorts will be blinded to treatment and treatment regimen. The MAD cohorts will be run in parallel with the remaining SAD cohorts. Based on the ongoing review of the safety data of the previous SAD and MAD cohort(s) the order of initiation of the MAD cohorts may be adjusted but at no time will the dose exceed the PK exposure from the SAD portion. MAD safety data from the previous cohort(s) will be used to determine the dose and dose regimen of the fourth planned cohort. An additional fifth cohort may be studied to obtain further safety and PK data, increasing the planned total number of subjects to approximately 50. At no time will the MAD dose exceed PK exposure from the SAD. The MAD subjects will receive SC administration of study drug (PF-06293620 or placebo) every 4 weeks (on study Days 1, 29 and 57) in 3 of the originally planned 75 mg, 150 mg and 250 mg cohorts. However, after150 mg/kg dose cohort, it was determined that it would be unnecessary to study doses higher than 150 mg/kg. A decision was made to study 50 mg/kg dose and to expand 75 mg/kg dose cohort for additional pharmacodynamics evaluations. The final study dose cohorts and number of subjects randomized are outlined in Table 2.

Table 2. Final MAD Cohorts and Dosage Levels

Dose	Route	Frequency	Number of Subjects
50mg Placebo	SC	Q4weeks	8 2
75mg Placebo	SC	Q4 weeks	16 4
150mg Placebo	SC	Q4weeks	8 2

4. STUDY OBJECTIVES

4.1. Primary Objective

- To evaluate the safety, tolerability and immunogenicity of single, ascending SC and IV doses and ascending multiple SC doses of PF-06293620 in subjects with T2DM on stable doses of metformin.

4.2. Secondary Objectives

- To characterize the pharmacokinetics of PF-06293620 after administration of single-doses of SC and IV PF-06293620 and multiple doses of SC PF-06293620 to subjects with T2DM on stable doses of metformin.

4.3. Exploratory Objectives

- To characterize the pharmacodynamics of PF-06293620.
- To characterize the effect of PF-06293620 on glucose, insulin, GLP-1, C-peptide and glucagon excursions over 4 hrs following an MMTT.
- To evaluate changes in fasting lipid parameters.
- Additional exploratory objectives in the MAD portion will include 24 hour ambulatory blood pressure monitoring, and central review of ECGs .

5. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

Planned interim analyses for each MAD cohort may be conducted after all subjects in the cohort have completed Day 169, and following completion of the SAD portion of the study. Additional interim analyses may be performed if warranted. All interim analyses results will be used for internal business decisions regarding future project planning.

Data from the SAD portion of the study may be reported in an interim clinical study report (CSR) should the Sponsor determine an interim report is warranted. The SAD is a double-blind (sponsor unblinded; subjects and Investigator blinded) portion. All analyseis will be descriptive in nature. Summary tables and data listings will be generated. Detailed analysis and summary will be described in a separate Interim Analysis Plan.

Data from the MAD portion of the study may be reported in another interim CSR should the Sponsor determine an interim report is warranted prior to all subjects completing up to 9 months of follow-up after the last scheduled visit for elevated ADA, glucagon, and/or liver enzymes (Section 6.3.29). The MAD is a double-blind (sponsor unblinded; subjects and Investigator blinded) portion. All analysis will be descriptive in nature. Summary tables and data listings will be generated. Detailed analysis and summary will be described in a separate Interim Analysis Plan.Planned interim analyses for each MAD cohort may be conducted after all subjects in the cohort have completed Day 169, and following completion of the SAD portion of the study. Additional interim analyses may be performed if warranted. All interim analyses results will be used for internal business decisions regarding future project planning.

Data from the MAD portion of the study may be reported in another interim CSR should the Sponsor determine an interim report is warranted prior to all subjects completing up to 9 months of follow-up after the last scheduled visit for elevated ADA, glucagon, and/or liver enzymes (Section 6.3.29). The MAD is a double-blind (sponsor unblinded; subjects and Investigator blinded) portion. All analysis will be descriptive in nature. Summary tables and data listings will be generated. Detailed analysis and summary will be described in a separate Interim Analysis Plan (IAP-MAD).

6. HYPOTHESES AND DECISION RULES

6.1. Statistical Hypotheses

This study is exploratory in nature, no pre-specified hypothsis tests are to be performed.

7. ANALYSIS SETS

7.1. Full Analysis Set

In general, the full analysis set is comprised of all randomized subjects. This population of subjects is not applicable for this study. Analysis sets for safety, PK, and pharmacodynamic data are defined in Sections 7.3, 7.4 and 7.5.

7.2. 'PER PROTOCOL' Analysis Set

n/a.

7.3. Safety Analysis Set

The Safety Analysis Set consists of all patients who receive any amount of dose of study medication. The Safety Analysis Set will be used for all analyses.

7.4. Pharmacokinetic (PK) Analysis Set

7.4.1. PK Concentration Analysis Set

The pharmacokinetic (PK) concentration population is defined as all enrolled subjects treated who have at least 1 measurable (>LLOQ) concentration value.

7.4.2. PK Parameter Analysis Set

The PK parameter analysis population is defined as all subjects randomized and treated who have at least 1 of the PK parameters of interest.

7.5. Pharmacodynamic (PD) Analysis Set

The PD population is defined as all subjects randomized and treated who have at least 1 measurable plasma concentration of studied medication (PF-06293620), and:

- Fasting plasma glucose,
- Fasting glucagon,
- Fasting GLP-1,
- Glucose, insulin, C-peptide, GLP-1after 4 hour mixed meal tolerance test (MMTT)
- 1,5-anhydroglucitol,
- fructosamine,
- HbA1c,
- AUC0-24hr of glucose,
- mean daily blood glucose levels (from fingerstick).

7.6. Other Analysis Sets

N/A.

7.7. Treatment Misallocations

All analyses will be performed on an "as-treated" basis and will not include data from subjects who are randomized but not treated.

If a subject takes a treatment that is not consistent with the treatment they are randomized to, subjects will be reported under the treatment that they actually received for all safety, PK and pharmacodynamic analyses, where applicable.

7.8. Protocol Deviations

Protocol deviations will be defined and this analysis plan updated before database lock.

7.8.1. Deviations assessed prior to randomization

At Screening, the investigator will assess subjects against the inclusion and exclusion criteria as set out in Sections 4.1 and 4.2 of the protocol.

7.8.2. Deviations assessed post-randomization

A full list of protocol deviations for the study report will be compiled prior to database closure. Any significant deviation from the protocol will be reviewed prior to database closure and a decision taken regarding evaluation for each analysis population.

8. ENDPOINTS AND COVARIATES

In general, Baseline is defined as the last available data prior to first study medication administration except for the following endpoints the Baseline is defined in Table 3.

Table 3. Baseline definition

Measurement	SAD	MAD
Fasting Weight	Mean of (Day -1, 1)	Mean of (Day -2, -1 and 1)
Temperature	Mean of (Day -1, 1)	Mean of (Day -2, -1 and 1)
Pulse Rate	Mean of (Day -1, 1)	Mean of (Day -2, -1 and 1)
Systolic Blood Pressure	Mean of (Day -1, 1)	Mean of (Day -2, -1 and 1)
Diastolic Blood Pressure	Mean of (Day -1, 1)	Mean of (Day -2, -1 and 1)
Fastimg Plasma Glucose	Mean of (Day -1, 1)	Day 1 pre-dose
Fasting Glucogon	Mean of (Day -1, 1)	Day 1 pre-dose
Fasting GLP-1	Mean of (Day -1, 1)	Day 1 pre-dose

For triplicate ECG and vital signs readings, baseline is defined as the mean value of triplicate mesurements prior to first study medication administration.

8.1. Efficacy Endpoint(s)

n/a.

8.2. Safety Endpoints

8.2.1. Vitals and ECGs

Temperature, supine vital signs will be summarized for the raw data and for the change from baseline data.

Triplicate 12-Lead ECG data will be summarized.

Incidence of QTC ≥500 msec, or ≥ 60 msec above baseline will be summarized.

8.2.2. Laboratory Data

Laboratory parameters will be summarized using summary tables on raw and change from baseline, and shift tables will also be generated.

8.2.3. Adverse Events

The incidence of adverse events will be summarized, for all adverse events (overall), for adverse events by relation to treatment, and adverse events by severity. The summaries will be prepared using Pfizer standards. The incidence of adverse events will be summarized by count of subject incidence. Any events observed following start of treatment or worsening in severity will be counted as treatment emergent.

The following parameters will be summarized:

- Incidence, severity and causal relationship of treatment emergent AEs (TEAEs).
- Incidence and severity of hypoglycemic events.
- Incidence of abnormal laboratory findings.

8.2.4. Anti-Drug Antibody

For subjects developing anti-drug antibody, incidence of abnormal laboratory findings will be summarized. Additional PK/PD subgroup analyses may be performed.

8.3. Pharmacokinetic and Pharmacodynamics Endpoint

8.3.1. PK Endpoints

The following PK parameters (if possible) in Table 2 (SAD Cohorts) and Table 3 (MAD Cohorts) will be calculated for PF-06293620 from the serum concentration-time data using standard noncompartmental methods in Table 4 and Table 5.

Table 4. PK Parameters for SAD Cohorts

PK Parameter	Analysis Scale	PF-06293620
AUC_{inf}*	ln	A, D
AUC_{last}	ln	A, D
C_{max}	ln	D
T_{max}	R	D
$t_{1/2}$*	R	D
V_Z/F* (for SC dose)	ln	D
CL/F* (for SC dose)	ln	D
Vss* (for IV dose)	ln	D
CL (for IV dose)	ln	D
AUC_{inf}(dn)*	ln	D
AUC_{last}(dn)	ln	D
C_{max}(dn)	ln	D

Key: A=analyzed using statistical model, D=displayed with descriptive statistics, ln=natural-log transformed, R=raw (untransformed), *=if data permits

Table 5. PK Parameters for MAD Cohorts

PK Parameter	Day(s)	Analysis Scale	PF-06293620
AUC_{τ}	1, 57	ln	D
C_{max}	1, 57	ln	D
C_{min}	1, 57	ln	D
T_{max}	1, 57	R	D
CL/F	57	ln	D
C_{av}	57	ln	D
$t_{1/2}$*	57	R	D
V_Z/F*	57	ln	D
R_{ac}	57	ln	D
$R_{ac,Cmax}$	57	ln	D
AUC_{τ}(dn)	1, 57	ln	D
C_{max}(dn)	1, 57	ln	D
C_{min}(dn)	57	ln	D

Key: D=displayed with descriptive statistics,
ln=natural-log transformed, R=raw (untransformed), *=if data permits; dn = dose normalized.

8.3.2. PD Endpoints

Pharmacodynamic parameters including:

- Fasting plasma glucose, fasting plasma glucagon, fasting plasma GLP-1, 1,5-anhydroglucitol, fructosamine, HbA1c, AUC0-24hr of blood glucose; and
- Mean daily blood glucose levels (from fingerstick);
- Post-Prandial PD endpoints including: glucose, glucagon, insulin, GLP-1 and C-peptide excursions defined as AUC0-4 (change from baseline) in response to MMTT;
- Apo-B (MAD only).

The relationship between changes in the values of these biomarkers with the pharmacokinetics of PF-06293620 may be explored. Exploratory PK/PD modeling may be performed if visual examination of the data is suggestive of a relationship.

8.3.3. Outcomes Research Endpoints

n/a.

8.4. Covariates

For all analyses of covariance, endpoints baseline measurements are to be used as a covariate. All other potential covariates may be introduced when appropriate.

9. HANDLING OF MISSING VALUES

Missing values will not be imputed.

10. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

10.1. Statistical Methods

- All analyses will be presented by dose group.
- Placebo subjects will be pooled across cohorts for analysis and presentation purpose.
- Continuous data will be summarized using descriptive statistics: number of subjects (n), mean, standard deviation, standard error, median, minimum and maximum. 90% confidence intervals (CI) may be provided for pharmacodynamics endpoints.
- Categorical data will be described using frequencies and percentages. The denominator for all percentages will be the number of subjects for whom there are data in the cohort/treatment group within the analysis set of interest, unless otherwise specified. Counts of subjects with missing data will be presented if applicable.
- All data will be presented in listings. Data that will only be listed (not summarized) are specified in the analysis section.

10.2. Statistical Analyses

Data will be summarized in a descriptive manner. MMRM analysis with treatment, visit, and visit by treatment as fixed effects, subject as a random effect, and baseline value as covariate adopting unstructured covariance structure may be performed as indicated.

10.2.1. Primary Analysis

10.2.2. Safety Analyses

Subject evaluation groups will show end of study subject disposition and will show which subjects were analysed for pharmacokinetics (PK), and for safety (adverse events and laboratory data). Subject counts will be supplied for subject discontinuation(s) by treatment.

A summarization of demographic data will be provided for age, race, weight, and height. Each will be summarized by sex at birth in accordance with the sponsor reporting standards.

- Discontinuations, adverse events, laboratory data, vital signs, ECG and concomitant medication data will be summarized by treatment and in accorandance with current Pfizer data standards. The adverse event risk difference will be summarized by treatment group. No p values and no multiplicity adjustments will be provided.

10.2.2.1. Laboratory Data

Laboratory data outlined in the study protocol will be summarized by study days, and listed in accordance with the sponsor reporting standards. For each planned timepoint, observed values and change from baseline values within each treatment will be summarized with

descriptive statistics. For laboratory parameters with categorical outcomes, subjects counts will be presented for each visit. No screening laboratory values will be presented in the summary tables. Line plots on mean (± 2*SE) will be generated.

10.2.2.2. Vital Signs Data

Observed values and changes from baseline in supine systolic and diastolic blood pressures, and pulse rate will be summarized by treatment and day. For each planned timepoint, observed values and change from baseline values within each treatment will be summarized with descriptive statistics (using sponsor default standards). Mean observed values, and mean changes from baseline will be plotted separately. On each plot there will be separate lines for each treatment, dose group against study day. Data from all treatments will be plotted on the same figure. Plots with and without (±SE) will be produced. For changes from baseline, the differences between each time point and baseline will be summarized (N, mean, 90% confidence interval) and plotted (mean) for each dose and time point (including baseline).

Maximum values and changes from baseline will be summarized descriptively by treatment using categories as defined in Appendix 1. Numbers and percentages of subjects meeting the categorical criteria will be provided. All planned and unplanned postdose timepoints will be counted in these categorical summaries. All values meeting the criteria of potential clinical concern will be listed.

These data will be listed in accordance with the sponsor reporting standards.

10.2.2.3. ECG Data

For each planned timepoint, baseline values and change from baseline values within each treatment will be summarized with descriptive statistics (using sponsor default standards). Absolute values and changes from baseline in PR, QT, QRS, heart rate, and QTcF will be summarized by treatment, and study day using the sponsor reporting standards. Mean plots (change from baseline values only), individual plots and tables for both observed values and change from baseline will be generated.

Changes from baseline in QTcF will be plotted separately against baseline for each planned study days per study window. These will be presented in scatter plots for all observations where QTcFs are recorded. Different symbols will be used for each treatment.

Maximum increase from baseline for QTcF, heart rate, QT, PR and QRS will be summarized by treatment and day. The number and percentages of subjects with QTcF interval ≥ 500 msec at any post-baseline time point will be summarized. The incidence of maximum post-dose QTcF values and maximum increases from baseline will be summarized descriptively (counts and percentages) according to the following categories:

Table 6. QTcF Category

QTcF (ms)	450 - < 480	480 - < 500	≥ 500
QTcF (ms) increase from baseline (ms)	30 - <60	≥ 60	

If more than one ECG is collected at a nominal time post dose, the mean of the multiple measurements will be used to represent a single observation at that time point for summary statistics tabulation. Changes from baseline will be defined as the change between QTcF post-dose and from the pre-dose values on Day 1. ECG endpoints and changes from baseline (QTcF, PR, QRS) will also be summarized descriptively by treatment using categories as defined in Appendix 1 (for QTc these correspond to ICH E14). Numbers and percentages of subjects meeting the categorical criteria will be provided. All planned and unplanned postdose timepoints will be counted in these categorical summaries. All values meeting the criteria of potential clinical concern will be listed.

Listings of subjects with any single change from baseline in QTcF ≥ 60 msec or postdose value ≥500 msec will also be produced. These data will be listed in accordance with the sponsor reporting standards.

10.2.2.4. Evaluation of Drug-Induced Serious Hepatotoxicity

Hepatocellular injury (usually detected by serum ALT or AST elevations) can be caused by drugs that cause severe DILI (eg, aspirin, tacrine, statins, and heparin) as well as by drugs that do cause such injury. In order to properly monitor any sign of drug induced liver injury due to study medication, summary tables of subject incidences according to the following criteria will be generated by timepoints:

- ALT, AST: >3x-, 5x-, 10x- and 20x ULRR;
- Total Bilirubin: > 2x ULRR.

Summary of subject incidence table of subjects having altered liver function that meets Hy's law definition defined below will also be produced.

- ALT or AST ≥3x ULRR;
- Alkaline phosphatase (ALP) ≤ 2x ULRR; and
- Total Bilirubin ≥ 2x ULRR.

Graphs will be produced to examine the peak total bilirubin versus the peak ALT values, and the peak AST values (normalized to the ULRR of the respective lab parameter), respectively, in order to assess the potential DILI. In addition, individual subject line plots, mean (± SE) plots, mean change from baseline (± SE) plots by treatment over time may also be generated if needed.

10.2.2.5. Ambulatory Blood Pressure Monitoring (ABPM)

For MAD portion of the study, ambulatroy blood pressure (ABP) reading will be acquired using the ABPM equipment provided by Biomedical Systems to evaluate potential treatment effect on ABP. Ambumlatory blood pressure are scheduled to be recorded at the following visits:

Table 7. ABPM Visit Schedule

Protocol Visit	Visit code to be selected
Day-2 / Day -1	Day -2
Day 1/ Day 2	Day 1
Day 7/ Day 8	Day 7
Day 63/ Day 64	Day 63
Day 84/ Day 85	Day 84
Unscheduled	UNS
Certification	CERT
Test	TEST

Summary of ABPM measures mSBP, mDBP, mHR, and mMAP represent weighted means of systolic blood pressure, diastolic blood pressure, heart rate and mean arterial pressure (MAP), respectively, and will be summarized in three time increments for a given measurement period: 24 Hour, Day Time (06:00 – 22:00), and Night Time (22:00 – 06:00). mXXX will be calculated using an area under the curve approach over the collection time interval, normalized by the time interval: AUC (0-t) / t. Mean over study days by treatment line plots will be produced along with spaghetti plots of individual profiles over study days grouped by treatment. The number and percentage of subjects with SBP > 140 mmHg, and DBP > 90 mmHg will be tabulated by treatment and Study Day, respectively. Additionally, mSBP, mDBP, mHR, and mMAP response will be modelled using a MMRM with corresponding baseline as covariate, and treatment and visit as fixed factors. Mean change from baseline over time with active treatment may be compared to the mean change from baseline over time with pooled placebo treated subjects using MMRM analysis with treatment, visit, and visit by treatment as fixed effects, subject as a random effect, and baseline value as covariate adopting unstructured covariance structure. For displaying purpose, Mean(± SE) of hourly average of absolute SBP, DBP, HR, MAP, and change from baseline will be plotted by Study Day and 24-hour time per treatment group; by treatment and 24-hour time per Study Day. Line plots of individual 20-min measurements of each subject will be plotted by study Day and time, and group by treatment and dose group. Least square means (± SE) of day Time, Night Time, and 24 Hour mSBP, mDBP, mHR, and mMAP will be plotted by treatment and Study Day. If warranted, a longitudinal Emax model may be developed to further characterize the potential treatment effect on ABPM.

10.2.2.6. Injection Site Reaction Evaluation

The injection sites were assessed for erythema, induration, ecchymosis, injection site pain, injection site pruritus, or other observed characteristics after investigational product administration. Injection site reaction evaluation will be summarized by dose and reaction response over time.

10.2.2.7. Other Safety Data – Screening and Other Special Purpose Data

The number and percentage of subject receiving study treatment administration will be summarized. The immunogenicity findings, for anti-drug PF-06293620) antibodies (ADA) will be summarized. All concomitant medication(s) as well as non-drug treatment(s) will be provided in the listings.

10.2.3. PK Analyses

10.2.3.1. Concentrations below the limit of quantification

In all data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to zero. (In listings BLQ values will be reported as "<LLQ", where LLQ will be replaced with the value for the lower limit of quantification.)

10.2.3.2. Deviations, missing concentrations and anomalous values

In summary tables and plots of the median values at each time point, statistics will be calculated having set concentrations to missing if 1 of the following cases is true:

1. A concentration has been collected as ND (ie not done) or NS (ie no sample),

2. A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist.

Note that summary statistics will not be presented at a particular time point if more than 50% of the data are missing.

10.2.3.3. Pharmacokinetic parameters

Actual PK sampling times will be used in the derivation of PK parameters.

If a PK parameter cannot be derived from a subject's concentration data, the parameter will be coded as NC (ie not calculated). (Note that NC values will not be generated beyond the day that a subject discontinues.)

In summary tables, statistics will be calculated by setting NC values to missing; and statistics will not be presented for a particular treatment if more than 50% of the data are NC. For statistical analyses (ie analysis of variance), PK parameters coded as NC will also be set to missing.

If an individual subject has a known biased estimate of a PK parameter (due for example to an unexpected event such as coughing during or immediately after inhalation before all of the drug is absorbed by the body), this will be footnoted in summary tables and will not be included in the calculation of summary statistics.

To assess the pharmacokinetics of PF-06293620, PK parameters will be listed and summarized for subjects in the PK analysis set (as defined in Section 7). Missing values will be handled as detailed above.

The PK parameters to be summarized by treatment are outline in Table 8.

Table 8. SAD and MAD Cohorts PK Parameters:

Parameter	Summary statistics
SAD Cohort	
AUCinf, AUClast, Cmax, Vz/F, Vss, CL/F, CL, AUCinf(dn), AUClast(dn), Cmax(dn)	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean, geometric CV%.
T_{max}	N, median, minimum, maximum.
$t_{1/2}$	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum.
MAD Cohorts	
AUC_{τ}, C_{max}, C_{min}, CL/F, C_{av}, V_Z/F, $R_{ac,}$ $R_{ac,Cmax}$, AUC_{τ}(dn), C_{max}(dn), C_{min}(dn)	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean, geometric CV%.
T_{max}	N, median, minimum, maximum.
t½	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum.

SAD Cohorts: To assess the relationship between the PK parameters and dose, dose normalized AUC_{inf}, AUC_{last} and C_{max} will be plotted against dose (using a logarithmic scale), and will include individual subject values and the geometric means for each dose. Geometric means will have a different symbol than the individual values. The values will be dose normalized (to a 1 mg/kg dose) by dividing the individual values and raw geometric means by dose. A footnote will be added to the plots to indicate that geometric means are presented on the plot.

Absolute/Relative bioavailability will be estimated as the ratio of dose-normalized adjusted geometric means for SC and IV for AUC_{last} and AUC_{inf}.

MAD Cohorts: To assess the relationship between the PK parameters and dose, dose normalized AUCτ and Cmax on Days 1 and 57, and dose normalized Cmin on Day 57, will be plotted against dose (using a logarithmic scale), and will include individual subject values and the geometric means for each dose. Geometric means will have a different symbol than the individual values. The values will be dose normalized (to a 1 mg/kg dose) by dividing the individual values and raw geometric means by dose. A footnote will be added to the plots to indicate that geometric means are presented on the plot.

Dose-normalized natural log transformed AUC (SAD):AUC_{inf} (data permitting) and AUC_{last}; and AUCτ (MAD)will be analyzed using a mixed effect model with treatment as fixed effects and subject as a random effect using a one-way analysis of variance (ANOVA). Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals will be obtained from the model. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% confidence intervals for the ratios. SC is the Test treatment , and the IV is the Reference treatment.

Residuals from the model will be examined for normality and the presence of outliers via visual inspection of plots of residuals vs predicted values and normal probability plots of residuals but these will not be included in the clinical study report. If there are major deviations from normality or outliers then the effect of these on the conclusions will be investigated through alternative transformations and/or analyses excluding outliers. Justification for any alternative to the planned analysis will be given in the report of the study.

10.2.3.4. PK Concentrations

To assess the single dose PK profile of PF-06293620, PK concentrations will be listed, summarized and plotted for subjects in the PK analysis set (as defined in Section 7), where missing and BLQ values will be handled as detailed in Section 10.2.3.1 above.

Presentations for PF-06293620 will include:

- A listing of all concentrations sorted by dose, subject ID, period (for SAD) or day (for MAD) and nominal time postdose. The listing of concentrations will include the actual sample collection times, and the time of dosing. Deviations from the nominal time will be given in a separate listing.

- A summary of concentrations by dose (and Day, for MAD), and nominal time postdose, where the set of statistics will include n, mean, median, standard deviation, coefficient of variation (cv), minimum, maximum and the number of concentrations above the lower limit of quantification.

- Median concentrations against nominal time postdose by dose (based on the summary of concentrations by dose and time postdose), with all doses presented on the same plot. Two plots will be generated, so that the concentrations can be presented on linear and logarithmic scales. For MAD separate plots will be generated for Day 1 and Day 57.

- Mean concentrations against nominal time postdose by dose (based on the summary of concentrations by dose and time postdose), with all doses presented on the same plot. Two plots will be generated, so that the concentrations can be presented on linear and logarithmic scales. For MAD separate plots will be generated for Day 1 and Day 57.

- Plots of individual concentrations against actual time postdose by treatment (separate plots for each dose, and for Days 1 and 57 of MAD). Two plots per dose and Day will be generated, so that the concentrations can be presented on linear and logarithmic scales.

- Plots of concentration against actual time postdose by subject (separate line for each dose for SAD, and for Days 1 and 57 of MAD). Two plots per subject will be generated, so that the concentrations can be presented on linear and logarithmic scales.

The range for the x-axes of these plots will be decided on review of the data, and will depend on how long PF-06293620 concentration is quantifiable in the matrix.

For summary statistics and median plots by sampling time, the nominal PK sampling time will be used. For individual subject plots by time, the actual PK sampling time will be used.

10.2.4. Pharmacodynamic Analyses

PD biomarker data will include fasting plasma glucose, fasting glucagon, fasting GLP-1, 24-hr glucose profile (finger-stick), mean daily glucose profile, HbA1c, fructosamine, 1,5-anhydroglucitol, and glucose, insulin, C-peptide, glucagon and GLP-1 AUC after mixed meal tolerance test (MMTT, 4 hr). The relationship between changes in the values of these biomarkers with the pharmacokinetics of PF-06293620 may be explored. Exploratory PK/PD modeling may be performed if visual examination of the data is suggestive of a relationship.

The change and percentage change from baseline for PD biomarkers over the period of the study will be tabulated by treatment. The mean change from baseline values over time per cohort will also be tabulated. Data will be presented in tabular and graphical format and summarized descriptively. Descriptive statistics on change from baseline in fasting plasma glucose, fasting glucagon, fasting GLP-1, 24-hr glucose profile (finger-stick), HbA1c, fructosamine, 1,5-anhydroglucitol, and glucose, insulin, C-peptide, glucagon and GLP-1 AUC after mixed meal tolerance test (MMTT, 4 hr), and lipid parameters will be provided separately for each treatment and the pooled placebo group. The mean change from baseline over time with active treatment may be compared to the mean change from baseline over time with pooled placebo treated subjects using MMRM analysis with treatment as fixed effect, subject as a random effect, and baseline value as covariate adopting unstructured covariance structure. Figures of absolute values, change from baseline, and percentage change from baseline over time may be produced if needed.

The relationship between changes in the values of these biomarkers with the pharmacokinetics of PF-06293620 will be explored. Exploratory PKPD modeling may be performed if visual examination of the data is suggestive of a relationship.

10.2.5. Summary of Efficacy Analyses

n/a.

11. REFERENCES

1. "A PHASE 1 DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED,SINGLE-ASCENDING DOSE STUDY TO ASSESS THE SAFETY, TOLERABILITY,AND PHARMACOKINETICS OF PF-06293620 IN SUBJECTS WITH TYPE2 DIABETES MELLITUS" Final Protocol Amendment 3 dated 02OCT2015.

12. APPENDICES

Appendix 1. Definition and use of visit windows in reporting

All analyses and summary tables will be conducted based on the Visit Window definition.

Single-Ascending Dose Cohort:

Study Day	Window
Screening	[-28 , -2]
1 (Baseline)	[-1,1]
2	2
3	3
4	4
5	5
8	[6, 12]
15	[13, 18]
16	(Day 15, Day 15 + 24 Hour]
22	(Day 15 + 24 Hour, 25]; if Day 15 is missing, then [19, 25]
29	[26, 36]
30	(Day 29, Day 29+24 Hour]
43	(Day 29+24 Hour, 50]; if Day 29 is missing, then [37,50]
57	[51, 70]
85	[71, 100]

If no planned visit data available, data collected on unplanned visits will follow the following selection criteria to determine its evaluation eligibility:

1. Order data based on the collection date
2. Calculate the corresponding study days for variables
3. Based on the visit window definition to associate each data with proper Visit Window
4. Within each window, data collected with study days closer to the planned visit days will be chosen for analysis.
5. If multiple data records with equal distance to a study planned visit, the one collected prior to the study planned visits will be used for analysis.

Multiple-Ascending Dose Cohort:

Study Day	Window
Screening	-50 - -4
Day -3	Nominal Day -3
Day -2	Nominal Day -2
Day -1	Nominal Day -1
Day 1	1
Day 2	2
Day 3	3
Day 6	4-6
Day 7	Nominal Day 7
Day 8	Nominal Day 8
Day 15	13, 20
Day 27	Nominal Day 27
Day 28	Nominal Day 28
Day 29	Nominal Day 29
Day 36	Nominal Day 29 +1,40
Day 43	41, 53
Day 57	Nominal Day 57
Day 58	Nominal Day 58
Day 59	Nominal Day 59
Day 62	**Nominal Day 59 +1, Nominal Day 63-1**
Day 63	**Nominal Day 63**
Day 64	Nominal Day 64
Day 71	Nominal Day 64+1, 75
Day 78	76 - 80
Day 84	Nominal Day 84
Day 85	Nominal Day 85
Day 99	Nominal Day 85 + 1 -105
Day 113	106 - 130
Day 141	131 - 160
Day 169	161 - 200

If no planned visit data available, data collected on unplanned visits will follow the following selection criteria to determine its evaluation eligibility:

1. Order data based on the collection date
2. Calculate the corresponding study days for variables
3. Based on the visit window definition to associate each data with proper Visit Window
4. Within each window, data collected with study days closer to the planned visit days will be chosen for analysis.
5. If multiple data records with equal distance to a study planned visit, the one collected prior to the study planned visits will be used for analysis.

Appendix 2. Categorical Classes for Vital Signs, QTcF, PR and QRS

Categories for Vital Signs

Systolic BP (mm Hg)	min. <90	
Systolic BP (mm Hg) change from baseline	max. decrease ≥30	max. increase ≥30
Diastolic BP (mm Hg)	min. <50	
Diastolic BP (mm Hg) change from baseline	max. decrease ≥20	max. increase ≥20
Supine pulse rate (bpm)	min. <40	max. >120
Standing pulse rate (bpm)	min. <40	max. >140

- Measurements that fulfill these criteria are to be listed in Appendix A of the report

Categories for QTcF

QTcF (ms)	450≤ max. <480	480≤ max.<500	max. ≥500
QTcF (ms) increase from baseline	30≤ max. <60	max. ≥60	

Categories for PR and QRS

PR (ms)	max. ≥300	
PR (ms) increase from baseline	Baseline >200 and max. ≥25% increase	Baseline ≤200 and max. ≥50% increase
QRS (ms)	max. ≥200	
QRS (ms) increase from baseline	Baseline >100 and max. ≥25% increase	Baseline ≤100 and max. ≥50% increase

Appendix 3. Definition of Protocol Deviations that relate to statistical analyses/populations

To be updated.

Appendix 4. Table Shells

To be provided.