CLINICAL PHARMACOLOGY PROTOCOL

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:	N/A
US IND Number:	118,523
European Clinical Trial Database (EudraCT) Number:	N/A
Protocol Number:	B3501001
Phase:	Phase 1a

Document History

Document	Version Date	Summary of Changes
Amendment 3	02 October 2015	Protocol Administrated Clarification Letters were incorporated to clarify Day 36 visit was added to allow for monitoring of vital signs, safety labs/PK 7 days after second dose (PACL 09OCT2015) and collection of ADA samples on Day -1 for all subjects enrolled in the MAD portion (PACL 22OCT2015) (Schedule of Activities- MAD). Added adverse event, concomitant medication and metformin compliance to all visits (Schedule of Activities – MAD). Contraception check added to Day -3 (Schedule of Activities – MAD). Footnote d: language was added to clarify duration of ADA and glucagon testing (Schedule of Activities- MAD). Footnote e: Language removed regarding timing of study drug administration on days when MMTT is performed. In MAD cohorts, MMTT and dosing does not occur on the same day in the MAD cohorts. Footnote l: Mean Daily Glucose profile text corrected to document the sample is assessing plasma glucose and clarify the timing of samples related to meals (Schedule of Activities- MAD). Footnote n: language added to clarify the placement of a PIV/ is optional (Schedule of Activities- MAD). Footnote p: Added to define requirements of safety lab tests required on Day 36 and Day 64 (Schedule of Activities- MAD). Footnote q: added to clarify that the dosing window for Days 29 and 57 may be extended to ±2 days to allow for evaluation of

		previously elevated ALT/AST >5xULN (Schedule of Activities- MAD). Footnote r: language was added to clarify ADA testing requirements for subjects who previously participated in a SAD cohort (Schedule of Activities- MAD). Language added for circumstances under which dosing should be interrupted in the MAD cohorts (Section 3.3). Exclusion Criteria #21: language added to clarify timing between dose on SAD and first dose on MAD and ADA/glucagon requirements for subjects who participate in both cohorts (Section 4.2). Exclusion #33: specific upper limit added for platelet count. Exclusion Criteria #36: added to exclude subjects with creatine kinase >2xULN (Section 4.2). Langauge added to describe meal requirements on days when mean daily glucose profile assessments are performed (Sections 4.4.1; 6.3.2; 6.3.12 and 6.3.25). Language removed regarding timing of study drug administration on days when MMTT is performed. In MAD cohorts, MMTT and dosing does not occur on the same day in the MAD cohorts. Deleted non-relevant template language (Section 5.2.4). Baseline creatine kinase added to screening visit for subjects enrolling in MAD cohorts only (Section 6.1). Added contraception check to Day -3 (Section 6.3.1). Added language to clarify the placement of PIV/heplock is optional (Sections 6.3.1;

		6.3.7; 6.3.11; 6.3.19 and 6.3.24). Language added to clarify the requirements for uploading the ABPM data to the vendor for the QC process (Sections 6.3.3, 6.3.5, 6.3.9, 6.3.21, 6.3.26 and 7.2.8). Day 36 visit and procedures added (Section 6.3.14). Added safety laboratory/liver function tests to Day 64 (Section 6.3.21). Banked specimen added at Day 85 visit (Section 6.3.26). Language added for extended follow-up requirements for elevated LFTs; (Section 6.3.29). Language clarified for duration of extended follow-up for elevated glucagon/ADA levels (Sections 6.3.29; 7.2.13; 7.4.1.1). Total blood volume increased to account for Day 36, Day 64 blood draws and additional banked specimen on Day 169 (Section 7.1). Table 9 Laboratory Tests: creatine kinase added to chemistry test. Language added to standardize the collection of blood pressure and pulse (Section 7.2.4). Language added to describe interpretation by vendor and Principal Investigator (Section 7.2.6). Language added to clarify meal requirements during the mean daily glucose profile (Section 7.2.10). Langauge added to require reporting of elevated ALT/AST ≥3xULN as AE (Section 8.4).

		Grade 0 added to Severity Assessment table (Section 8.7). Tables provided showing standard abbreviations and which parameters are applicable for SAD and MAD; added dose normalized parameters; removed derived via statistical analysis from the parameter table and describe the statistical methods in text instead (Section 9.3.1). Language revised to align with Section 9.3.1 (Section 9.3.2). Definition of baseline added (Section 9.4). Multiple minor editorial clarifications throughout the protocol to correct typos, syntax, format etc.; add clarity, and alignment across sections.
Amendment 2	05 June 2015	Protocol Administrated Clarification Letters (PACL) were incorporated to clarify contraception requirements for male subjects (PACL 16NOV2014); clarify collection of triplicate vital signs and Fasting Plasma Glucose/Glucagon/GLP-1 in conjunction with MMTT (PACL 04NOV2014); clarify collection of vital signs in Day 1 and change to Section 8.7 Severity Assessment, change of severity coding for AEs from Mild/Moderate/Severe to CTCAE Grade 1-5 (PACL 05FEB2015); SAD Dose escalation based on all subjects enrolled and at least 6 of 8 subjects completing Day 15 (PACL 30APR2015) Removed reference to the 10 mg/kg IV SAD Cohort (Sections 1.3.3, 3.1) Added preliminary, unpublished, safety and PK data from first 4 SAD Cohorts. (Section 1.3.2) Added Multiple Ascending Dose (MAD)

		Schedule of Activites Added language for Multiple Ascending Dose Cohorts (Sections 1.2, 1.3.1, 1.3.3, 3.1, 3.2 and 3.3, 5.1, 5.2.4, 7.1, 7.2.6, 7.4.1.2, 9.1) Inclusion & Exclusion critieria updated for MAD cohorts (Sect 4.1 & 4.2) Added Rescue Therapy for MAD cohorts (Section 5.5). Revised study period (Sect 6.2) to focus on SAD cohort and added MAD specifc study period (Section 6.3). Added language to clarify proper collection technique for blood pressure and pulse (Section 7.2.4). Added language for Ambulatory Blood Pressure Monitoring (Section 7.2.8). Added language for Mean Daily Glucose Profile (Sections 7.2.10 & 7.4.1.4). Added language to allow potential use of PK samples for the evaluation of bioanalytical methods (Section 7.4). Additional PK parameter added for evaluation (Section 9.3.1). Added central review of MAD ECGs (Section 9.5.1). Added Interim Analysis (Section 9.7). Updated Sponsor publications template language (Section 15.1).
Amendment 1	12-JUN-2014	Schedule of Activities – extended follow-up from Day 57 to Day 85 necessitating an additional visit; revised procedures to align with end of treatment at Day 85 (SOA and

		Sect. 6.2.11) Clarified CTCAE listed in toxicity criteria with detailed definitions; provided timeframe for history of severe hypoglycemia; clarified exclusion for drug allergies and positive drug screen for prescription medications (Sect. 3.2.1) Added exclusion criterion for type 1 diabetes mellitus and pancreatic neuroendocrine neoplasm (Sect. 4.2) Clarified restrictions on caffeine (Sect. 4.4) Provided instructions on how to measure waist circumference (Sects 6.2.2, 6.2.12 and 7.2.3) Added vital signs at 1 hour post-dose (Sect. 6.2.3) Revised blood volume to account for additional visit (Sect. 7.1) Clarified post-study follow-up for ADA to avoid indefinite follow-up (Sect. 7.2.11) Clarified post-study follow-up for glucagon to avoid indefinite follow-up (Sect. 7.4.1) Clarified which physical exams will be collected for the database (Sect. 9.5) Multiple minor editorial clarifications throughout the protocol to correct typos, syntax, format etc.; add clarity, and alignment across sections Updated Medication Errors language, Adverse Event language, and Communication of Results by Pfizer

		language.
Original protocol	18-FEB-2014	N/A

This amendment incorporates all revisions to date including amendments made at the request of country health authorities, institutional review boards/ethics committees (IRBs/ECs), etc.

SUMMARY

PF-06293620 (RN909) is a glucagon receptor antagonist being developed for the treatment of type 2 diabetes mellitus (T2DM).

Glucagon counteracts glucose-lowering by insulin via the promotion of hepatic glucose production, thereby maintaining euglycemia and protecting against hypoglycemia; thus, mitigating the effects of hyperglucagonemia in T2DM is an attractive approach for treating hyperglycemia.

PF-06293620 is a humanized IgG2Δa monoclonal antibody that binds to, and blocks glucagon signaling through, the human glucagon receptor. PF-06293620 ameliorates elevations in plasma glucose, which are in part mediated by hyperglucagonemia, through normalization of dysregulated hepatic glucose production. Furthermore, as this mechanism is not dependent on functional pancreatic beta cells, it is anticipated to have a durable effect of improved glycemic control in subjects with T2DM.

The first-in-human study is a randomized, double-blinded (Sponsor-open), placebo-controlled, single ascending-dose (SAD) and multiple ascending dose (MAD) study in subjects with T2DM on a stable regimen of metformin. This population was chosen because it is the target population for this investigational drug and the preclinical studies support its safety for initiating clinical trials in medically-stable T2DM subjects. The SAD portion of the study will be conducted in approximately 5 planned cohorts (a 6:2 ratio of active drug to placebo) with a total of up to approximately 40 subjects in an effort 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) after the SC doses.

Based on a review of the preliminary, unpublished safety, pharmacokinetics (PK) and pharmacodynamics (PD) results from the first four SAD dose cohorts, a randomized, double-blind (Sponsor open), placebo-controlled, multiple ascending dose (MAD) portion will be initiated to evaluate the safety and tolerability of ascending multiple dosages and dosing-schedules. The MAD cohorts will run in parallel with the remaining SAD cohorts. This portion will be conducted in approximately 4 planned cohorts (a 8:2 ratio of PF-06293620:placebo) with a total of up to approximately 40 subjects in an effort to seek a maximum tolerated dose (MTD) when multiple doses are administered. Both subjects and the site personnel will be blinded to treatment and treatment regimen. The Q4 week dosing cohorts subjects will receive a subcutaneous administration of study drug (PF-06293620 or placebo) every 4 weeks (on Days 1, 29 and 57) at 75 mg, 150 mg or 250 mg. 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. Ongoing MAD safety data will be used to determine the dose and dose regimen of the fourth planned cohort. At no time will the MAD dose exceed the PK exposure from the SAD. An additional fifth cohort may be studied to obtain further safety and PK data, increasing the planned total number of subjects to approximately 50.

The MAD cohorts will run in parallel with the later (Cohort 4 and higher) cohorts of the SAD study. Subjects who participate in the SAD portion of the study and tolerate PF-06293620 may enroll in the MAD portion of the study after a sufficient wash-out period, if they are negative for anti-drug antibodies (ADA), and they meet all other eligibility criteria.

Plasma glucagon and GLP-1 levels will be used as biomarkers to assess pharmacodynamics (PD) related to target modulation. A number of glycemic parameters will be used to assess pharmacodynamics related to glycemic control: fasting plasma glucose (FPG), postprandial glycemia (during mixed meal tolerance test [MMTT]), 24 hour glucose area under the curve (AUC) and mean daily glucose (from fingerstick assessment), 1,5-anhydroglucitol, fructosamine and HbA1c. In conjunction with some of these tests (eg, MMTT), insulin and C-peptide levels will also be measured to gain additional insights into PF-06293620 effects on glucose homeostasis.

The primary objective of this first in human study is to evaluate the safety, tolerability and immunogenicity of single, ascending, subcutaneous (SC) and intravenous (IV) administration of PF-06293620 and multiple, ascending SC administration of PF-06293620 in subjects with T2DM on stable doses of metformin.

The secondary objective is to characterize the pharmacokinetics of PF-06293620 after administration of single-doses of SC and IV PF-06293620 and multiple-dose of SC PF-06293620 to subjects with T2DM on stable doses of metformin. Exploratory objectives include characterizing the pharmacodynamics of PF-06293620 and characterizing the effect of PF-06293620 on glucose, insulin, GLP-1, C-peptide and glucagon excursions over 4 hrs following an MMTT, and 24 hour glucose profiles. Additional exploratory objectives in the MAD portion will include 24 hour ambulatory blood pressure monitoring, and central review of electrocardiograms (ECGs).

This study is exploratory in nature; no pre-planned hypothesis testing is to be performed. The sample size determination is not based on statistical power considerations. Dose cohort size in the SAD portion is generally 8 subjects with a 6:2 ratio of active drug to placebo in a randomized manner and is generally 10 subjects with a 8:2 ratio of active drug to placebo in a randomized manner in the MAD portion. Additional subjects may be added at a dose level to further evaluate safety and/or tolerability after discussions between the Pfizer study team and the investigators.

Adverse events, electrocardiograms (ECG), blood pressure, pulse rate, continuous cardiac monitoring (SAD only), ambulatory blood pressure monitoring (MAD cohorts only), and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of subjects. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

The serum pharmacokinetic (PK) parameters ($AUC_{(0-\infty)}$, C_{max}, C_{av}, C_{min}, $AUC_{(0\text{-}t[last])}$, AUC_{τ}, T_{max}, $T_{1/2,}$ R_{ac}, CL or CL/F, Vz/F or Vss and F) for RN909 (PF-06293620) will be summarized descriptively by dose as appropriate. Serum concentrations will be listed and summarized descriptively by dose and nominal PK sampling time. Individual subject,

summary profiles (mean and median plots) of the serum concentration-time data will be plotted by treatment and PK sampling time.

The change and percentage change from baseline for PD biomarkers over the period of the study will be tabulated by individual subject. Summary statistics of change from baseline values over time per dose group will also be tabulated. Data will be presented in tabular and/or graphical format and summarized descriptively. Placebo subjects will be pooled across all dose cohorts for the respective stages of the study, ie, SAD placebo subjects and MAD placebo subjects. To explore the treatment effect, the mean change from baseline over time with active treatment will be compared to the mean change from baseline over time with placebo treated subjects.

Schedule of Activities for Single-Ascending Dose Cohorts

The Schedule of Activities table provides an overview of the protocol visits and procedures for the SAD cohorts. 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.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the wellbeing of the subject.

Protocol Activity	Screen -28 to -3	Day -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 15	Day 16	Day 22	Day 29	Day 30	Day 43	Day 57	Day 85/ET
Admission to/Discharge from CRU		X	→	→	→	→	→	X									
Visit window	N/A	N/A	N/A	0	0	0	0	0	±1	±1	N/A	±1	±2	N/A	±3	±3	±3
Informed Consent	X																
Inclusion/Exclusion criteria	X																
Demographic Data	X																
Medical History	X		X														
Full Physical Exam	X							X									
Limited Physical Exam			X							X			X			X	X
Height [a]	X																
Fasting Weight [a]	X		X	X			X	X		X			X			X	X
Triplicate Waist Circumference[a]			X														X
Single Supine 12-lead ECG	X																
Triplicate 12-Lead ECG[j]				X	X			X		X			X			X	X
Single Supine Vital Signs[b]	X																
Temperature, supine pulse & triplicate supine blood pressure[b]			X	X	X	X	X	X	X	X		X	X		X	X	X
Screening Labs[c]	X																
Urine Drug Screen	X	X															
Hematology	X			X	X			X	X	X		X	X		X	X	X
Blood Chemistry (fasting)	X			X	X			X	X	X		X	X		X	X	X

Protocol Activity	Screen -28 to -3	Day -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 15	Day 16	Day 22	Day 29	Day 30	Day 43	Day 57	Day 85/ET
Visit Window	N/A	N/A	N/A	0	0	0	0	0	±1	±1	N/A Outpatient	±1	±2	N/A Outpatient	±3	±3	±3
Urinalysis (clean catch; mid-stream)	X			X	X			X	X	X		X	X		X	X	X
Fasting Lipid Profile	X		X				X			X			X			X	X
Coagulation panel, Serum Amylase and Lipase	X			X				X		X			X			X	X
HbA1c	X		X										X			X	X
Fasting Plasma Glucose[l]	X			X (SC only)	X	X	X (IV only)	X	X			X			X	X	X
Fasting Plasma Glucagon[d,l]				X (SC only)	X	X	X (IV only)	X	X			X			X	X	X[d]
Fasting Plasma GLP-1[l]				X (SC only)			X (IV only)									X	X
Mixed Meal Tolerance Test – SC cohorts[e]			X				X			X			X				
Mixed Meal Tolerance Test – IV cohorts[e]			X	X						X			X				
24h glucose profiles (fingersticks)[f]			X	X	X (0300 & pre-breakfast only)		X	X (0300 & pre-breakfast only)		X	X (0300 & pre-breakfast only)		X	X (0300 & pre-breakfast only)			
Fructosamine			X				X			X			X			X	X
1,5-anhydroglucitol			X				X			X			X			X	X
Serum PK Samples				X[g]	X[k]	X	X	X	X	X		X	X		X	X	X
Serum Anti-PF-06293620 Antibodies Samples (ADA)			X							X			X			X	X[d]
Banked biospecimens			X														
Cardiac Telemetry			X	X	X												
Randomization			X														
Administer Study Drug				X													

Injection site assessment/infusion reaction assessment[h]				X	X			X									
Metformin compliance[i]			X							X			X			X	X
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	X		X	X		X	X	X
Contraception check[m]	X	Refer to Sections 4.4.3.2 & 4.4.3.3															
Adverse Event Monitoring		X	X	X	X	X	X	X	X	X		X	X		X	X	X

a. Weight measure in gown, undergarments and socks while fasting and empty bladder. Height measured with wall-mounted stadiometer at screening only in stocking feet and carried forward.

b. Vital signs: blood pressure, pulse, temperature. Only blood pressure should be collected in triplicate. On Day 1 obtain vital signs prior to dose and at 1, 2, 4, 8 and 12 hours after dosing.

c. Screening labs include FSH in women only, TSH, C-peptide, HIV, hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody.

d. Subjects will continue to be monitored beyond the last scheduled visit, if necessary, for elevated glucagon or ADA levels (at approximately 1-3 month intervals) until their glucagon/ADA levels return to approximate baseline or establish a new steady-state level.

e. Samples for MMTT assessment should be collected prior to the MMTT (0 minutes/fasting) and after the start of the liquid meal at 15, 30, 60, 120, 180 and 240 minutes. Blood glucose, C-peptide, insulin, glucagon and GLP-1 will be measured at all timepoints.

f. Fingersticks with glucometer measurements to be taken before breakfast (fasting), 2-hr post-breakfast, before lunch, 2-hr post-lunch, before dinner, 2-hr post-dinner, prior to snack (between 9 and 10 pm) at 0300 and before breakfast (fasting) the following day (Day 2, Day 5 Day 16 & Day 30). Day 16 and Day 30 are performed by the subjectat home, no clinic visit required.

g. PK Day 1: sample at hours 0 (predose), 1, 4, 8, and 12 hours after dosing.

h. Perform injection site assessment immediately after injection, 15 minutes, 30 minutes, 1 hour, and 2 hours post administration. Additional assessments should be performed as needed after the last assessment of 2 hrs post-dose on Day 1.

i. Subject to be questioned about compliance with metformin.

j. Triplicate ECG: All ECGs will be reviewed at the site. On Day 1, collect triplicate ECG at 1, 2, 4, 8 and 12 hours after dosing.

k. PK Day 2: samples collected at 24 and 36 hours after Day 1 dosing.

l. Fasting plasma glucose, glucagon and GLP-1 are not collected on days when MMTT are performed – these analytes will be captured as part of the MMTT Time 0/fasting timepoint.

m. Confirm subject is using appropriate contraception methods per Sections 4.4.3.2 and 4.4.3.3 for methods and duration.

Schedule Of Activities for Multiple-Ascending Dose Cohorts

The Schedule of Activities table provides an overview of the protocol visits and procedures for the MAD cohorts. 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.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the wellbeing of the subject.

Study Period	Screen	Baseline				Treatment																					Follow-up			
Study Day/Protocol Activity	-42 to -4	-3	-2	-1	1	2	3	6	7	8	15	27	28	29[q]	36	43	57[q]	58	59	62	63	64	71	78	83	84	85	99	113	141	169/ ET
Visit window	N/A	0	0	0	0	0	0	0	0	0	±1	±1	0	0	±1	±1	±1	0	0	±1	0	0	±1	±1	+1	0	0	±5			
In Patient Stay		X	→	→	→	→	X	X	→	X		X	→	X						X	→	X			X	→	X				
Informed Consent	X																														
Inclusion/Exclusion criteria	X																														
Demographic Data	X																														
Medical History	X			X																											
Full Physical Exam	X					X																									
Limited Physical Exam				X							X			X			X										X				X
Height[a]	X																														
Fasting Weight[a]	X		X	X	X	X	X		X	X	X		X	X	X	X	X				X	X	X			X	X	X	X	X	X
Triplicate Waist Circumference				X																							X				X
Single Supine 12-lead ECG	X																														
Triplicate 12-Lead ECG[j]					X	X				X	X			X			X				X		X				X				X
Single Supine Vital Signs[b]	X																														
Temperature, supine pulse & supine triplicate blood pressure[b]			X	X	X	X	X		X	X	X		X	X	X	X	X				X	X	X			X	X	X	X	X	X
Screening Labs[c]	X																														
Urine Drug Screen	X	X																													
Hematology	X			X	X	X				X	X			X		X	X						X				X		X		X
Blood Chemistry (fasting)	X			X	X	X				X	X			X	X[p]	X	X					X[p]	X				X	X	X	X	X

	Screen	Baseline				Treatment																					Follow-up			
Study Day/Protocol Activity	**-42 to -4**	**-3**	**-2**	**-1**	**1**	**2**	**3**	**6**	**7**	**8**	**15**	**27**	**28**	**29[q]**	**36**	**43**	**57[q]**	**58**	**59**	**62**	**63**	**64**	**71**	**78**	**83**	**84**	**85**	**99**	**113**	**141**	**169/ ET**
Visit Window	N/A	0	0	0	0	0	0	0	0	0	±1	±1	0	0	±1	±1	±1	0	0	±1	0	0	±1	±1	+1	0	0	±5			
Urinalysis (clean catch; mid-stream)	X				X	X				X	X			X		X	X						X				X				X
Fasting Lipid Profile	X			X						X	X			X		X	X					X	X				X		X		X
Apo-B	X			X						X	X			X		X	X					X	X				X		X		X
Coagulation panel, Serum Amylase and Lipase	X				X						X			X			X										X				X
HbA1c	X			X										X			X										X		X	X	X
Fasting Plasma Glucose[k]	X				X	X	X				X		X	X	X	X	X	X	X				X	X		X	X	X	X	X	X	X
Fasting Plasma Glucagon[k]					X	X	X							X		X	X						X	X			X	X	X	X	X	X[d]
Fasting Plasma GLP-1[k]					X									X			X							X			X		X		X	X
Mixed Meal Tolerance Test[e]				X						X												X										
24h glucose profiles (fingersticks)[f]				X	end					X												X										
Mean Daily Glucose Profile[l]			X	end									X	end												X	end					
24 hour ambulatory BP monitoring[m]			X	end	X	end			X	end											X	end				X	end					
Fructosamine				X							X			X			X						X				X		X		X
1,5-anhydro-glucitol				X							X			X			X						X				X		X		X
Serum PK Samples[g]					X[g]	X	X		X	X	X	X	X	X[g]	X	X	X[g]	X	X		X	X	X	X		X	X	X	X	X	X	X

	Screen	Baseline				Treatment																						Follow-up			
Study Day/Protocol Activity	**-42 to -4**	**-3**	**-2**	**-1**	**1**	**2**	**3**	**6**	**7**	**8**	**15**	**27**	**28**	**29[q]**	**36**	**43**	**57[q]**	**58**	**59**	**62**	**63**	**64**	**71**	**78**	**83**	**84**	**85**	**99**	**113**	**141**	**169/ ET**
Visit Window	N/A	0	0	0	0	0	0	0	0	0	±1	±1	0	0	±1	±1	±1	0	0	±1	0	0	±1	±1	+1	0	0	±5			
Serum Anti-PF-06293620 Antibodies Samples (ADA)[d]	X[r]			X							X			X			X										X		X	X	X[d]
Banked Specimens				X																							X				
Randomization				X																											
Administer Study Drug					Refer to Section 3.1 for cohort dosing schedules																											
Injection site assessment[h]					Refer to Section 3.1 for cohort dosing schedules																											
Placement of Peripheral IV/HepLock[n]		X	→	→	→	→	X	X	→	X		X	→	X						X	→	X			X	→	X				
Metformin compliance[i]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/ Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Monitoring		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Contraception check[o]	X	X	Refer to Sections 4.4.3.2 & 4.4.3.3																												

a. Weight measure in gown, undergarments and socks (or in comparable standard garments used by the CRU) while fasting and empty bladder. Height measured with wall-mounted stadiometer at screening only in stocking feet and carried forward.

b. Vital signs: blood pressure, pulse, temperature. Only blood pressure should be collected in triplicate. On dosing days obtain at prior to dose and at 1, 2, and 4 hours after dosing.

c. Screening labs include FSH in women only, TSH, C-peptide, HIV, hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody.

d. Subjects will continue to be monitored, at approximately 1-3 month intervals, for up to 9 months beyond the last scheduled visit, if necessary, for elevated glucagon levels and/or presence of anti-PF-06293620 antibodies,

e. Samples for MMTT assessment should be collected prior to the MMTT (0 minutes/fasting) and after the start of the liquid meal at 15, 30, 60, 120, 180 and 240 minutes. Blood glucose, C-peptide, insulin, glucagon and GLP-1 will be measured at all timepoints.

f. Fingersticks with glucometer measurements to be taken before breakfast (fasting), 2-hr post-breakfast, before lunch, 2-hr post-lunch, before dinner, 2-hr post-dinner, prior to snack (between 9 and 10 PM) and then at 0300 and before breakfast (fasting) the following days (Day 1, Day 9 and Day 65). Days 9 and 65 are done as outpatient, at home.

g. PK: on dosing days, PK sample will be collected at hours 0 (predose), 1 and 4 hours post dose.

h. Perform injection site assessment immediately after injection, 15 minutes, 30 minutes, 1 hour, and 2 hours post administration. Additional assessments should be performed as needed after the last assessment of 2 hrs post-dose on dosing days.

i. Subject to be questioned about compliance with metformin.

j. Triplicate ECG: All ECG will be submitted to Central ECG vendor for independent review. On dosing days, collect triplicate ECG prior to study drug administration (pre-dose) and 1, 2, and 4 hours after dosing.

k. Fasting plasma glucose, glucagon and GLP-1 are not collected on days when MMTT are performed – these analytes will be captured as part of the MMTT Time 0/fasting timepoint.

l. Mean Daily Glucose Profile: blood sample for plasma glucose level will be collected: 30 minutes before and immediately prior to AM meal, 30, 60, 90, 120 and 180 minutes after the start of the AM meal; immediately prior to the midday meal, 60, 120 and 180 minutes after the start of the midday meal; immediately prior to the evening meal, 60, 120 and 180 minutes after the start of the evening meal; approximately at 11:00 PM; 0300 AM and 0730 (immediately prior to the AM meal). On days when mean daily glucose profiles are being collected meals will be given at approximately 08:00 AM, 12:00 PM and 6:00 PM. Subjects will have 30 minutes to finish the meal and must consume the entire meal. Collection times are from the start of the meal.

m. 24 hour ambulatory blood pressure monitoring: blood pressure assessments will be initiated in the AM on scheduled days and will be initiated at approximately the same time for a subject throughout the duration of the study.

n. A peripheral IV or heplock may be placed upon admission to the CRU and will be maintain according to site standards. The PIV/heplock will be removed prior to discharge.

o. Confirm subject is using appropriate contraception methods per Sections 4.4.3.2 and 4.4.3.3 for methods and duration.

p. On Day 36 and Day 64 only the following tests from the chemistry panel are to be performed: ALT, AST, GGT, LDH, alkaline phosphatase, total bilirubin, direct bilirubin, indirect bilirubin and CK.

q. Dosing window: The dosing windows for Day 29 or Day 57 may be extended to ±2 days to allow for evaluation of ALT/AST if subject experiences ≥3 x ULN, ALT or AST following the Day 1 dose. See Section 3.3.

r. Screening ADA sample collected only from subjects who participated in the SAD cohort and want to participate in the MAD portion as well.

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1. INTRODUCTION

1.1. Indication

PF-06293620 (RN909) is a glucagon receptor antagonist being developed for the treatment of type 2 diabetes mellitus (T2DM).

1.2. Background

Type 2 diabetes mellitus (T2DM) is a metabolic disorder afflicting over 25 million Americans and is growing rapidly in prevalence. Hyperglycemia is the primary clinical characteristic of T2DM, and is attributed to an underlying pathophysiology of insulin resistance, excess hepatic glucose production and deficient insulin production. Longstanding T2DM can lead to macro- and microvascular disease, resulting in a variety of complications, the most prevalent being cardiovascular disease, nephropathy, retinopathy and neuropathy. A number of large clinical outcome trials have demonstrated that improved glycemic control is associated with decreased microvascular complications (Patel; Turner).

In addition to insulin, glucagon is a major hormone maintaining moment-to-moment glucose homeostasis. Glucagon counteracts glucose-lowering by insulin via the promotion of hepatic glucose production, thereby maintaining euglycemia and protecting against hypoglycemia. There is a growing appreciation for the potential role of glucagon in contributing to hyperglycemia in T2DM stemming from the observation that glucagon levels are inappropriately elevated in the T2DM hyperglycemic milieu (Ali; Dunning). Therefore, mitigating the effects of hyperglucagonemia in T2DM is an attractive approach for treating hyperglycemia.

PF-06293620 is a humanized IgG2Δa monoclonal antibody that binds to, and blocks glucagon signaling through, the human glucagon receptor. Glucagon binding activates glucagon receptors found primarily on hepatocytes, leading to increased hepatic glucose production by a number of mechanisms including increased gluconeogenesis and glycogenolysis. PF-06293620 ameliorates elevations in plasma glucose, which are in part mediated by hyperglucagonemia, through normalization of dysregulated hepatic glucose production. Furthermore, as this mechanism is not dependent on functional pancreatic beta cells, it is anticipated to have a durable effect of improved glycemic control in subjects with T2DM.

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1.3. Rationale

1.3.1. Study Rationale

The first-in-human study is a randomized, double-blinded (Sponsor-open), placebo-controlled, single ascending-dose (SAD) and multiple ascending-dose (MAD) study in subjects with T2DM on a stable regimen of metformin. This population was chosen because it is the target population for this investigational drug and the preclinical studies support its safety for initiating clinical trials in medically-stable T2DM subjects. Furthermore, studying this population affords the opportunity to obtain an earlier assessment of this investigational drug's pharmacodynamic activities, allowing for dose selection in future studies. Plasma glucagon and GLP-1 levels will be used as biomarkers to assess pharmacodynamics related to target modulation. A number of glycemic parameters will be used to assess pharmacodynamics related to glycemic control: fasting plasma glucose (FPG), postprandial glycemia (during mixed meal tolerance test [MMTT]), 24 hour glucose AUC and weighted mean daily glucose (from fingerstick assessment), 1,5-anhydroglucitol, fructosamine and HbA1c. In conjunction with some of these tests (eg, MMTT), insulin and C-peptide levels will also be measured to gain additional insights into PF-06293620 effects on glucose homeostasis.

To fully characterize the safety profile, the investigational drug will be administered subcutaneously (SC) and intravenously (IV) in the SAD cohorts. PF-06293620 will be dosed in an ascending fashion with staggered dosing starts within each cohort to ensure adequate clinical safety has been ascertained before proceeding with the remainder of the subjects within the cohort. In addition, data collected for each SAD cohort will be reviewed when at least 8 subjects have completed Day 15 assessments before proceeding to the next higher dosage level.

Based on a review of the preliminary, unpublished safety, pharmacokinetic (PK) and PD results from the first four SAD dose cohorts, a randomized, double-blind (Sponsor open), placebo-controlled, multiple asceding dose (MAD) portion will be initiated to evaluate the safety and tolerability of ascending multiple dosages and dosing-schedules. The MAD cohorts will 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. MAD safety data from the previous cohort(s) will be used to determine the dose and dose regimen of the fourth planned cohort. At no time will the MAD dose exceed the PK exposure from the SAD. An additional fifth cohort may be studied to obtain further safety and PK data, increasing the planned total number of subjects to approximately 50. For MAD dose escalation, the decision to proceed to the next dose will be made by the Pfizer study team and the Investigators after review of the available safety and tolerability data after 80% of the subjects in the previous cohort have received one dose and have been followed for 14 days post first dose. Enrollment in the previous cohort must be completed before initiating enrollment in a new cohort.

1.3.2. Preliminary Unpublished Data (blinded)

Subject Disposition and Baseline Characteristics (data-cutoff May 19, 2015)

Thirty-six subjects have been randomized, of which 12 have completed the study. To date, three subjects have discontinued from the study. One subject in Cohort 4 was no longer willing to participate and discontinued on Day 8; this subject was replaced with another subject. Two other subjects were no longer willing to participate in the study and were terminated early (1 each in the 1.0 mg/kg cohort and the 3.0 mg/kg cohort) and were not replaced.

The baseline characteristics of the subjects randomized to date in the SAD study are summarized in Table 1 below.

Table 1. Baseline Characteristics – SAD Cohorts, Study B3501001

Characterisitcs	Placebo N=9	Cohort 1 (0.3 mg/kg) N=6	Cohort 2 (1.0 mg/kg) N=6	Cohort 3 (3.0 mg/kg) N=6	Cohort 4 (6.0 mg/kg) N=9
Age[1,2]	57.1 ± 6.5	60.7 ± 4.5	60.7 ± 6.2	57.7 ± 4.5	57.4 ± 8.7
Gender[2] (M:F)	4:5	5:1	2:4	3:3	5:4
Weight[1,2] (kg)	89 ± 21	93 ± 9	77 ± 14	90 ± 11	88 ± 16
BMI[1,2] (kg/m^2)	31.0 ± 4.6	32.3 ± 3.7	29.1 ± 3.3	30.8 ± 3.2	32.1 ± 3.4
Duration T2DM[3] (years)	10.9	13.4	10.0	8.5	8.1
Baseline HbA1c[1,4] (%)	8.7 ± 1.0	8.1 ± 0.9	7.7 ± 0.6	8.2 ± 0.5	8.3 ± 0.7

[1] Mean ± SD; Source; [2] Table 14.1.2.1 (B3501001 IND Tables); [3] Table 14.1.2.2 (B3501001 IND Tables); [4] Table 14.4.7.5.1 (B3501001 IND Tables).

Pharmacokinetics (data-cutoff May 19, 2015)

As of May 19th 2015, preliminary, unpublished PK of PF-06293620 are available from the first 4 cohorts (0.3, 1, 3, and 6 mg/kg) in the ongoing single ascending dose study in subjects with T2DM. Following administration of single subcutaneous doses of PF-06293620, absorption was slow with median C_{max} occurring approximately 4-10 days post dose. After that the decline in concentration was slow and multiphasic with mean terminal half-life ($t_{1/2}$) ranging from 9 to 18 days as the doses increased from 0.3 to 3 mg/kg. Both C_{max} and total

exposure (AUC_{inf}) increased slightly greater than dose proportionally with increasing doses up to 6 mg/kg. Table 2 below summarizes the PF-06293620 preliminary, unpublished PK parameters.

Table 2. Geometric Mean (%CV) Plasma PF-06293620 Pharmacokinetic Parameter Values, Study B3501001 (Preliminary, unpublished, based on QCed data)

Parameter	PF-06293620 Treatment			
	0.3 mg/kg SC	1 mg/kg SC	3 mg/kg SC	6 mg/kg SC
N, n	6,2	6,5	6,6	6,0
AUC_{inf} (µg·hr/mL)	260	1748 (46)	6606 (45)	NC
AUC_{last} (µg·hr/mL)	88.7 (69)	1062 (68)	5788 (38)	1267 (54)[a]
C_{max} (µg/mL)	0.39 (54)	2.48 (66)	7.22 (38)	25.4 (52)
T_{max} (hr)	168 (72 – 336)	168 (48 – 504)	252 (96 – 504)	168 (96 – 504)
$t_{1/2}$ (hr)	217	268 (27)	437 (27)	NC
CL/F (mL/kg/hr)	1.14	0.570 (39)	0.452 (52)	NC
Vz/F (mL/kg)	349	214 (30)	275 (59)	NC

Geometric mean (%CV) for AUC_{inf}, AUC_{last}, C_{max}, CL/F and Vz/F; arithmetic mean (%CV) for $t_{1/2}$; median (range) for T_{max}.
[a]Based on partial AUC up to Day 28.
N = Number of subjects; n = Number of subjects contributing to the mean for AUC_{inf}, $t_{½}$, CL/F, and Vz/F.
NC = Parameter not calculated due to incomplete data.
Source: Supportive Table 1 (RN909 Study B3501001: Preliminary PK Report, May 2015)

Safety (Preliminary B3501001 IND Tables - data-cutoff May 19, 2015)

A total of 37 treatment-emergent adverse events occurred in 16 subjects. The most common adverse events were gastrointestinal (n=6) and infections/infestations (n=5). The remainder of the adverse events were evenly distributed across a number of system organ classes and, based on preferred terms, there was not one particular adverse event that predominated.

One serious adverse event of bilary colic and cholelithiasis (Cohort 1: 0.3 mg/kg or placebo [PBO]) was reported.

This PPD-year-old PPD, PPD, PPD) PPD subject received blinded therapy (0.3 mg/kg PF-06293620 or PBO) by a single subcutaneous injection on Day 1 (PPD).

PPD

PPD

PPD

PPD

In the opinion of the investigator, the biliary colic and cholelithiasis were not considered to be related to blinded study drug. The Investigator considered the elevated transaminases to be related to the cholelithiasis and not to be related to blinded study drug.

In addition to the subject who experienced elevations in liver transaminases is conjuction with the SAE of bilary colic and cholelithiasis, three other subjects experienced ≥3-fold elevations in liver transaminases. To date, 2 of these have been reported as AEs.

Cohort 3 (3 mg/kg vs PBO): This PPD year-old PPD , PPD , PPD subject received blinded therapy (3 mg/kg PF-06293620 or PBO) by a single subcutaneous injection on Day 1. PPD

PPD

Cohort 4 (6 mg/kg vs. PBO): This PPD year-old PPD , PPD , PPD subject received blinded therapy (6 mg/kg PF-06293620 or PBO) by a single subcutaneous injection on Day 1. PPD The Investigator considered the elevated transaminases to be related to study drug.

PPD

Cohort 4 (6 mg/kg vs. PBO): This PPD year-old PPD , PPD PPD subject received blinded therapy (6 mg/kg PF-06293620:PBO) by a single subcutaneous injection on Day 1.

PPD The Investigator considered the elevated transaminases to be related to study drug.

PPD

None of these cases met Hy's Law criteria nor were assocated with abnormal elevations in total bilirubin. No concomitant use of alcohol or acetominaphen by these subjects has been reported in the database. No clinical signs and symptoms pertinent to the abnormal lab tests were reported. These subjects continue to be monitored closely.

1.3.3. Dose Rationale

The initial starting dose was selected based upon the results from preclinical pharmacological, PK and toxicology studies as well as PK/PD modeling and simulation. The maximum recommended human starting dose (MRSD) was determined based on the "no-observed-adverse-effect-level" (NOAEL) in the pivotal, 3-month, monkey toxicology study. Proposed doses, along with anticipated safety margins are listed in Table 3 below.

Table 3. Proposed PF-06293620 SAD Doses and Predicted Safety Margins based on the Exposures in Monkeys

Proposed PF-06293620 FIH Dose (mg/kg)	Route	Predicted PF-06293620 Human Exposure		Projected Safety Margin* (fold)	
		C_{max} (μg/mL)	AUC_{inf} (μg*hr/mL)	C_{max}	AUC
0.3	SC	3.16	1144	620	162
1	SC	10.5	3812	187	49
3	SC	31.6	11435	62	16
6	SC	63.2	22870	31	8
1	IV	38.5	7059	314	89

Exposure at NOAEL doses (200 mg/kg) in monkeys:
IV: C_{max} = 12,100 μg/mL; AUC = 625,000 μg*hr/mL
SC: C_{max} = 1,960 μg/mL; AUC = 185,000 μg*hr/mL
*Margin calculated based on the NOAEL exposure/predicted human exposure
Source: Table 2.5-2 (Clinical Overview)

The proposed starting dose of 0.3 mg/kg SC represents a 667-fold lower dose than the NOAEL dose of 200 mg/kg (SC) in the pivotal, 3-month, toxicity study. Furthermore, the starting dose is approximately 3-fold less than the minimum efficacious dose of 1 mg/kg in monkey and is expected to show no to minimal pharmacological response in humans. The predicted maximal PF-06293620 concentration (C_{max}) of 3.16 μg/mL is 620-fold lower than the observed C_{max} and the predicted AUC of 1144 μg·h/mL is 162-fold lower than the observed AUC at the NOAEL dose of 200 mg/kg (SC) in the 3-month toxicity study in monkeys. The maximum dose proposed for this study is 10 mg/kg IV. The predicted human C_{max} and AUC at the highest proposed dose would be approximately 31- and 9-fold below the maximum observed exposures at 200 mg/kg (IV) in monkey in the pivotal, 3-month, toxicity study, respectively. The dosage range encompasses the theoretical efficacious dose. However, based on preliminary, unpublished PD results in subjects receiving single ascending doses up to 6 mg/kg SC, maximal (nadir) decrease in FPG appeared to plateau by 3 mg/kg and no additional FPG lowering is expected at 10 mg/kg IV. Therefore, it is not necessary to test the highest dose, 10 mg/kg IV, initially proposed in the study and hence has been removed in the current amendment.

MAD

The proposed PF-06293620 doses in the MAD portion were selected based on the preliminary PK/PD analysis and simulation from available data from the first 4 cohorts in the ongoing SAD study. Fixed dosages of 75, 150 and 250 mg Q4W were selected for this study to allow for adequate characterization of both the dose-response relationship for glycemic analytes (FPG, MMTT, mean daily glucose [MDG] and HbA1C), as well as to identify the maximum tolerated dose. Modeling suggests minimal accumulation (Rac=1.14) of PF-06293620 after 3 dosages at 75 mg Q4W and approximately 1.4 and 1.6-fold increase in the exposure is predicted at 150 and 250 mg Q4W dosages, respectively. However, the predicted exposure at the highest dose (250 mg Q4W, ~3.1 mg/kg) is not expected to exceed the observed exposure at 6 mg/kg single-dose. The 6 mg/kg dose was found to be safe and well-tolerated. Guided by the dose-response relationship for baseline-adjusted FPG, the doses of 75 mg, 150 mg and 250 mg Q4W are deemed appropriate and adequate to allow for characterization of the dose-response relationship for PK, and PD changes. The 250 mg dose is expected to result in maximal fasting plasm glucose lowering. The 75 mg Q4W would approximately represent the dose for 50% maximal effect (ED50) and an intermediate dose of 150 mg Q4W was also proposed.

Proposed MAD doses, along with anticipated safety margins are listed in Table 4 below. The predicted human C_{max} and AUC_{tau} at the highest proposed dose would be approximately 122- and 20-fold below, respectively, the maximum observed exposures at 200 mg/kg (SC) in monkey in the pivotal, 3-month, toxicity study.

Table 4. Proposed PF-06293620 MAD Doses and Predicted Safety Margins based on the Exposures in Monkeys

Proposed PF-06293620 MAD Doses (mg)	Regimen	Predicted PF-06293620 Human Exposure		Projected Safety Margin*(fold)	
		C_{max} (µg/mL)	AUC_{tau} (µg*hr/mL)	C_{max}	AUC
75	Q4W	3.0	1471	653	126
150	Q4W	8.0	4486	245	41
250	Q4W	16.1	9448	122	20
TBD	TBD	--	--	--	--

Exposure at NOAEL doses (200 mg/kg) in monkeys:
IV: C_{max} = 12,100 µg/mL; AUC = 625,000 µg*hr/mL
SC: C_{max} = 1,960 µg/mL; AUC = 185,000 µg*hr/mL
*Margin calculated based on the NOAEL exposure/predicted human exposure
Source: Supportive Table 6 (RN909 Study B3501001: Preliminary PK report, May 2015)

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. 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.

2.1.2. 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.

2.1.3. Exploratory Objectives

- To characterize the pharmacodynamics of PF-06293620.
- To characterize the effect of PF-06293620 on (post-prandial) 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 .

2.2. Endpoints

2.2.1. Primary Endpoints

- Incidence of dose limiting or intolerable treatment related adverse events (AEs).
- Incidence, severity and causal relationship of treatment emergent AEs (TEAEs).
- Incidence of anti-drug-antibodies.

2.2.2. Secondary Endpoints

- Single- and multiple-dose pharmacokinetic parameter estimates of PF-06293620 include: C_{max}, C_{av}, C_{min}, T_{max}, CL or CL/F, Vss or Vz/F, half-life, AUC_{last}, AUC_{τ}, R_{ac} and AUC_{inf} as the data permit and as appropriate for SAD and MAD cohorts.

2.2.3. Exploratory Endpoints

- Change in pharmacodynamic parameters, including FPG, glucagon, GLP-1, 1,5-anhydroglucitol, fructosamine, HbA1c, AUC_{0-24hr} 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 AUC_{0-4} (change from baseline) in response to MMTT.

- 24-hour glucose AUC and weighted mean daily glucose.

- Lipid parameters (change from baseline) including: triglycerides, total cholesterol, HDL-C, and LDL-C.

- 24 hour ambulatory blood pressure monitoring, and central review of ECGs (MAD Cohorts only).

3. STUDY DESIGN

3.1. Study Overview

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 the 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 in an effort 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 planned dosages, the route of administration, frequency of administration and the approximate number of subjects for the SAD cohorts are shown in Table 5 and for the MAD cohorts in Table 6 below.

Single-Dose Cohorts:

The SAD portion will be conducted in approximately 5 planned cohorts (a 6:2 ratio of active drug to placebo) with a total of up to approximately 40 subjects in an effort 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. Subjects will be required to be on stable, daily dosages of metformin. Subjects will receive a single dose of study treatment (PF-06293620 or placebo) on Day 1, with multiple PK and safety assessments during the confinement period in Clinical Research Unit (CRU) on study Days -1, 1, 2, 3 and 4 and will be discharged on Day 5. The subjects will return to the CRU for subsequent visits at which time safety assessments, including AE monitoring, clinical laboratory tests, vital signs, and ECG, as well as PK, MMTT, lipid and PD biomarker labs will be performed (See **Schedule of Activities**- SAD). In each SAD cohort, the first 2 subjects will be dosed with either PF-06293620 or placebo and observed for 24 hours. If no acute toxicity is observed in the first 24 hours, as defined in Section 3.3.1, the remaining subjects in the cohort will proceed with dosing of either PF-06293620 or placebo. Dose escalation will not occur until all subjects in the cohort are enrolled and at least 6 subjects in

the cohort reach Day 15 post-dose, and the safety data have been thoroughly reviewed by the Sponsor and Investigators.

Table 5. Anticipated Number of Cohorts and Dosage Levels

Cohort	RN909 Dose	Route	Number of Subjects
1	0.3 mg/kg Placebo	SC	6 2
2	1 mg/kg Placebo	SC	6 2
3	3 mg/kg Placebo	SC	6 2
4	6 mg/kg Placebo	SC	6 2
5	1 mg/kg Placebo	IV	6 2

Multiple-Dose Cohorts

Based on a review of the preliminary, unpublished safety, PK and PD results from the first four SAD dose cohorts, a randomized, double-blinded (Sponsor-open), placebo-controlled, multiple ascending dose (MAD) portion will be initiated to evaluate the safety and tolerability of different dosages and dosing schedules. This 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. 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 screening period will last up to 42 days, the treatment period will last 85 days the follow-up period will last approximately 85 days (Days 86-169). Subjects will be required to be on stable, daily dosages of metformin. 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 currently planned 75 mg, 150 mg and 250 mg cohorts.

Subjects will be confined to the CRU prior to dosing (Day -3) for baseline testing, then will receive the first dose of study drug on Day 1. Subsequently, multiple PK and safety assessments after dosing will continue in the CRU until discharged on Day 3. The subjects will return to the CRU for subsequent visits at which time safety assessments, including AE monitoring, clinical laboratory tests, vital signs, and ECG, as well as PK, MMTT, lipid and PD biomarker labs will be performed (see Schedule of Activities - MAD). These visits will

include confinement for closer monitoring and PD testing (Days 6-8, 27-29, 62-64, and 83-85) with outpatient visits interspersed at regular intervals (generally Q2 weeks).

Table 6. Anticipated Number of MAD Cohorts and Dosage Levels

RN909 Dose	Route	Frequency	Number of Subjects
75 mg Placebo	SC	Q4 weeks	8 2
150 mg Placebo	SC	Q4 weeks	8 2
250 mg Placebo	SC	Q4weeks	8 2
TBD Placebo	SC	TBD*	8 2

TBD: to be determined; *Dose frequency will be determined based on the review of the safety and PK data from the previous cohort(s). Frequency may range from Q2weeks to Q8weeks.

The order of MAD cohorts may be adjusted based on the safety of the previous cohort(s), but at no time will the dose exceed the PK exposure from the SAD portion. An additional cohort may be added to obtain additional safety and PK data.

3.2. Planned Number of Subjects

The overall planned number of subjects enrolled is approximately 80 subjects (approximately 40 subjects across the SAD cohorts and approximately 40 subjects across the MAD cohorts). Table 2 and Table 3, above, outline how the subjects will be distributed across the cohorts and treatments.

3.3. Dose Escalation and Stopping Rules

Dose escalation stopping rules will be used to determine whether the maximal tolerated dose has been attained. Dose escalation may be stopped if it is determined that the dose or dose regimen is deemed not to be tolerable. This decision will be made after a discussion takes place between the Pfizer study team and the investigator(s). The Pfizer study team may not overrule the Investigators' decision to stop dose escalation. If dose escalation is stopped due to any of these findings, additional cohorts may receive the same or lower doses of the investigational compound. Additional subjects may be added at a dose level to further evaluate safety and/or tolerability after discussions between the Pfizer study team and the investigators.

Single Ascending Dose Portion (n=8; 6 active treatment and 2 placebo)

Dose escalation will be terminated based on the following criteria:

- Two or more subjects receiving PF-06293620 drug (but not placebo subjects) develop similar clinically significant laboratory, ECG or vital signs abnormalities, or severe AEs in the same organ class, indicating dose-limiting toxicity as outlined in

Table 3 (Exception: dose escalation will be terminated if one (1) subject experiences ≥2 hypoglycemic events of Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥3 which do not meet SAE criteria; see Table 7).

- It is determined that the dose is deemed intolerable. This decision will be made following discussions between the Study Team and the Investigator.

Other findings that, at the discretion of the Study Team and Investigator, indicate that dose escalation should be halted.

In the single dose cohorts, for any treatment-related serious adverse event (SAE) , the subject will continue with the safety assessments until completion of the study.

Progression to the next dose will occur if the last dose was well tolerated and after satisfactory review of the available safety data.

Multiple Ascending Dose Portion (n= 8 PF-06293620 drug :2 PBO)

For dose escalation, the decision to proceed to a higher dose will be made by the Pfizer study team and the Investigators after review of the available safety and tolerability data after 80% of the subjects in the previous cohort have received one dose and have been followed for 14 days post first dose. Enrollment in the previous cohort must be completed before initiating enrollmnet in a new cohort. If ≤2 subjects in a cohort discontinues the study prior to reaching Day 15, for reasons other than safety (eg, withdraw of consent), the subject(s) will be included in the dose escalation data review and do/does not need to be replaced for the purposes of determining dose escalation. The order of MAD regimen cohorts may change depending on the ongoing review of safety/PK data but at no time will doses be administered that exceed the PK exposure determined in the SAD portion. Dose escalation will be terminated based on the following criteria:

- Two (2) or more subjects receiving PF-06293620 drug (but not placebo subjects) develop similar clinically significant laboratory, ECG or vital signs abnormalities, or severe AEs in the same organ class, indicating dose-limiting toxicity as outlined in Table 3 (Exception: dose escalation will be terminated if one (1) subject experiences ≥2 hypoglycemic events of CTCAE Grade ≥3 which do not meet SAE criteria; see Table 7).

- The limit of safety and/or tolerability has been reached.

- If dose escalation in the single ascending dose is terminated AND the exposure of the dose cohort in the multiple ascending dose portion is equal to or higher than the exposure of the dose determined to be the MTD after the single doses.

Dose Interruption

- If ALT or AST are increased ≥3 x ULN, ALT and AST will be monitored at least weekly. If ALT or AST continues to rise ≥3 to ≤5x ULN prior to the next dose, the investigator and Sponsor will review the subject's clinical data prior to administering the next dose and dosing may be interrupted.

- Dosing will be interrupted in individual subjects when the following occurs:

    a. Serum AST or ALT are increased to >5 × ULN (CTCAE Grade ≥3); confirmed within 7 days (by both local and central labs).

    b. Confirm creatine kinase (CK) WNL and source of enzyme elevation is not muscle related.

If ALT or AST elevation of >5 × ULN (CTCAE Grade ≥3) is confirmed, ALT and AST will be monitored weekly until liver enzymes have returned to WNL if subject was WNL at baseline; or to <2xULN if was between 1 – 2xULN at baseline. Once ALT/AST levels have returned to WNL if subject was WNL at baseline; or to <2xULN if was between 1 – 2xULN at baseline, the results must be confirmed within 7 days (by both local and central labs), at which point dosing may resume as scheduledper protocol. Missed doses will not be made up. If dosing is interrupted, all study visits and procedures will continue as per protocol, with the exception of dosing and subject will be followed to the end of the study.

If following the Day 1 dosing is interrupted due to ALT or AST elevation, the dosing windows for Day 29 or Day 57 may be extended to ±2 days to allow for evaluation of ALT/AST.

3.3.1. Toxicity Criteria

Table 7. Toxicity Criteria

Parameter	Definition[1]
Serious adverse event	Serious adverse event;
Increased liver transaminases[2]	Serum AST[3] and/or ALT[4] are both increased to >5 × ULN[5] (CTCAE[6] Grade ≥3);
Increased direct bilirubin[2] (in absence of ALT/AST elevations)	Adapted from CTCAE[6] Grade ≥2;
Hypoglycemia	One (1) subject experiences ≥2 hypoglycemic events of <40 mg/dL (CTCAE[6] Grade ≥3) which do not meet SAE criteria;
Pancreatitis	Severe pain, vomiting; medical intervention indicated (CTCAE[6] Grade ≥3);
Decreased platelet count[2]	Thrombocytopenia to <100,000/μL [$<100 \times 10^9$/L];
Hypertriglyceridemia[2]	>1000 mg/dL (CTCAE[6] Grade ≥4);
Increased serum creatinine[2]	Serum creatinine to 2.2 × ULN[5] (CTCAE[6] Grade ≥3);
Diarrhea, enteritis or nausea	Increase of >6 stools/day over baseline; incontinence; hospitalization indicated; inadequate oral caloric or fluid intake (CTCAE[6] Grade ≥3);
ECG changes from baseline	Clinically significant ECG change from baseline including but not limited to interval changes (eg, PR, QTcF), ST-T wave changes, appearance of Q waves, atrial or ventricular rhythm abnormality, QRS axis deviation or ventricular conduction defect associated with clinical symptoms;
Prolongation of QT_cF interval[2,7]	QT_cF >500 msec (ie, CTCAE[6] Grade ≥3) or increase from baseline of ≥60 msec;
Unspecified	If considered appropriate by the medical monitor and investigator.

1. Unless considered to be unrelated to study medication by Investigator and Sponsor.
2. To be confirmed by a repeat test.
3. AST = aspartate aminotransferase.
4. ALT = alanine aminotransferase.
5. ULN = upper limit of normal reference range of the clinical laboratory.
6. CTCAE = Common Terminology Criteria for Adverse Events.
7. QT_cF = QT interval (Fridericia's correction).

In the event that a subject develops any of the toxicities outlined in Table 7, the subject will be followed until resolution and/or referred to an appropriate specialist

4. SUBJECT SELECTION

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject.

4.1. Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team before subjects are included in the study.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Men and women of *non-childbearing potential* between the ages of 18 and 70 years, inclusive, with type 2 diabetes mellitus. Women subjects of *non-childbearing potential must meet* at least one of the following criteria:

    a. Achieved postmenopausal status, defined as: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and have a serum follicular stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal women;

    b. Have undergone a documented hysterectomy and/or bilateral oophorectomy;

    c. Have medically confirmed ovarian failure.

    All other women subjects (including women with tubal ligations and women that do NOT have a documented hysterectomy, bilateral oophorectomy and/or ovarian failure) will be considered to be of childbearing potential, and are not eligible for the study.

2. Body Mass Index (BMI) of 22.0 to 40.0 kg/m^2; and a total body weight >50 kg (110 lbs) and ≤150 kg, and ≤125 kg for Cohort 4 (SAD).

3. Subjects on stable metformin dose x 30 days prior to the first Screening visit and will remain on stable dose throughout the study.

    - SAD Cohorts: metformin dose ≥1500 mg daily

    - MAD Cohorts: metformin dose ≥1000 mg daily

4. HbA1c 7.0 - 10.0% (SAD Cohorts) or HbA1c 6.5-10.5% (MAD Cohorts) inclusive at Screening.

5. Fasting C-peptide >1.21 ng/mL (SAD cohorts) or ≥0.8 ng/mL (MAD cohorts) at Screening.

6. Evidence of a personally signed and dated informed consent document indicating that the subject (or a legal representative) has been informed of all pertinent aspects of the study.

7. Subjects who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, and other study procedures.

4.2. Exclusion Criteria

Subjects presenting with any of the following will not be included in the study:

Exclusions for General Health

1. History of type 1 diabetes mellitus

2. Evidence or history of diabetic complications with significant end-organ damage including but not limited to:

   - proliferative retinopathy;
   - macular edema;
   - diabetic nephropathy;
   - severe neuropathy;
   - neuropathic ulcers.

3. History of chronic pancreatitis or at high risk for pancreatitis including but not limited to gall bladder disease, hypertriglyceridemia, hypercalcemia, or alcohol abuse.

4. Risk of pancreatic neuroendocrine neoplasm including but not limited to personal or family history of islet cell tumor, multiple endocrine neoplasia 1 (MEN) syndrome, Von Hippel-Lindau syndrome or neurofibromatosis.

5. History of severe hypoglycemia (ie, requiring assistance) or hypoglycemia unawareness within 1 year of randomization.

6. Poorly controlled hypertension (systolic blood pressure >160 mm Hg or a diastolic blood pressure >90 mm Hg, even with treatment). Subjects who have hypertension and are controlled on stable dosages of anti-hypertensive medications can be included.

7. History of a cardiovascular or cerebrovascular event or procedure (eg, MI, stroke, stent) within one year of randomization.

8. Heart failure, NY Class 2, 3, 4.

9. Past or current history of alcoholism or drug addiction according to Diagnostic Statistical Manual (DSM) IV criteria, or use of any recreational drugs within 12 months prior to the first Screening visit.

10. History of diabetic ketoacidosis (DKA), hyperosmolar coma, or lactic acidosis.

11. History of cancer within the last 5 years (except for cutaneous basal cell or squamous cell cancer resolved by excision).

12. Regular alcohol consumption >2 drinks/day (1 drink = 5 ounces [150 mL] of wine or 12 ounces [360 mL] of beer or 1.5 ounces [45 mL] of hard liquor) within 30 days prior to the first Screening visit.

13. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 56 days prior to dosing or plans to donate during the conduct of the study.

14. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, immunologic, hepatic, psychiatric, neurologic, or allergic disease (exception: untreated, asymptomatic, seasonal allergies at the time of dosing allowed) unless deemed not clinically significant by the Investigator and Sponsor.

Exclusions Related to Medications

15. Treatment with anti-diabetic therapies other than metformin within 4 weeks of Screening (8 weeks for thiazolinediones).

16. Change in dietary supplement or herbal medicine within 2 weeks of Screening.

17. Contraindication to metformin therapy, per the metformin label.

18. Known hypersensitivity to metformin.

19. Subject participating in or expecting to participate in other clinical trials.

20. Subjects on chronic systemic corticosteroids [ie, oral, IV or intramuscular (IM)].

21. Treatment with a marketed or investigational monoclonal antibody within 6 months or 5 half-lives (whichever is longer) of Day -1. (Subjects that participated in the SAD portion of the study may participate in the MAD portion of the study with dosing for the MAD starting 6 months after Day 1 in the SAD study [ie, count from day of when single dose administered in SAD]) provided they are ADA negative and their last measured glucagon levels during the SAD portion are not above 3X baseline (baseline: pre-dose value prior to dosing in the SAD portion of the study).

22. History of allergic or anaphylactic reaction to any therapeutic or diagnostic monoclonal antibody (IgG protein) or molecules made of components of monoclonal antibodies (eg, Enbrel® which is the Fc portion of an antibody or Lucentis® which is a Fab).

23. History of sensitivity to heparin or heparin-induced thrombocytopenia (if heparin is used to flush intravenous catheters) or known or suspected hypersensitivity to any of the components of drug product.

24. Treatment with an investigational small molecule drug within 90 days or 5 half-lives of Day -1, whichever is longer.

25. Need for radiologic studies involving use of intravascular iodinated contrast materials.

Exclusions for abnormal screening labs or procedures:

Abnormal labs or procedures may be repeated once for confirmation at the discretion of the Investigator (repeat only the abnormal test, not entire panel).

26. FPG <60 or >250 mg/dL.

27. Creatinine clearance ≤60 mL/min/1.73m^2 based on the MDRD.

28. Fasting triglycerides >400 mg/dL.

29. Hemoglobin <11 g/dL in females; <12 g/dL in males .

30. Positive anti-drug antibody (ADA) test for PF-06293620, if the subject previously participated in SAD portion (MAD portion of the study only).

31. Positive human immunodeficiency virus (HIV) antibody, hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), or hepatitis C antibody tests indicative of present or prior infection.

    NOTE: If a subject tests negative for HBsAg, but positive for HBcAb, the subject will be considered eligible if the subject tests positive for antibody to HB surface antigen (HBsAb or anti-Hbs).

32. AST or ALT >2xULN at Screening. If the subject participated in SAD, no ALT or AST elevation ≥3xULN during the SAD.

33. Direct bilirubin >ULN.

34. TSH < LLN or > ULN.

35. Platelets < LLN or >450,000 U/uL.

36. Creatine kinase >2xULN.

37. Positive urine drug (illicit) screen (positive drug screen for prescription drugs, eg benzodiazepines, allowed if approved by Sponsor).

38. 12 lead ECG demonstrating QTc >450 msec or a QRS interval >120 msec at Screening. If QTc exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated two more times and the average of the three QTc or QRS values should be used to determine the subject's eligibility.

39. Any abnormal hematology values, clinical chemistries, urinalysis, or ECGs judged by the Investigator or Sponsor as clinically significant.

Other Exclusions:.

40. Pregnant or breast-feeding women.

41. Men who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 60 days after the last dose of investigational product.

42. Unwilling or unable to comply with the Lifestyle guidelines described in this protocol.

43. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

44. Subjects who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the Investigator, or subjects who are Pfizer employees directly involved in the conduct of the study.

4.3. Randomization Criteria

Subjects will be randomized into the study provided they have satisfied all subject selection criteria.

4.4. Lifestyle Guidelines

The following guidelines are provided:

4.4.1. Meals and Dietary Restrictions

- Subjects must abstain from all food and drink (except water) at least 10 hours prior to any fasting laboratory evaluations. Water may be consumed without restriction. Non-caffeinated drinks may be consumed with meals and the evening snack.

- Breakfast will be provided in the morning during in-patient confinement periods. On days when MMTT is being performed, the liquid meal for the MMTT will substitute for breakfast and will be provided after an overnight fast of at least 10 hours.

- Lunch will be provided approximately 4 hours after dosing (and after completion of MMTT on days in which this procedure occurs), or approximately 12 noon on non-dosing days.

- Dinner will be provided approximately 9 to 10 hours after dosing, or approximately 6 pm on non-dosing days.

- An evening snack may be permitted approximately 13 to 15 hours after dosing, or approximately 10 PM on non-dosing days.

- While confined, the total daily nutritional composition should be approximately 50% carbohydrate, 35% fat and 15% protein. A BMI adjusted diet is also acceptable. The daily caloric intake per subject should be adequate to maintain current weight.

- The meals and snacks provided during confimement for mean daily glucose (MDG) will standardized and should be approximately 50% carbohydrate, 35% fat and 15% protein Within each subject, the same meals and snacks must be provided during every MDG profile. On days when mean daily glucose profiles are being collected meals will be given at approximately 08:00 AM, 12:00 PM and 6:00 PM. Subjects will have 30 minutes to finish the meal and must consume the entire meal. Collection times are from the start of the meal.

- For 72 hours prior to each confinement, the subjects should be counseled to consume >150 g carbohydrates/day as an outpatient and provided when confined in the CRU.

4.4.2. Alcohol, Caffeine and Tobacco

- Subjects will abstain from alcohol for 24 hours prior to admission to the CRU (Clinical Research Unit) and during confinement in the research unit. Subjects will abstain from alcohol for 24 hours prior to all remaining study visits. Subjects may undergo an alcohol breath test at the discretion of the investigator.

- Subjects will abstain from caffeine-containing products for 24 hours prior to the start of dosing and 24 hours prior to all remaining study visits. Plus 4 hours after dosing on dosing days.

- Subjects will abstain from the use of tobacco- or nicotine-containing products for 24 hours prior to dosing, 24 hours after dosing and 24 hours prior to all remaining study visits.

4.4.3. Activity

- Subjects will abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests. Walking at a normal pace will be permitted.

4.4.3.1. Contraception

4.4.3.2. Women– Childbearing Potential

Only women of non-child bearing potential will be enrolled in this study. The criteria for defining women of non-child bearing potential is in Section 4.

4.4.3.3. Men

All men who, in the opinion of the investigator, are biologically capable of having children and are sexually active, must agree to use a highly effective method of contraception consistently and correctly for the duration of the study and for at least 60 days after the last dose of investigational product. The investigator or his/her designee, in consultation with the subject, will confirm the subject has selected the most appropriate method of contraception for the individual subject and his partner from the permitted list of contraception methods (see below) and instruct the subject in its consistent and correct use. Subjects need to affirm that they meet at least one of the selected methods of contraception. The investigator or his/her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the Schedule of Activities (SOA) and document such conversation in the subject's chart. In addition, the investigator or his/her designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected.

Highly effective male contraception include: male condom WITH a spermicide (ie, foam, gel, film, cream or suppository) and male sterilization with the absence of sperm in the post-vasectomy ejaculate. In addition, males will not donate sperm during and 60 days post trial.

4.5. Sponsor Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list.

To facilitate access to appropriately qualified medical personnel on study related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, subject study number, contact information for the investigational site and contact details for a help desk in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subjects participation in the study. The help desk number can also be used by investigational staff if they are seeking advice on medical questions or problems, however it should only be used in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace the established communication pathways between the investigational site and study team for advice on medical questions or problems that may arise during the study. The help desk number is not intended for use by the subject directly and if a subject calls that number they will be directed back to the investigational site.

5. STUDY TREATMENTS

5.1. Allocation to Treatment

The investigator's knowledge of the treatment should not influence the decision to enroll a particular subject or affect the order in which subjects are enrolled.

The investigator will assign subject numbers sequentially to the subjects as they are screened for the study. Pfizer will provide a randomization schedule to the investigator and, in accordance with the randomization numbers, the subject will receive the study treatment regimen assigned to the corresponding randomization number.

Eligible subjects will be randomly assigned through an Interactive Voice Response System (IVRS) to a study treatment cohort. Randomization numbers will be assigned by the IVRS. Subjects in the SAD portion will be randomized to receive a single-dose of either PF-06293620 SC 0.3 mg/kg to 6 mg/kg (Cohorts 1 through 4) or placebo, or PF-06293620 IV 1 mg/kg (Cohort 5) or placebo, in a 6:2 ratio PF-06293620:placebo in all cohorts. All subjects will receive PF-06293620 or placebo once in the study treatment period.

Subjects in the MAD portion will be randomized to receive multiple-doses of either PF-06293620 or placebo SC every 4 weeks in an 8:2 ratio PF-06293620:placebo. Based on the ongoing review of the safety data of the previous cohort(s) will be used to determine the dose and dose regimen of the fourth planned cohort.

5.2. Breaking the Blind

At the initiation of the study, the study site will be instructed on the method for breaking the blind. The method will be either a manual or electronic process. Blinding codes should only be broken in emergency situations for reasons of subject safety. Whenever possible, the investigator or sub-investigator should consult with a member of the study team prior to breaking the blind. When the blinding code is broken, the reason must be fully documented and entered on the case report form (CRF)/data collection tool (DCT).

Only the investigator site(s) and the study monitor(s) will be blinded to study treatment. Pfizer personnel will be unblinded to subject treatments in order to permit real-time interpretation of the safety and pharmacokinetic data; and provide information necessary to potentially alter the dose escalation sequence. The study monitor will remain blinded to treatment until all monitoring for the study has been completed. To minimize the potential for bias, treatment randomization information will be kept confidential by Pfizer personnel and will not be released to the investigator or investigator site personnel until the study database has been locked.

Blood specimens will be obtained from all subjects for pharmacokinetic analysis to maintain the study blind at the investigator site Specimens from subjects randomized to placebo will not be routinely analyzed.

5.2.1. Drug Supplies

5.2.2. Formulation and Packaging

PF-06293620 will be provided as a solution for injection in a 20 mM histidine buffer at pH 5.8, at a concentration of 50 mg/mL. The drug product is supplied in 6 mL Type 1 clear glass vial sealed with a coated serum stopper and an aluminum seal, with a nominal fill volume of 4 mL

PF-06293620 will be shipped under refrigerated conditions (2-8°C) and should be stored under refrigerated conditions (2-8°C).

The placebo will be an appropriate sterile diluent solution supplied by the study site. The placebo formulation will be specified in the Dosage and Administration Instructions.

5.2.3. Preparation and Dispensing

PF-06293620 and placebo will be prepared according to the Dosage and Administration Instructions (DAI) that will be provided to the site. Drug will be prepared by qualified unblinded site personnel and administered by blinded staff in a blinded fashion to the subject. Following preparation for administration, PF-06293620 or placebo should be administered as soon as possible. The prepared solution may be stored at refrigerated conditions (2-8°C) or at room temperature (15-25°C) for a limited time until the time of administration, as specified in the DAI. Product should be prepared and used on the same day.

Details of dose preparation will be given under a separate cover (DAI).

Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents.

5.2.4. Administration

Following an overnight fast of least 10 hours, subjects will receive study medication at approximately 0800 hours (plus or minus 2 hours). Qualified and trained investigator site personnel will administer study drug to subjects either by subcutaneous injection (SAD Cohort 1-4 and all MAD Cohorts) to the abdomen, or as a single IV infusion (SAD Cohort 5 only) by rate controlled intravenous infusion device over approximately 60 minutes. For subjects receiving two or more subcutaneous injections, study drug should be administered to two or more different quadrants of the abdomen; one or two injections per quadrant. Study staff should refer to the DAI for specific instructions on the handling and administration of study medication.

Subjects should take their metformin according to their usual time schedule and regimen. On Day 1 (all SAD and MAD cohorts), and on additional days where study drug is administered (MAD cohorts only) metformin should be taken prior to receiving study treatment.

Medication errors may result, in this study, from the administration or consumption of the wrong product,by the wrong subject, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the medication error case report form (CRF) which is a specific version of the adverse event (AE) page and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving subject exposure to the investigational product.
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Whether or not a medication error is accompanied by an AE, as determined by the investigator, the medication error is captured on the medication error version of the adverse event (AE) page and, if applicable, any associated adverse event(s) are captured on an adverse event (AE) CRF/DCT page.

5.2.5. Compliance

PF-06293620/placebo will be administered by appropriately trained site personnel in the clinic.

Subjects will self administer metformin during their participation in the study. On specific days (See Schedule of Activities), site personnel will ask subjects the number of doses taken since the last visit. The information will be recorded on the eCRF.

Subjects will be educated on the importance of taking their daily dosages of metformin during the study period.

5.3. Drug Storage and Drug Accountability

PF-06293620 active vials should be stored refrigerated at 2-8°C. Storage conditions stated in the SRSD (*ie, Investigator Brochure [IB], Core Data Sheet [CDS], United States Package Insert [USPI], Summary of Product Characteristics [SPC], or Local Product Document [LPD])* will be superseded by the label storage.

Investigators and site staff are reminded to check temperatures daily (ie, manually or by using alarm system to alert of any excursions) on working days only, and to ensure that thermometers are working correctly as required for proper storage of investigational products. These include thermometers for both the room storage and refrigerator storage. Any temperature excursions should be addressed according to appropriate standard operating procedures.

The investigational product(s) must be stored as indicated. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor. Once a deviation is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product.

At the end of the study, Pfizer will provide instructions as to disposition of any unused investigational product. If Pfizer authorizes destruction at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental

regulations, institutional policy, and any special instructions provided by Pfizer. Destruction must be adequately documented.

5.4. Concomitant Medication(s)

Sporadic use of any homeopathics or nutritional supplements should be discouraged as they may confound interpretation of study treatment results. Subject may be on dietary supplement or herbal medicine as long as dose is stable within 2 weeks of screening and throughout the duration of the study.

All concomitant medications taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All subjects will be questioned about concomitant medication at each clinic visit.

Medications taken within 28 days before the first dose of study medication will be documented as a prior medication. Medications taken after the first dose of study medication will be documented as concomitant medications.

5.4.1. Permitted Medications

Subjects should remain on their dosage of metformin throughout the study. They are allowed to take metformin during the fasting period. As noted in Section 5.4, the date, the time of dose and the dosage must be recorded.

Medications required for treatment of preexisting, stable medical conditions are permitted.

5.5. Rescue Therapy

Standard medical supportive care must be provided to manage AEs. For medical management of hypoglycemia (See Section 7.6), the investigator should obtain a blood sample for glucose first and then may administer oral carbohydrate, glucagon or IV glucose according to medical judgment.

For the MAD portion of the study, if a subject has sustained high fasting plasma glucose concentrations on two consecutive measurements (ie, measured on different days), based on the ranges below, the investigator should recommend further follow-up and treatment.

- Fasting Plasma Glucose >270 mg/dL (15 mmol/L) at Week 6.
- Fasting Plasma Glucose >240 mg/dL (13.3 mmol/L) at Week 12.
    - Reinforcement of an appropriate diet is encouraged.

6. STUDY PROCEDURES

6.1. Screening

Subjects will be screened within 28 days prior to administration of the study medication for the SAD cohorts and 42 days prior to administration of the study medication for the MAD cohorts to confirm that they meet the subject selection criteria for the study. The investigator

(or an appropriate delegate at the investigator site) will obtain informed consent from each subject in accordance with the procedures described in Section 12.3 on Subject Information and Consent. If the time between Screening and dosing exceeds 28 days for the SAD cohorts or 42 days for the MAD cohort as a result of unexpected delays (eg, delayed drug shipment) or current cohort enrollment complete (eg, subject eligible but to be considered in future cohort) then subjects do not require re-screening if the eligibility laboratory assessments are repeated prior to randomization – and the results meet the eligibility criteria. Also, a subject who qualified for this protocol but did not enroll from an earlier cohort may be used in a subsequent cohort without re-screening provided the eligibility laboratory assessments are repeated prior to randomization and laboratory results meet the eligibility criteria for this study. If a subject fails to meet eligibility due to a laboratory test, the test may be repeated once within the 28 days (SAD Cohorts)/42 days (MAD Cohorts) prior to administration of the study medication, at the Investigator's discretion, in an effort to confirm eligibility.

The following procedures will be completed for subjects screening for the SAD and MAD portion, unless otherwise noted:

- Obtain written informed consent.
- Review Inclusion and Exclusion criteria.
- Collect demographic information (age, gender, ethnicity, etc)
- Obtain medical history, including history of recreational drug, alcohol and tobacco use.
- Obtain complete medication history of all prescription or nonprescription drugs, and dietary and herbal supplements taken within 28 days prior to the planned first dose.
- Conduct full physical examination including height and weight (See Section 7.2 for height and weight instructions).
- Confirm subject is using appropriate contraception methods per Sections 4.4.3.2 and 4.4.3.3.
- Obtain temperature and supine vital signs.
- Collect standard supine 12-lead electrocardiogram (ECG).
- Collect urinalysis (clean catch, midstream) and urine drug test (illicit drugs).
- Following at least 10-hr fast, collect blood specimens for the following:
    - Safety laboratory tests [hematology, chemistry];
    - Screening labs (TSH, C-peptide, HIV, hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody);

- Serum FSH concentration (women only);
- Fasting lipid profile;
- Creatine kinase (performed in MAD cohorts only as part of MAD routine serum chemistry);
- Apo B (MAD only);
- Coagulation panel, amylase and lipase;
- HbA1c;
- Fasting plasma glucose (FPG);
- ADA (collected only from subjects who participated in the SAD portion, and are undergoing screening for the MAD portion).

To prepare for study participation, subjects will be instructed on the use of the Lifestyle Guidelines and Concomitant Medication(s) sections of the protocol.

6.2. Study Period – SAD Cohorts

For the study period described below, when multiple procedures are scheduled at the same time point(s) relative to dosing, the following chronology of events should be adhered to, where possible.

- ECGs: obtain prior to vital signs and as close as possible to scheduled time, but prior to blood specimen collection;
- Blood pressure/pulse rate: obtain as close as possible to scheduled time, but prior to blood specimen collection;
- Pharmacokinetic blood specimens: obtain at scheduled time within 10% of the nominal time from dosing;
- Other procedures: obtain all other procedures as close as possible to the scheduled time, but may be obtained before or after blood specimen collection.

6.2.1. Day -2 (SAD)

Subjects will be admitted to the Clinical Research Unit. Subjects will be required to stay in the Clinical Research Unit for 6 nights and will be discharged on Day 5.

Site staff will review concomitant medications, adverse events and contraception method. Concomitant medications will be recorded in medication history. Any noted adverse events will be recorded as prior medical history.

On admittance to the CRU, subjects will undergo a urine drug screen (for illicit drugs).

6.2.2. Day-1 - SAD

On Day -1, after an overnight fast of at least 10 hours, and the following procedures will be completed:

- Review medical history including recreational drug, alcohol and tobacco use, and medication history.
- Conduct limited physical exam of the skin, heart, lungs, abdomen and extremities by trained medical personnel at the investigator site.
- Collect fasting weight and triplicate waist circumference.
    - To measure waist circumference, use a spring-loaded tape measure, and starting at the top of the hip bone, bring it all the way around, level with the navel. Tape measure should not be too tight and parallel with the floor. Instruct subject to not hold their breath. Measurement should not include navel.
- Obtain temperature and supine pulse and supine triplicate blood pressure. Blood pressure will be the only vital sign collected in triplicate.
- Collect blood samples for the following:
    - Fasting lipid profile;
    - HbA1c;
    - Fructosamine;
    - 1,5-anhydroglucitol;
    - ADA;
    - Banked Specimen (Pharmacogenomics).
- Collect adverse events.
- Question subjects regarding metformin compliance.
- Obtain fingerstick glucose before breakfast (before MMTT).
- Before MMTT, collect 0 minute fasting timepoint blood samples for FPG, C-peptide, insulin, glucagon and GLP-1 (all cohorts).

- Administer MMTT in AM; begin sample collection (glucose, C-peptide, insulin, glucagon and GLP-1):
    - 15 minutes from start of meal (first sample collected 5 minutes post meal; the liquid should take 10 minutes to consume; See Section 7.4.1.2);
    - 30 minutes;
    - 60 minutes;
    - 120 minutes;
    - 180 minutes;
    - 240 minutes.
- Obtain fingerstick glucose measurements 2 hr post- breakfast, before lunch, 2-hr post-lunch, before dinner, 2-hr post-dinner, prior to snack (between 9 and 10 PM).
- Initiate continuous cardiac telemetry at least 12 hours prior to dosing on Day 1.
- Randomize subject to study treatment.

6.2.3. Day 1 - SAD

Prior to dosing, the following procedures will be completed:

- Obtain finger-stick glucose measurement at 0300 and prior to breakfast.
- Obtain fasting weight.
- Collect a blood sample for pharmacokinetic analysis.
- Collect blood samples for the following:
    - Hematology;
    - Fasting clinical chemistry;
    - Coagulation panel, amylase and lipase.
- Collect blood for FPG, fasting glucagon and fasting GLP-1 (SAD SC Cohorts 1-4).
- **For SAD IV Cohort 5 only,** collect the time 0 minute fasting blood samples for FPG, C-peptide, insulin, glucagon and GLP-1 (prior to MMTT).
- Collect urine for Urinalysis (clean catch, midstream).

- Collect triplicate 12-Lead ECG.
- Collect temperature and supine pulse and supine triplicate blood pressure. Blood pressure is the only vital sign to be collected in triplicate.
- Maintain continuous cardiac telemetry.
- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Administer the study medication (see Study Treatments and Administration Sections).

After dosing, the following procedures will be completed:

- Assess temperature,supine pulse rate and supine triplicate blood pressure at 1, 2, 4, 8 and 12 hours after dosing. Blood pressure is the only vital sign to be collected in triplicate.
- Obtain triplicate 12-lead ECG measurements at 1, 2, 4, 8 and 12 hours after dosing.
- Collect blood samples for pharmacokinetic analysis at 1, 4, 8 and 12 hours following dosing on Day 1.
- Maintain continuous cardiac telemetry following dose administration.
- Injection site assessment:
    - SC administration: immediately after injection, 15 and 30 minutes, 1, and 2 hours post administration. Additional assessments should be performed as needed after the last assessment of 2 hrs post-dose on dosing days.
- Infusion reaction assessment during and immediately after infusion:
    - IV administration: 15 and 30 minutes, 1 and 2 hours post administration.
- Record concomitant medication.
- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"
    - IV administration only **(SAD Cohort 5 only):** Administer MMTT (within approximately 15 minutes) at the end of the IV infusion and collect samples (glucose, insulin, C-peptide, glucagon and GLP-1) at:
        - 15 minutes (5 minutes after fluid meal is consumed which requires 10 minutes, See Section 7.4.1.2);

- 30 minutes;
- 60 minutes;
- 120 minutes;
- 180 minutes;
- 240 minutes.

- Obtain fingerstick glucose (2-hr post breakfast, before lunch, 2-hr post-lunch, before dinner, 2-hr post-dinner, prior to snack (between 9 and 10 pm).

6.2.4. Day 2 – SAD

The following procedures will be completed:

- Obtain fingerstick glucose at 0300 and before breakfast.
- Assess injection site for reactions if necessary (required if reaction was noted on Day 1).
- Collect blood samples for pharmacokinetic analysis at 24 and 36 hours after Day 1 dosing.
- Collect blood samples for FPG and fasting glucagon.
- Collect fasting blood and urine samples for safety laboratory tests 24 hours after Day 1 dosing (hematology, chemistry, urinalysis (clean catch, midstream).
- Assess temperature, supine pulse and triplicate supine blood pressure 24 hours after Day 1 dosing. Blood pressure is the only vital sign to be collected in triplicate.
- Obtain triplicate 12-lead ECG measurements 24 hours after Day 1 dosing.
- Discontinue continuous cardiac telemetryin AM before breakfast.
- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as “How do you feel?”
- Record concomitant medications.

6.2.5. Day 3 - SAD

The following procedures will be completed:

- Obtain temperature, supine pulse and supine triplicate blood pressure. Blood pressure is the only vital sign to be collected in triplicate.

- Collect blood samples for pharmacokinetic analysis 48 hours after Day 1 dosing.
- Collect blood samples for FPG and fasting glucagon.
- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Record concomitant medications.

6.2.6. Day 4 - SAD

The following procedures will be completed:

- Obtain fasting weight.
- Obtain temperature, supine pulse and supine triplicate blood pressure. Blood pressure is the only vital sign to be collected in triplicate.
- Collect blood sample for fasting lipids.
- Collect blood sample for fructosamine and 1,5-anhydroglucitol.
- Collect blood sample for FPG, fasting glucagon and fasting GLP-1 **(SAD IV Cohort 5).**
- Collect blood sample for 72 hr PK analysis.
- Obtain fingerstick glucose before breakfast.
- Prior to MMTT, collect the time 0 minute fasting blood samples for FPG, C-peptide, insulin, glucagon and GLP-1 (**SAD SC Cohorts 1-4**).
- Administer MMTT in AM. (**SAD SC Cohorts 1-4**) Collect samples (glucose, C-peptide, insulin, glucagon and GLP-1) at:
  - 15 minutes (5 minutes after fluid meal is consumed which requires 10 minutes; See **Section 7.4.1.2**);
  - 30 minutes;
  - 60 minutes;
  - 120 minutes
  - 180 minutes;
  - 240 minutes.

- Obtain fingerstick glucose 2-hr post breakfast, before lunch, 2-hr post-lunch, before dinner, 2-hr post-dinner, prior to snack (between 9 and 10 pm).

- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

- Record concomitant medications.

6.2.7. Day 5 - SAD

The following procedures will be completed:

- Obtain fingerstick glucose at 0300 and before breakfast.

Prior to discharge from the clinical research unit:

- Conduct full physical exam.

- Obtain fasting weight.

- Collect triplicate 12-Lead ECG.

- Obtain temperature, supine pulse rate and supine triplicate blood pressure. Blood pressure will be the only vital sign to be collected in triplicate.

- Collect fasting blood and urine samples for safety labs.

- Collect blood samples for coagulation panel, amylase and lipase.

- Collect blood samples for FPG and fasting glucagon.

- Collect blood sample for 96 hr PK.

- Assess injection site (required if reaction was noted on Day 1).

- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

- Record concomitant medications.

If a subject has any clinically significant, study-related abnormalities at the conclusion of a scheduled inpatient portion of the study, the Pfizer medical monitor (or designated representative) should be notified and the subject may be asked to remain in the Clinical Research Unit until such abnormalities are deemed not clinically significant, or it is safe for outpatient follow-up. If the subject is unable or unwilling to remain in the Clinical Research Unit and/or when outpatient follow-up is deemed appropriate, the Pfizer medical monitor (or designated representative) should be so notified, and the investigator should make every

effort to arrange follow-up evaluations at appropriate intervals to document the course of the abnormalities.

6.2.8. Days 8 (±1), 22 (±1) and 43 (±3) - SAD

The following procedures will be completed:

- Obtain temperature, supine pulse rate and triplicate supine blood pressure. Blood pressure will be the only vital sign collected in triplicate.
- Collect fasting blood and urine samples for safety labs.
- Collect blood samples for FPG and fasting glucagon (all cohorts).
- Collect blood sample for PK analysis.
- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Record concomitant medications.
- Confirm contraception method.

6.2.9. Days 15 (±1) and 29 (±2) - SAD

The following procedures will be completed:

- Conduct limited physical examination.
- Obtain fasting weight.
- Collect triplicate 12-Lead ECG.
- Obtain temperature, supine pulse rate and triplicate supine blood pressure. Blood pressure will be the only vital sign collected in triplicate.
- Collect fasting blood and urine samples for safety labs.
- Collect blood sample for fasting lipid profile.
- Collect blood sample for PK analysis.
- Collect blood sample for ADA analysis.
- Collect blood samples for fructosamine and 1,5-anhydoglucitol.
- Collect blood sample for HbA1c (Day 29 only).

- Collect blood samples for coagulation panel, amylase and lipase.
- Obtain fingerstick glucose before breakfast (MMTT).
- Prior to MMTT, collect the 0 minute timepoint fasting blood samples for FPG, C-peptide, insulin, glucagon and GLP-1.
- Administer MMTT in AM. Collect samples (glucose, C-peptide, insulin, glucagon and GLP-1) at:
  - 15 minutes (5 minutes after fluid meal is consumed which requires 10 minutes; See **Section 7.4.1.2**);
  - 30 minutes;
  - 60 minutes;
  - 120 minutes;
  - 180 minutes;
  - 240 minutes.
- Obtain fingerstick glucose before breakfast, 2-hr post breakfast, before lunch, 2-hr post-lunch, before dinner, 2-hr post-dinner, prior to snack (between 9 and 10 pm).
- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Record concomitant medications.
- Question subject on metformin compliance.
- Confirm contraception method.

6.2.10. Day 16 (±2) and Day 30 (±2) - SAD

The following procedures will be completed by the subject at home, no clinic visit is required:

- Obtain fingerstick glucose at 0300 and prior to breakfast.

6.2.11. Day 57 (±3) - SAD

The following procedures will be completed:

- Conduct limited physical examination.

- Obtain fasting weight.
- Collect triplicate 12-Lead ECG.
- Obtain temperature,supine pulse rate and triplicate supine blood pressure. Blood pressure will be the only vital sign collected in triplicate.
- Collect fasting blood and urine samples for safety labs.
- Collect blood sample for fasting lipid profile.
- Collect blood sample for PK analysis.
- Collect blood sample for ADA analysis.
- Collect blood samples for fructosamine and 1,5-anhydoglucitol.
- Collect blood sample for HbA1c.
- Collect blood samples for coagulation panel, amylase and lipase.
- Collect blood samples for FPG,fasting glucagon and fasting GLP-1.
- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as “How do you feel?”
- Record concomitant medications.
- Question subject on metformin compliance.
- Confirm contraception method.

6.2.12. Day 85 (±3)/Early Termination – SAD

The following procedures will be performed:

- Conduct limited physical exam of the skin, heart, lungs, abdomen and extremities by trained medical personnel at the investigator site.
- Assess temperature, supine pulse rate and triplicate supine blood pressure. Blood pressure will be the only vital sign collected in triplicate.
- Collect fasting weight and triplicate waist circumference.
- To measure waist circumference, use a spring-loaded tape measure, and starting at the top of the hip bone, bring it all the way around, level with the navel. Tape measure

should not be too tight and parallel with the floor. Instruct subject to not hold their breath. Measurement should not include navel.

- Collect triplicate 12-lead ECG.
- Collect fasting blood and urine samples for safety labs.
- Collect blood sample for fasting lipid profile.
- Collect blood sample for fructosamine and 1,5-anhydroglucitol.
- Collect blood samples for coagulation panel, amylase and lipase.
- Collect blood sample for HbA1c.
- Collect blood samples for FPG, fasting glucagon and fasting GLP-1.
- Collect blood sample for PK analysis.
- Collect blood sample for ADA analysis.
- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Record concomitant medications.
- Question subject on metformin compliance.
- Confirm contraception method.
- Schedule 1-3-month extended follow-up visit – site will be notified if visit will be required once data is available.

Note for extended follow-up: Subjects will continue to be monitored beyond the last scheduled visit, if necessary, for elevated glucagon levels and/or presence of anti-PF-06293620 antibodies (at approximately 1-3 month intervals) until their glucagon/ADA levels return to approximate baseline or establish a new steady-state level.

6.3. Study Procedures - MAD

For the study period described below, when multiple procedures are scheduled at the same time point(s) relative to dosing, the following chronology of events should be adhered to, where possible.

- ECGs: obtain prior to vital signs and as close as possible to scheduled time, but prior to blood specimen collection; all ECGs will be submitted to Central ECG vendor for

independent review. On dosing days, collect triplicate ECG prior to study drug administration (pre-dose) and 1, 2, and 4 hours after dosing.

- Blood pressure/pulse rate: obtain as close as possible to scheduled time, but prior to blood specimen collection.

- Pharmacokinetic blood specimens: obtain at scheduled time within 10% of the nominal time from dosing.

- Other procedures: obtain all other procedures as close as possible to the scheduled time, but may be obtained before or after blood specimen collection.

6.3.1. Day -3 (MAD)

Subjects will be admitted to the Clinical Research Unit. Subjects will be required to stay in the Clinical Research Unit for 5 nights and will be discharged on Day 3.

Site staff will review concomitant medications, adverse events and contraception method. Concomitant medications, including metformin compliance, will be recorded in medication history. Any noted adverse events will be recorded as prior medical history.

On admittance to the CRU, subjects will undergo the following procedures:

- Urine drug screen (for illicit drugs).

- Peripheral IV (PIV)/hep lock may be placed, in accordance with site policies, for serial blood collections on Day -2.

- Question subject on metformin compliance.

- Confirm contraception method.

6.3.2. Day -2 (MAD)

On Day -2, after an overnight fast of at least 10 hours, the following procedures will be performed:

- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as “How do you feel?”

- Collect fasting weight.

- Assess patency of peripheral IV (PIV)/heplock, in accordance with site policies,

    - If no longer patent remove and insert a new PIV/heplock in accordance with site policies. Allow subject to rest at least 1 hour prior to obtaining vital signs and initiating 24 hour ambulatory blood pressure monitoring.

- Assess temperature, supine pulse rate and triplicate supine blood pressure. Blood pressure will be the only vital sign collected in triplicate.

- Initiate 24 hour ambulatory blood pressure monitoring.

    - Placement of cuff must not be on the same arm as the PIV.

- Initiate mean daily glucose profile.

    - Collect blood sample at the following timepoints: 30 minutes before and immediately prior to AM meal, 30, 60, 90, 120 and 180 minutes after the start of the AM meal; immediately prior to the midday meal, 60, 120 and 180 minutes after the start of the midday meal; immediately prior to the evening meal, 60, 120 and 180 minutes after the start of the evening meal; approximatey at 11:00 PM.

    - On days when mean daily glucose profiles are being collected meals will be given at approximately 08:00 AM, 12:00 PM and 6:00 PM. Subjects will have 30 minutes to finish the meal and must consume the entire meal. Collection times are from the start of the meal.

- Record concomitant medications.

- Question subject on metformin compliance.

6.3.3. Day -1 MAD

On Day -1, after an overnight fast of at least 10 hours, the following procedures will be completed:

- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as “How do you feel?”

- Review medical history

- Assess patency of peripheral IV (PIV)/heplock, in accordance with site policies,

    - If no longer patent remove and insert a new PIV/heplock in accordance with site policies. Allow subject to rest at least 1 hour prior to obtaining vital signs.

- Obtain blood sample at approximately 03:00 AM and 07:30 AM (immediately prior to breakfast) to complete the mean daily glucose profile.

- Obtain temperature, supine pulse and triplicate supine blood pressure.

- Complete 24 hour ambulatory blood pressure monitoring.

  - NOTE: Before proceeding with any other Day -1 assessments, immediately upload the Day -2 Ambulatory blood pressure monitoring (ABPM) data to the vendor to determine if the data passes vendor technical quality control (QC). If the data fails technical QC, immediately restart/repeat the ABPM on Day -1 to ensure a baseline/pre-dose dataset is obtained. Then start the remaining Day -1 procedures.

- Conduct limited physical exam of the skin, heart, lungs, abdomen and extremities by trained medical personnel at the investigator site.

- Collect fasting weight and triplicate waist circumference.

  - To measure waist circumference, use a spring-loaded tape measure, and starting at the top of the hip bone, bring it all the way around, level with the navel. Tape measure should not be too tight and parallel with the floor. Instruct subject to not hold their breath. Measurement should not include navel.

- Collect blood samples for the following:

  - Fasting serum chemistry;
  - Hematology;
  - Fasting lipid profile;
  - Apo B;
  - HbA1c;
  - Fructosamine;
  - 1,5-anhydroglucitol;
  - ADA;
  - Banked Specimen (Pharmacogenomics).

- Obtain fingerstick glucose before breakfast (fasting) before MMTT.

- Before MMTT, collect 0 minute fasting timepoint blood sample for FPG, C-peptide, insulin, glucagon and GLP-1 (all cohorts).

- Administer MMTT in AM; begin sample collection (glucose, C-peptide, insulin, glucagon and GLP-1):

  - 15 minutes from start of meal (first sample collected 5 minutes post meal; the liquid should take 10 minutes to consume; **See Section 7.4.1.2**);

    - 30 minutes;
    - 60 minutes;
    - 120 minutes;
    - 180 minutes;
    - 240 minutes.
- Obtain fingerstick glucose measurements 2 hr post- breakfast, before lunch, 2-hr post-lunch, before dinner, 2-hr post-dinner, prior to snack (between 9 and 10 PM).
- Record concomitant medications.
- Question subject on metformin compliance.
- Randomize subject to study treatment.

6.3.4. Day 1 - MAD

On Day 1, after an overnight fast of at least 10 hours, the following procedures will be completed **Prior to dosing**:

- Obtain finger-stick glucose measurement at 0300.
- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Assess patency of peripheral IV (PIV)/heplock, in accordance with site policies.
    - If no longer patent remove and insert a new PIV/heplock in accordance with site policies. Allow subject to rest at least 1 hour prior to obtaining vital signs and initiating 24 hour ambulatory blood pressure monitoring.
- Collect triplicate 12-Lead ECG.
- Collect temperature, supine pulse and triplicate supine blood pressure.
- Obtain finger-stick glucose measurement prior to breakfast (fasting).
- Obtain fasting weight.
- Collect a blood sample for pharmacokinetic analysis (pre-dose).
- Collect blood samples for the following:
    - Hematology;

  - Fasting clinical chemistry;
  - Coagulation panel, amylase and lipase.
- Collect blood for FPG, fasting glucagon and fasting GLP-1.
- Collect urine for urinalysis (clean catch, midstream).
- Initiate 24 hour ambulatory blood pressure monitoring (at least 1 hour prior to study drug administration).
  - Placement of cuff must not be on the same arm as the PIV.
- Administer the study medication (see STUDY TREATMENTS and Administration Sections).

After dosing, the following procedures will be completed:

- Assess temperature, supine pulse rate and triplicate supine blood pressure at 1, 2, and 4 hours after dosing. Blood pressure is the only vital sign to be collected in triplicate.
- Obtain triplicate 12-lead ECG measurements at 1, 2, and 4 hours after dosing.
- Collect blood samples for pharmacokinetic analysis at 1 and 4 hours following dosing.
- Injection site assessment immediately after injection at: 15 and 30 minutes, 1, and 2 hours post administration. Additional assessments should be performed as needed after the last assessment of 2 hrs post-dose on dosing days.
- Record concomitant medication.
- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as “How do you feel?”
- Question subject on metformin compliance.

6.3.5. Day 2 - MAD

On Day 2, after an overnight fast of at least 10 hours, the following procedures will be completed:

- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as “How do you feel?”
- Assess patency of peripheral IV (PIV)/heplock, in accordance with site policies,

    - If no longer patent remove and insert a new PIV/heplock in accordance with site policies. Allow subject to rest at least 1 hour prior to obtaining vital signs.

- Complete 24 hour continuous blood presure monitoring.

    - NOTE: Before proceeding with any other Day 2 assessments, immediately upload the ABPM data to the vendor to determine if the data passes vendor QC. If the data fails technical QC, immediately restart/repeat the ABPM on Day 2 to ensure a complete dataset is obtained. Then start the remaining Day 2 procedures. If the 24 hour ambulatory blood pressure monitoring cannot be repeated on Day 2 please contact the sponsor to discuss alternative times.

- Conduct full physical exam.

- Obtain fasting weight.

- Collect blood sample for pharmacokinetic analysis at 24 hours after Day 1 dosing.

- Collect blood samples for FPG and fasting glucagon.

- Collect fasting blood and urine samples for safety laboratory tests 24 hours after Day 1 dosing.

- Obtain triplicate 12-lead ECG measurements 24 hours after Day 1 dosing.

- Assess temperature, supine pulse and triplicate supine blood pressure 24 hours after Day 1 dosing. Blood pressure is the only vital sign to be collected in triplicate.

- Assess injection site for reactions if necessary (required if a reaction was observed on Day 1).

- Record concomitant medications.

- Question subject on metformin compliance.

6.3.6. Day 3 - MAD

On Day 3, after an overnight fast of at least 10 hours, the following procedures will be completed:

- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as “How do you feel?”

- Assess patency of peripheral IV (PIV)/heplock, in accordance with site policies,

    - If no longer patent remove and insert a new PIV/heplock in accordance with site policies. Allow subject to rest at least 1 hour prior to obtaining vital signs.

- Obtain fasting weight.
- Obtain temperature, supine pulse and triplicate supine blood pressure. Blood pressure is the only vital sign to be collected in triplicate.
- Collect blood samples for pharmacokinetic analysis 48 hours after Day 1 dosing.
- Collect blood samples for FPG and fasting glucagon.
- Record concomitant medications.
- Question subject on metformin compliance.
- Remove PIV/heplock prior to discharge.

If a subject has any clinically significant, study-related abnormalities at the conclusion of a scheduled inpatient portion of the study, the Pfizer medical monitor (or designated representative) should be notified and the subject may be asked to remain in the Clinical Research Unit until such abnormalities are deemed not clinically significant, or it is safe for outpatient follow-up. If the subject is unable or unwilling to remain in the Clinical Research Unit and/or when outpatient follow-up is deemed appropriate, the Pfizer medical monitor (or designated representative) should be so notified, and the investigator should make every effort to arrange follow-up evaluations at appropriate intervals to document the course of the abnormalities.

6.3.7. Day 6 – MAD

Subjects will be admitted to the Clinical Research Unit. Subjects will be required to stay in the Clinical Research Unit for 2 nights and will be discharged on Day 8.

Site staff will review adverse events, concomitant medications, metformin compliance and confirm contraception method. Concomitant medications will be recorded in medication history. Any noted adverse events will be recorded as prior medical history.

- PIV/heplock may be placed, in accordance with site policies, for serial blood collections on Day 7 and 8.

6.3.8. Day 7 – MAD

On Day 7, after an overnight fast of at least 10 hours, the following procedures will be completed:

- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as “How do you feel?”
- Assess patency of peripheral IV (PIV)/heplock, in accordance with site policies,

    - If no longer patent remove and insert a new PIV/heplock in accordance with site policies. Allow subject to rest at least 1 hour prior to obtaining vital signs.

- Collect fasting weight.

- Obtain temperature, supine pulse and triplicate supine blood pressure. Blood pressure is the only vital sign to be collected in triplicate.

- Initiate 24 hour ambulatory blood pressure monitoring.

    - Placement of cuff must not be on the same arm as the PIV.

- Collect blood sample for pharmacokinetic analysis.

- Record concomitant medications.

- Question subject on metformin compliance.

6.3.9. Days 8 - MAD

On Day 8, after an overnight fast of at least 10 hours, the following procedures will be completed:

- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as “How do you feel?”

- Assess patency of peripheral IV (PIV)/heplock, in accordance with site policies,

    - If no longer patent remove and insert a new PIV/heplock in accordance with site policies. Allow subject to rest at least 1 hour prior to obtaining vital signs.

- Obtain fasting weight.

- Obtain temperature, supine pulse rate and triplicate supine blood pressure. Blood pressure will be the only vital sign collected in triplicate.

- Collect triplicate 12-Lead ECG.

- Collect fasting blood and urine samples for safety labs (hematology, chemistry, urinalysis (clean catch, midstream).

- Collect blood sample for fasting lipids and Apo B.

- Collect blood sample for PK analysis.

- Obtain fingerstick glucose before breakfast (before MMTT).

- Complete 24-hour ambulatory blood pressure monitoring.
    - NOTE: Before proceeding with any other Day 8 assessments, immediately upload the Day 7 ABPM data to the vendor to determine if the data passess vendor QC. If the data fails technical QC, immediately restart/repeat the ABPM on Day 8 to ensure a complete dataset is obtained. Then proceed with the remaining Day 8 procedures. If the 24 hour ambulatory blood pressure monitoring cannot be repeated on Day 8 please contact the sponsor to discuss alternative times.
- Before MMTT, collect 0 minute fasting timepoint blood sample for FPG, C-peptide, insulin, glucagon and GLP-1 (all cohorts).
- Administer MMTT in AM; begin sample collection (glucose, C-peptide, insulin, glucagon and GLP-1):
    - 15 minutes from start of meal (first sample collected 5 minutes post meal; the liquid should take 10 minutes to consume; **See Section 7.4.1.2**);
    - 30 minutes;
    - 60 minutes;
    - 120 minutes;
    - 180 minutes;
    - 240 minutes.
- Obtain fingerstick glucose measurements 2 hr post- breakfast, before lunch, 2-hr post-lunch, before dinner, 2-hr post-dinner, prior to snack (between 9 and 10 PM).
    - Afternoon, evening, 0300 (Day 9) and before breakfast (Day 9) fingersticks will be performed by the subject after discharge from the CRU.
- Record concomitant medications.
- Question subject on metformin compliance.
- Remove PIV/heplock prior to discharge.

If a subject has any clinically significant, study-related abnormalities at the conclusion of a scheduled inpatient portion of the study, the Pfizer medical monitor (or designated representative) should be notified and the subject may be asked to remain in the Clinical Research Unit until such abnormalities are deemed not clinically significant, or it is safe for outpatient follow-up. If the subject is unable or unwilling to remain in the Clinical Research Unit and/or when outpatient follow-up is deemed appropriate, the Pfizer medical monitor (or designated representative) should be so notified, and the investigator should make every

effort to arrange follow-up evaluations at appropriate intervals to document the course of the abnormalities.

6.3.10. Day 15 (±1) – MAD

On Day 15, after an overnight fast of at least 10 hours, the following procedures will be completed:

- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Conduct limited physical exam of the skin, heart, lungs, abdomen and extremities by trained medical personnel at the investigator site.
- Collect fasting weight.
- Collect triplicate 12-Lead ECG.
- Obtain temperature, supine pulse rate and triplicate supine blood pressure. Blood pressure will be the only vital sign collected in triplicate.
- Collect fasting blood and urine samples for safety labs (hematology, chemistry, urinalysis (clean catch, midstream).
- Collect the following blood samples:
    - Fasting lipid panel;
    - Apo B;
    - Fasting plasma glucose;
    - Coagulation panel, amylase and lipase;
    - Fructosamine;
    - 1,5-anhydroglucitol;
    - Pharmacokinetic analysis (pre-dose);
    - ADA.
- Record concomitant medications.
- Question subject on metformin compliance.
- Confirm contraception method.

6.3.11. Day 27 (±1) - MAD

Subjects will be admitted to the Clinical Research Unit. Subjects will be required to stay in the Clinical Research Unit for 2 nights and will be discharged on Day 29.

Site staff will review concomitant medications, metformin compliance, adverse events and contraception method. Concomitant medications will be recorded in medication history. Any noted adverse events will be recorded as prior medical history.

- PIV/helpock may be placed, in accordance with site policies, for serial blood collections on Day 28 and 29.

- Collect sample for pharmacokinetic analysis.

6.3.12. Day 28 - MAD

On Day 28, after an overnight fast of at least 10 hours, the following procedures will be completed:

- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as “How do you feel?”

- Assess patency of peripheral IV (PIV)/heplock, in accordance with site policies,

    - If no longer patent remove and insert a new PIV/heplock in accordance with site policies. Allow subject to rest at least 1 hour prior to obtaining vital signs.

- Obtain fasting weight.

- Obtain temperature, supine pulse rate and triplicate supine blood pressure. Blood pressure will be the only vital sign collected in triplicate.

- Collect fasting plasma glucose.

- Collect a blood sample for pharmacokinetic analysis.

- Initiate mean daily glucose profile.

    - Collect blood sample at the following timepoints: 30 minutes before and immediately prior to AM meal, 30, 60, 90, 120 and 180 minutes after the start of the AM meal; immediately prior to the midday meal, 60, 120 and 180 minutes after the start of the midday meal; immediately prior to the evening meal, 60, 120 and 180 minutes after the start of the evening meal; approximately at 11:00 PM.

    - On days when mean daily glucose profiles are being collected meals will be given at approximate;y 08:00 AM, 12:00 PM and 6:00 PM. Subjects will have 30 minutes to finish the meal and must consume the entire meal. Collection times are from the start of the meal.

- Record concomitant medications.
- Question subject on metformin compliance.

6.3.13. Day 29 - MAD

On Day 29, after an overnight fast of at least 10 hours, the following procedures will be completed **prior to study drug administration**:

- Obtain blood sample at approximately 03:00 AM and 07:30 AM (immediately prior to breakfast) for mean daily glucose profile.
- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Assess patency of peripheral IV (PIV)/heplock, in accordance with site policies,
    - If no longer patent remove and insert a new PIV/heplock in accordance with site policies. Allow subject to rest at least 1 hour prior to obtaining vital signs.
- Conduct limited physical exam of the skin, heart, lungs, abdomen and extremities by trained medical personnel at the investigator site.
- Collect fasting weight.
- Collect triplicate 12-Lead ECG.
- Obtain temperature, supine pulse rate and triplicate supine blood pressure. Blood pressure will be the only vital sign collected in triplicate.
- Obtain blood sample immediately prior to breakfast (fasting) to complete the mean daily glucose profile.
- Collect fasting blood and urine samples for safety labs (hematology, chemistry, urinalysis (clean catch, midstream).
- Collect blood samples for:
    - Fasting lipid profile;
    - Apo B;
    - Coagulation panel, amylase and lipase;
    - HbA1c;
    - FPG, fasting glucagon and fasting GLP-1;

- Fructosamine;
- 1,5-anhydroglucitol;
- Pharmacokinetic analysis;
- ADA.

- Administer the study medication (see STUDY TREATMENTS and Administration Sections).

After dosing, the following procedures will be completed:

- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Injection site assessment immediately after injection at: 15 and 30 minutes, 1, and 2 hours post administration. Additional assessments should be performed as needed after the last assessment of 2 hrs post-dose on dosing days.
- Assess temperature, supine pulse rate and supine triplicate blood pressure at 1, 2, and 4 hours after dosing. Blood pressure is the only vital sign to be collected in triplicate.
- Obtain triplicate 12-lead ECG measurements at 1, 2, and 4 hours after dosing.
- Collect blood samples for pharmacokinetic analysis at 1 and 4 hours following dosing.
- Record concomitant medications.
- Question subject on metformin compliance.
- Remove PIV/heplock prior to discharge.

If a subject has any clinically significant, study-related abnormalities at the conclusion of a scheduled inpatient portion of the study, the Pfizer medical monitor (or designated representative) should be notified and the subject may be asked to remain in the Clinical Research Unit until such abnormalities are deemed not clinically significant, or it is safe for outpatient follow-up. If the subject is unable or unwilling to remain in the Clinical Research Unit and/or when outpatient follow-up is deemed appropriate, the Pfizer medical monitor (or designated representative) should be so notified, and the investigator should make every effort to arrange follow-up evaluations at appropriate intervals to document the course of the abnormalities.

6.3.14. Day 36 (±1) – MAD

On Day 36, after an overnight fast of at least 10 hours, the following procedures will be completed:

- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Record concomitant medications.
- Question subject on metformin compliance.
- Confirm contraception method.
- Obtain fasting weight, temperature, supine pulse rate and triplicate supine blood pressure. Blood pressure will be the only vital sign collected in triplicate.
- Collect blood samples for:
    - Liver Function Test: ALT. AST, GGT, lactate dehydrogenase (LDH), alkaline phosphatase, total bilirubin, indirect bilirubin, direct bilirubin and creatine kinase;
    - FPG;
    - Pharmacokinetic analysis.

6.3.15. Day 43 (±1) – MAD

On Day 43, after an overnight fast of at least 10 hours, the following procedures will be completed:

- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Collect fasting weight.
- Obtain temperature, supine pulse rate and triplicate supine blood pressure. Blood pressure will be the only vital sign collected in triplicate.
- Collect fasting blood and urine samples for safety labs (hematology, chemistry, urinalysis (clean catch, midstream).
- Collect blood samples for:
    - Fasting lipid profile;
    - Apo B;

- FPG and fasting glucagon;
- Pharmacokinetic analysis.

- Record concomitant medications.
- Question subject on metformin compliance.
- Confirm contraception method.

6.3.16. Day 57 (±1)- MAD

On Day 57, after an overnight fast of at least 10 hours, the following procedures will be completed **prior to study drug administration**:

- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Collect fasting weight.
- Conduct limited physical exam of the skin, heart, lungs, abdomen and extremities by trained medical personnel at the investigator site.
- Obtain triplicate 12-lead ECG measurements.
- Obtain temperature, supine pulse rate and triplicate supine blood pressure. Blood pressure will be the only vital sign collected in triplicate.
- Collect fasting blood and urine samples for safety labs (hematology, chemistry, urinalysis (clean catch, midstream).
- Collect blood samples for:
  - Fasting lipid profile;
  - Apo B;
  - Coagulation panel, amylase and lipase;
  - HbA1c;
  - FPG, fasting glucagon and fasting GLP-1;
  - Fructosamine;
  - 1,5-anhydroglucitol;

  - ADA;
  - Pharmacokinetic analysis.
- Administer the study medication (see STUDY TREATMENTS and Administration Sections).

After dosing, the following procedures will be completed:

- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Injection site assessment immediately after injection at: 15 and 30 minutes, 1, and 2 hours post administration. Additional assessments should be performed as needed after the last assessment of 2 hrs post-dose on dosing days.
- Assess temperature, supine pulse rate and supine triplicate blood pressure at 1, 2, and 4 hours after dosing. Blood pressure is the only vital sign to be collected in triplicate.
- Obtain triplicate 12-lead ECG measurements at 1, 2, and 4 hours after dosing.
- Collect blood samples for pharmacokinetic analysis at 1 and 4 hours following dosing.
- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Record concomitant medications.
- Question subject on metformin compliance.
- Confirm contraception method.

6.3.17. Day 58 – MAD

On Day 58, after an overnight fast of at least 10 hours, the following procedures will be completed.

- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Collect blood samples for:
  - Fasting plasma glucose;
  - Pharmacokinetic sample.

- Record concomitant medications.
- Question subject on metformin compliance.

6.3.18. Day 59 - MAD

On Day 59, after an overnight fast of at least 10 hours, the following procedures will be completed

- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Collect blood samples for:
  - Fasting plasma glucose;
  - Pharmacokinetic sample.
- Record concomitant medications.
- Question subject on metformin compliance.
- Confirm contraception method.

6.3.19. Day 62 (±1) – MAD

Subjects will be admitted to the Clinical Research Unit. Subjects will be required to stay in the Clinical Research Unit for 2 nights and will be discharged on Day 64.

Site staff will review concomitant medications, metformin compliance, and adverse events. Concomitant medications will be recorded in medication history. Any noted adverse events will be recorded as prior medical history.

- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- PIV/heplock may be placed, in accordance with site policies, for serial blood collections on Day 63 and 64.
- Confirm contraception method.

6.3.20. Day 63 - MAD

On Day 63, after an overnight fast of at least 10 hours, the following procedures will be completed:

- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

- Assess patency of peripheral IV (PIV)/heplock, in accordance with site policies,
    - If no longer patent remove and insert a new PIV/heplock in accordance with site policies. Allow subject to rest at least 1 hour prior to obtaining vital signs and initiating 24 hour ambulatory blood pressure monitoring.
- Obtain fasting weight.
- Obtain triplicate 12-lead ECG measurements.
- Obtain temperature, supine pulse rate and triplicate supine blood pressure. Blood pressure will be the only vital sign collected in triplicate.
- Initiate 24 hour ambulatory blood pressure monitoring.
    - Placement of cuff must not be on the same arm as the PIV.
- Collect a blood sample for pharmacokinetic analysis.
- Record concomitant medications.
- Question subject on metformin compliance.

6.3.21. Day 64 (±1) - MAD

On Day 64, after an overnight fast of at least 10 hours, the following procedures will be completed:

- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Assess patency of peripheral IV (PIV)/heplock, in accordance with site policies,
- If no longer patent remove and insert a new PIV/heplock in accordance with site policies. Allow subject to rest at least 1 hour prior to obtaining vital signs.
- Complete 24 hour blood pressure monitoring.
    - NOTE: Before proceeding with any other Day 64 assessments, immediately upload the Day 63 ABPM data to the vendor to determine if the data passes vendor QC. If the Day 63 data fails technical QC, immediately restart/repeat the ABPM on Day 64 to ensure a complete dataset is obtained. Then perform the remaining Day 64 procedures. If the 24 hour ambulatory blood pressure monitoring cannot be repeated on Day 64 please contact the sponsor to discuss alternative times.
- Obtain fasting weight.

- Obtain temperature, supine pulse rate and triplicate supine blood pressure. Blood pressure will be the only vital sign collected in triplicate.
- Collect blood samples for:
  - Liver Function Test: ALT. AST, GGT, lactate dehydrogenase (LDH), alkaline phosphatase, total bilirubin, indirect bilirubin, direct bilirubin and creatine kinase;
  - Fasting lipid profile;
  - Apo B;
  - Pharmacokinetic analysis;
  - Obtain fingerstick glucose before breakfast (before MMTT);
  - Prior to MMTT, collect the time 0 minute fasting blood samples for FPG, C-peptide, insulin, glucagon and GLP-1;
  - Administer MMTT in AM. Collect samples (glucose, C-peptide, insulin, glucagon and GLP-1) at:
    - 15 minutes (5 minutes after fluid meal is consumed which requires 10 minutes; See **Section 7.4.1.2**);
    - 30 minutes;
    - 60 minutes;
    - 120 minutes;
    - 180 minutes;
    - 240 minutes.
- Obtain fingerstick glucose measurements 2 hr post- breakfast, before lunch, 2-hr post-lunch, before dinner, 2-hr post-dinner, prior to snack (between 9 and 10 PM).
  - Afternoon, evening, 0300 (Day 65) and before breakfast (Day 65) fingersticks will be performed after discharge from the CRU.
- Record concomitant medications.
- Question subject on metformin compliance.
- Remove PIV/heplock prior to discharge.

If a subject has any clinically significant, study-related abnormalities at the conclusion of a scheduled inpatient portion of the study, the Pfizer medical monitor (or designated representative) should be notified and the subject may be asked to remain in the Clinical Research Unit until such abnormalities are deemed not clinically significant, or it is safe for outpatient follow-up. If the subject is unable or unwilling to remain in the Clinical Research Unit and/or when outpatient follow-up is deemed appropriate, the Pfizer medical monitor (or designated representative) should be so notified, and the investigator should make every effort to arrange follow-up evaluations at appropriate intervals to document the course of the abnormalities.

6.3.22. Day 71 (±1) - MAD

On Day 71, after an overnight fast of at least 10 hours, the following procedures will be completed:

- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Obtain fasting weight.
- Obtain triplicate 12-lead ECG measurements.
- Obtain temperature, supine pulse rate and triplicate supine blood pressure. Blood pressure will be the only vital sign collected in triplicate.
- Collect fasting blood and urine samples for safety labs (hematology, chemistry, urinalysis (clean catch, midstream).
- Collect blood samples for:
    - Fasting lipid profile;
    - Apo B;
    - FPG and fasting glucagon;
    - Fructosamine;
    - 1,5-anhydroglucitol;
    - Pharmacokinetic analysis (pre-dose).
- Record concomitant medications.
- Question subject on metformin compliance.
- Confirm contraception method.

6.3.23. Day 78 (±1) MAD

On Day 78, after an overnight fast of at least 10 hours, the following procedures will be completed:

- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Collect blood sample for:
  - FPG, fasting glucagon and fasting GLP-1;
  - Pharmacokinetic analysis;
  - Record concomitant medications;
  - Question subject on metformin compliance;
  - Confirm contraception method.

6.3.24. Day 83 (±1) MAD

Subjects will be admitted to the Clinical Research Unit. Subjects will be required to stay in the Clinical Research Unit for 2 nights and will be discharged on Day 85.

Site staff will review concomitant medications, metformin compliance, adverse events and contraception method. Concomitant medications will be recorded in medication history. Any noted adverse events will be recorded as prior medical history.

- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- PIV/heplock may be placed, in accordance with site policies, for serial blood collections on Day 84.

6.3.25. Day 84 (±1) MAD

On Day 84, after an overnight fast of at least 10 hours, the following procedures will be completed:

- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Record concomitant medications.
- Question subject on metformin compliance.
- Obtain fasting weight.

- Obtain temperature, supine pulse rate and triplicate supine blood pressure. Blood pressure will be the only vital sign collected in triplicate.

- Assess patency of peripheral IV (PIV)/heplock, in accordance with site policies,

    - If no longer patent remove and insert a new PIV/heplock in accordance with site policies. Allow subject to rest at least 1 hour prior to obtaining vital signs and initiating 24 hour ambulatory blood pressure monitoring.

- Collect blood samples for:

    - Fasting plasma glucose;

    - Pharmacokinetic analysis.

- Question subject on metformin compliance.

- Initiate 24-hour ambulatory blood pressure monitoring.

    - Placement of cuff must not be on the same arm as the PIV.

- Initiate mean daily glucose profile.

    - Collect blood sample at the following timepoints: 30 minutes before and immediately prior to AM meal, 30, 60, 90, 120 and 180 minutes after the start of the AM meal; immediately prior to the midday meal, 60, 120 and 180 minutes after the start of the midday meal; immediately prior to the evening meal, 60, 120 and 180 minutes after the start of the evening meal; approximately at 11:00 PM.

    - On days when mean daily glucose profiles are being collected meals will be given at approximately 08:00 AM, 12:00 PM and 6:00 PM. Subjects will have 30 minutes to finish the meal and must consume the entire meal. Collection times are from the start of the meal.

6.3.26. Day 85 - MAD

On Day 85, after an overnight fast of at least 10 hours, the following procedures will be completed:

- Obtain blood samples at approximately 0300 AM and 0730 AM (immediately prior to breakfast) for mean daily glucose profile.

- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as “How do you feel?”

- Assess patency of peripheral IV (PIV)/heplock, in accordance with site policies,

- If no longer patent remove and insert a new PIV/heplock in accordance with site policies. Allow subject to rest at least 1 hour prior to obtaining vital signs.

- Complete 24-hour ambulatory blood pressure.

  - NOTE: Before proceeding with any other Day 85 assessments, immediately upload the Day 84 ABPM data to the vendor to determine if the data passes vendor QC. If the Day 84 data fails technical QC, immediately restart/repeat the ABPM on Day 85 to ensure a complete dataset is obtained. Then perform the remaining Day 85 procedures. If the 24 hour ambulatory blood pressure monitoring cannot be repeated on Day 85 please contact the sponsor to discuss alternative times.

- Conduct limited physical examination.

- Obtain fasting weight and triplicate waist circumference.

  - To measure waist circumference, use a spring-loaded tape measure, and starting at the top of the hip bone, bring it all the way around, level with the navel. Tape measure should not be too tight and parallel with the floor. Instruct subject to not hold their breath. Measurement should not include navel.

- Collect triplicate 12-Lead ECG.

- Obtain temperature,supine pulse rate and triplicate supine blood pressure. Blood pressure will be the only vital sign collected in triplicate.

- Obtain blood sample immediately prior to breakfast (fasting) to complete the mean daily glucose profile.

- Collect fasting blood and urine samples for safety labs (hematology, chemistry, urinalysis (clean catch, midstream).

- Collect blood samples for:

  - Fasting lipid panel;

  - Apo B;

  - Coagulation panel, amylase and lipase;

  - HbA1c;

  - FPG, fasting plasma glucagon and fasting GLP-1;

  - Fructosamine;

  - 1,5-anhydroglucitol;
  - Pharmacokinetic analysis;
  - ADA analysis;
  - Banked specimen (pharmacogenomics).
- Record concomitant medications.
- Question subject on metformin compliance.
- Remove PIV/heplock prior to discharge.

If a subject has any clinically significant, study-related abnormalities at the conclusion of a scheduled inpatient portion of the study, the Pfizer medical monitor (or designated representative) should be notified and the subject may be asked to remain in the Clinical Research Unit until such abnormalities are deemed not clinically significant, or it is safe for outpatient follow-up. If the subject is unable or unwilling to remain in the Clinical Research Unit and/or when outpatient follow-up is deemed appropriate, the Pfizer medical monitor (or designated representative) should be so notified, and the investigator should make every effort to arrange follow-up evaluations at appropriate intervals to document the course of the abnormalities

6.3.27. Days 99 (±5) & 141(±5) – Follow-up MAD

On Days 99 and 141, after an overnight fast of at least 10 hours, the following procedures will be completed:

- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as “How do you feel?”
- Obtain fasting weight.
- Obtain temperature,supine pulse rate and triplicate supine blood pressure. Blood pressure will be the only vital sign collected in triplicate.
- Collect blood samples for:
  - Blood chemistry;
  - Fasting plasma glucose;
  - Fasting plasma glucagon;
  - Pharmacokinetic analysis;

- HbA1c (**Day 141 only**);
- ADA analysis (**Day 141 only**).

- Record concomitant medications.
- Question subject on metformin compliance.
- Confirm contraception method.

6.3.28. Day 113 (±5) – Follow-up MAD

On Day 113, after an overnight fast of at least 10 hours, the following procedures will be completed:

- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Obtain fasting weight.
- Obtain temperature,supine pulse rate and triplicate supine blood pressure. Blood pressure will be the only vital sign collected in triplicate.
- Collect blood samples for:
  - Blood chemistry;
  - Hematology;
  - Fasting lipid panel;
  - Apo B;
  - HbA1c;
  - Fasting plasma glucose;
  - Fasting plasma glucagon;
  - Fasting GLP-1;
  - Fructosamine;
  - 1,5-anhydroglucitol;
  - Pharmacokinetic analysis;
  - ADA.

- Record concomitant medications.
- Question subject on metformin compliance.
- Confirm contraception method.

6.3.29. Day 169 (±5) or Early Termination MAD

On Day 169, after an overnight fast of at least 10 hours, the following procedures will be completed:

- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Conduct a limited physical examination.
- Obtain fasting weight and triplicate waist circumference.
    - To measure waist circumference, use a spring-loaded tape measure, and starting at the top of the hip bone, bring it all the way around, level with the navel. Tape measure should not be too tight and parallel with the floor. Instruct subject to not hold their breath. Measurement should not include navel.
- Obtain temperature,supine pulse rate and triplicate supine blood pressure. Blood pressure will be the only vital sign collected in triplicate.
- Collect triplicate 12-Lead ECG.
- Collect urine sample for urinalysis (clean catch; mid-stream).
- Collect blood samples for:
    - Hematology;
    - Blood chemistry;
    - Fasting lipid panel;
    - Apo B;
    - Coagulation panel, serum amylase and lipase;
    - HbA1c;
    - Fasting plasma glucose;
    - Fasting plasma glucagon;

  - Fasting GLP-1;
  - Fructosamine;
  - 1,5-anhydroglucitol;
  - Pharmacokinetic analysis;
  - ADA.
- Record concomitant medications.
- Question subject on metformin compliance.
- Confirm contraception method.
- Schedule extended follow-up visit – site will be notified if visit will be required once data is available.

Note for extended follow-up: Subjects will continue to be monitored, at up to 3 month intervals, beyond the last scheduled visit, if necessary, for:

- Elevated liver enzymes: if a subject had ≥3xULN elevations in liver enzymes at any time after the first dose of study drug, follow-up will continue, beyond the last scheduled visit, at up to 3–month intervals until enzymes have returned to:
  - WNL if subject was WNL at baseline, or
  - <2xULN if was between 1 – 2xULN at baseline.
- Elevated glucagon levels (ie, >3 X baseline) and/or presence of treatment-emergent anti-PF-06293620 antibodies will be followed,at approximately 1-3 month intervals, for up to 9 months after the last visit until their glucagon/ADA levels return to approximate baseline (ie, ≤3 X baseline), or if glucagon remains above baseline, no further visits are necessary if the glucagon/ADA has stabilized at consecutive visits with no related adverse events. **(see Section 7.4.1.1 for more details).**

6.4. Subject Withdrawal *(Early Termination)*

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or, behavioral reasons, or the inability of the subject to comply with the protocol required schedule of study visits or procedures at a given study site.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. The Investigator should attempt to contact the subject twice. After two attempts, CRU staff may send a registered letter. If no response is received from the subject, the

subject will be considered lost to follow up. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request the subject to return for a final visit, if applicable, and follow-up with the subject regarding any unresolved adverse events (AEs).

If the subject withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Subjects who withdraw from the study may be replaced at the discretion of the investigator upon consultation with the sponsor provided the nature of the safety event does not preclude dose escalation and exposure stopping limits are observed.

7. ASSESSMENTS

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well being of the subject. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventative actions which s/he has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

7.1. Blood Volume

The total blood sampling volume for individual subjects across the entire duration of this study (screening, active phase and follow-up) is approximately 490 mL for the SAD cohorts and approximately 722 mL for the MAD cohorts. The actual collection times of blood sampling may change, but the total blood volume collected will not increase. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 30 consecutive days. The estimated volumes of each test is listed in Table 8.

Table 8. Blood Volume

Sample Type	Approxiamte Sample Volume per timepoint (mL)
Unique Screening Labs	15.5
Chemistry	2.5
Hematology	2
Coagulation, amylase, lipase	1.8
HbA1c	2
Banked biospecimen	4
PK	6
Fasting plasma glucose	2
Fasting plasma glucagon	2
Fasting plasma GLP-1	2
Fasting Lipid Panel	5
Apo-B	2.5
Finger-stick glucose	0.03
Fructosamine	2.5
1,5-anhydroglucitol	
Immunogenicity (ADA)	4
Mixed meal tolerance test (glucose, insulin, C-peptide, glucagon, GLP-1)	7

This total volume does not include discarded blood from pre-draws used to remove fluid from flushed catheters.

7.2. Safety

7.2.1. Laboratory Tests

The following safety laboratory tests will be performed at times defined in the Study Procedures section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory; or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical labs may be obtained at any time during the study to assess any perceived safety concerns.

A central lab vendor will be used to analyze the tests to ensure accuracy and consistency in test results. The vendor will transmit all results for protocol tests, scheduled and unscheduled, to the sponsor for inclusion in the clinical database. Urinalysis will be performed on mid-stream, clean catch specimens.

Table 9. Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN/urea and Creatinine Glucose (fasting) Calcium Sodium Potassium Chloride Total CO2 (Bicarbonate) AST, ALT GGT[e] LDH[e] Total bilirubin Indirect bilirubin Direct bilirubin Alkaline phosphatase Uric acid Albumin Total protein Creatine kinase	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[a]	Apo B FSH[b] Urine drug screen[c] HIV Hepatitis Screen • Hepatitis B Surface Ag • Hepatitis B Core Ab • Hepatitis C Ab Amylase Lipase HbA1c Fasting lipid profile (total cholesterol, LDL-C, HDL-C, non-HDL-C, triglycerides)\ TSH PK ADA Fructosamine 1, 5-anhydroglucitol
Coagulation	**Additional Tests[d]**		**MMTT**
(aPTT/PT/INR)	AST, ALT (repeat) Total bilirubin (repeat) Albumin (repeat) Alkaline phosphatase (repeat) Direct bilirubin (repeat) Indirect bilirubin (repeat) GGT (repeat)		Fasting Plasma Glucose Fasting GLP-1 Fasting Glucagon C-Peptide Insulin

[a] Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.
[b] At Screening only, in women only
[c] At Screening and Day -2 (SAD only) and Day -3 (MAD only).
[d] Additional testing for potential Hy's Law cases only
[e] GGT and LDH: SAD Cohorts: will be performed in subjects with ALT and/or AST ≥3xULN; MAD Cohorts: will be performed in all subjects

The following applies to urine drug testing:

Minimum requirement for drug testing includes: cocaine, THC, opiates/opioids, and amphetamines

Subjects may undergo random urine drug testing at the discretion of the investigator. Drug testing conducted prior to dosing must be negative for subjects to receive study medication (exception: positive drug test for medications prescribed by a physician and approved by the Sponsor are allowed).

7.2.2. Physical Examinations

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation. A complete physical examination will include head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, breast (unless subject refuses), gastrointestinal, musculoskeletal, and neurological systems. The limited or abbreviated physical examination will be focused on general appearance, the respiratory and cardiovascular systems, as well as towards subject reported symptoms.

7.2.3. Height, Weight and Waist Circumference

Body height and weight recordings will be measured at times specified in Schedule of Activities section of this protocol. Height will be measured in centimeters using a wall mounted stadiometer in stocking feet at screening only and carried forward . Weight will be measured in kilograms using a calibrated scale and at approximately the same time of day at each nominal timepoint. The weight measurement should be taken with subjects wearing a gown (or other standard clothing provided by the CRU), undergarments, and socks (no shoes), while fasting and after the subject has been asked to void (e.g. empty bladder).

Waist circumference will be measured in triplicate at times specified in the Schedule of Activities section of this protocol. The waist circumference measurement should be taken with the subject wearing a gown. To measure waist circumference, use a spring-loaded tape measure, and starting at the top of the hip bone, bring it all the way around, level with the navel. Tape measure should not be too tight and parallel with the floor. Instruct subject to not hold their breath. Measurement should not include navel.

7.2.4. Blood Pressure and Pulse Rate

Blood pressure and pulse rate will be measured at times specified in Study Procedures section of this protocol. Additional collection times, or changes to collection times of blood pressure and pulse rate will be permitted, as necessary, to ensure appropriate collection of safety data.

Supine blood pressure will be measured with the subject's arm supported at the level of the heart and recorded to the nearest mm Hg after 5 minutes of rest. Rest is defined as quiet period with no talking, cellphone, television (TV) etc. until all blood pressure measurements are completed. Subjects should be instructed not to speak during measurements. The same arm (preferably the non-dominant arm in MAD portion of the study) will be used throughout the study. Blood pressure should not be taken from the arm with a peripheral IV, heplock or an intravenous infusion. Subjects should be instructed not to speak during measurements.

The same properly sized and calibrated blood pressure cuff will be used to measure blood pressure each time. Triplicate measurements should be conducted at approximately 2 minute intervals. The use of an automated device for measuring individual BP and pulse rate is preferred. When using an automated device, all efforts should be made to use the same device for each time point. When pulse rate is assessed manually, it will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements

coincides with a blood collection, blood pressure and pulse rate should be obtained prior to the nominal time of the blood collection.

7.2.5. Temperature

It is preferred that body temperature be collected using the tympanic or oral methods and that the same method be used consistently throughout the study. No eating, drinking or smoking is allowed for 15 minutes prior to the measurement.

7.2.6. Electrocardiogram

Electrocardiograms (ECGs) should be collected at times specified in the Study Procedures section of this protocol.

All scheduled ECGs should be performed after the subject has rested quietly for at least 10 minutes in a supine position.

All ECGs will be reviewed by the Investigator or designated MD prior to subject leaving the clinic. In addition, all ECGs performed in the MAD cohorts will be sent to a central vendor for independent review/assessment. Data transferred from the vendor will be assessed as Normal, Abnormal, or Not Evaluable; however interpretation of overall clinical significance will be determined by the Investigator. To ensure safety of the subjects and potential reporting purposes, a qualified individual at the investigator site will make comparisons to baseline measurements. Since there may be multiple baseline ECGs, the predominant findings observed can be used for the purposes of comparison. If the QTc interval is increased by >45 msec from the baseline, or an absolute QTc value is ≥500 msec for any scheduled ECG, then 2 additional ECGs will be collected, approximately 2-4 minutes apart, to confirm the original measurement. If either of the QTc values from these repeated ECGs remains above the threshold value (>45 msec from the baseline; or is ≥500 msec), then a single ECG must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified physician's interpretation determines that the QTc values are in the acceptable range.

7.2.7. Continuous Cardiac Monitoring by Telemetry (SAD Cohorts only)

All abnormal rhythms will be recorded and reviewed by the study physician for the presence of rhythms of potential clinical concern. The time, duration, and description of the clinically significant event will be recorded in the CRF/DCT. In addition, a printed record of the tracing(s) of the clinically significant rhythm(s) will be made and retained with other source documents.

Telemetry should be collected using a centralized system that also allows for the storage and advanced analysis of all recorded data in order to preserve important events for future evaluations. Holter monitoring should not be used in parallel with continuous telemetry, unless it is the only means of data storage available at the study site, or verifiable arrhythmia quantification is required. Telemetry will be initiated on Day -1, at least 12 hours prior to dosing on Day 1 and continue for 24 hours.

Telemetry may be stopped within a reasonably short period of time prior to dosing, in order to avoid interference with study operations conducted immediately before dosing. However, it is expected that the telemetry leads will be in place and the system connected prior to dosing.

7.2.8. Ambulatory Blood Pressure Monitoring (MAD Cohorts Only)

Twenty-four (24) hour ambulatory blood pressure monitoring (ABPM) will be performed in the MAD cohorts, at times specified in the STUDY PROCEDURES section of this protocol. Blood pressure assessments will be initiated in the AM on scheduled days and will be initiated at approximately the same time for a subject throughout the duration of the study. The start/stop time and description of any events that may effect blood pressure (eg, blood pressure medication, meals, sleep) will be recorded in the eCRF. Blood pressures will automatically be assessed approximately every 20 minutes between 0600 and 2200 and approximately every 30 minutes between 2200 and 0600**.**

Blood pressure readings will be collected using a centralized system that also allows for the storage and advanced analysis of all recorded data in order to preserve important events for future evaluations. All data will be electronically transferred to a central vendor for the analysis. Ambulatory blood pressure monitoring will be conducted on Day -2 to obtain a baseline dataset; the baseline dataset will be immediately uploaded to the central vendor for technical QC before proceeding with any Day -2 procedures. If the baseline (Day -2) data fails technical QC the baseline (Day -2) procedure must be repeated starting on Day-1. Twenty-four hour ABPM will also be collected beginning on Day 1, at least 1 hour prior to study drug administration; Day 7, Day 63 and then again on Day 84 and data will immediately uploaded to the central vendor for technical QC before proceeding with any Day 2, 8, 64 or 85 procedures.

If any of the Day 1 through Day 85 ABPM fail technical QC the procedures should be repeated the following day, if feasible. If the 24 hour ambulatory blood pressure monitoring cannot be repeated the following day, please contact the sponsor immediately to discuss alternative time points.

7.2.9. Fingerstick Glucose Monitoring

Investigators (when subjects are confined in the CRU) and subjects (when they are outpatients) will monitor glucose with fingersticks to obtain a drop of capillary blood for the glucometer measurement for safety assessments. Fingerstick glucose will be measured when subjects report symptoms of low blood sugar, prior to intervention. In addition, 24-hour glucose profiles will be performed as specified in Section 6.

7.2.10. Mean Daily Glucose Profile

Investigators will monitor the subjects mean glucose profile with multiple venous collections over a 24-hour period as specified in Section 6. The meals and snacks provided during confimement for mean daily glucose (MDG) will standardized as indicated in Section 4.4.1 and should be approximately 50% carbohydrate, 35% fat and 15% protein. Within each subject, the same meals and snacks must be provided during every MDG profile. On days when mean daily glucose profiles are being collected meals will be given at approximately 08:00 AM, 12:00 PM and 6:00 PM. Subjects will have 30 minutes to finish the meal and must consume the entire meal. Collection times are from the start of the meal.

7.2.11. Subject Monitoring During Injection or Infusion

All subjects should be closely observed while receiving investigational product and monitoring for clinical signs of a systemic reaction will continue during the clinic confinement period for clinical signs of allergic reactions/hypersensitivity including but not limited to rash, flushing, urticaria, dyspnea, oral temperature >38°C, symptomatic bronchospasm, allergy-related edema/angioedema, hypotension, and anaphylaxis.

In case of an allergic reaction/hypersensitivity, the Investigator should institute treatment measures deemed medically appropriate. Medications to treat hypersensitivity reactions should be available, such as IV saline, ibuprofen, and emergency drugs, including IV epinephrine, diphenhydramine, methylprednisolone, and albuterol. Any episode of infusion reaction must be captured in the source documents and on the Infusion Reaction Form in the Case Report Form.

7.2.12. Injection Site Reaction Evaluation

Assessments made of the injection sites in the abdominal fat fold to monitor local tolerability to PF- 06293620 subcutaneous injections will be performed up to at least 2 hours following study drug administration at times specified in the **Schedule of Activities** section of this protocol. Site tolerability assessments should continue after each dosing day visit, only if injection site pain or ISR characteristics continue to persist. The assessments should continue at regularly scheduled visits until the symptoms resolve. Additional assessments should be performed as needed after the last assessment of 2 hrs post-dose on Day 1.

The injection sites will be assessed for erythema, induration, ecchymosis, injection site pain, injection site pruritus, or other observed characteristics after investigational product administration. The diameter of the affected area will be measured and the condition of the injection site will be recorded in the Subcutaneous Injection Site Assessment CRF. Any observed abnormality at the injection site will be judged by the investigator to determine whether a corresponding AE should be reported. Injection site reactions should be immediately photographed in color, with a scaled ruler placed by the reaction, and these photographs should be included in the subject's source documentation. Dermatologic photos will be redacted/remove any personal identifying information and will only contain the subject study ID. When appropriate, at the discretion of the investigator, a subject with an ISR may be referred for a dermatological consultation and a skin biopsy may be obtained for further histological examination of the ISR.

7.2.13. Immunogenicity

Assays for the determination of human anti-PF-06293620 antibodies (ADA) will be performed. All samples that are positive in a screening assay will be confirmed for antibody specificity and further characterized for titer. Samples may also be analyzed in neutralization assays to determine whether or not they are neutralizing or non-neutralizing. Samples for ADA should be collected at times specified in the Schedule of Activities section of this protocol.

Following dosing, if a subject tests positive in the validated confirmatory ADA assay, this subject will be observed closely for signs and symptoms of hypersensitivity reactions including but not limited to changes in white blood cell count, platelet count and vital signs. Subjects found to have anti- PF-06293620 antibodies still present at the end of study will be requested to return to the clinic at 1-3 month intervals, for up to 9 months after the last scheduled visit, for blood collection to assess ADA until antibody levels return to baseline, or if ADA titers remains above baseline, no further visits are necessary if the titers have stabilized at consecutive visits and there are no signs and symptoms associated with the ADA lab result.

Blood samples (**4 mL)** to provide a minimum of 2 mL of serum for anti-PF-06293620 antibody analysis will be collected into appropriately labeled tubes. Additional instructions for sample collection, processing, storage and shipment will be provided in the laboratory manual.

Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.

7.3. Pharmacokinetics

7.3.1. Serum for Analysis of PF-06293620

Blood samples (approximately 6 mL) to provide a minimum of 3 mL serum for pharmacokinetic analysis will be collected into appropriately labeled tubes containing at times specified in the Study Procedures section of the protocol.

The actual times may change but the number of samples will remain the same. All efforts will be made to obtain the pharmacokinetic samples at the exact nominal time relative to dosing. However, samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60 minute sample) from dosing will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (eg, CRF/DCT).

- Samples will be centrifuged at approximately 1700 x g for about 10 minutes at 4°C. The serum will be stored in appropriately labeled screw-capped polypropylene tube at approximately -20°C within 1-hour of collection.

- Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.

- As part of understanding the pharmacokinetics of the study drug, samples may be used for metabolite identification and/or evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the clinical report. Samples collected for this purpose will be retained in accordance to local regulations and if not used within this timeframe, will be destroyed.

7.3.2. Shipment of Pharmacokinetic Samples

The shipment address and assay lab contact information will be provided to the investigator site prior to initiation of the study.

7.4. Pharmacodynamics

PD samples (eg, fasting plasma glucose, glucagon, GLP-1, lipid profile) should be collected at times specified in the Schedule of Activities section of this protocol. On Day 1 PD samples must be collected prior to dosing. All efforts will be made to obtain the PD samples at the exact nominal time relative to dosing. However, samples obtained within 2 hours prior to dosing will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (eg, CRF).

Blood samples will be collected following a 10 hour fast at the times specified in the Schedule of Activities section of the protocol with the exception of postprandial PD samples (ie, mixed meal tolerance test, 24 hour blood glucose profile, PK samples). Additional instructions for sample collection, processing, storage and shipment will be provided in the laboratory manual.

As part of understanding the PD of the biomarker, samples may be used for evaluation of the bioanalytical method. These bioanalytical method data will be used for internal exploratory purposes and will not be included in the clinical report.

7.4.1. Pharmacodynamic Markers

7.4.1.1. Fasting plasma glucose, fasting plasma glucagon, fasting plasma GLP-1 and HbA1c

Blood samples for the assessment of FPG, fasting glucagon, fasting GLP-1 and HbA1c will be collected at times specified in the protocol. Fasting samples will be obtained following at least a 10 hour fast. Instructions for sample collection, processing, storage and shipment will be provided in the laboratory manual.

Subjects found to have elevated glucagon levels (ie, >3 X baseline) at the end of study will be requested to return to the clinic at 1-3 month intervals, for up to 9 months after the last scheduled visit, for blood collection to assess whether or not the glucagon levels return to approximate baseline (ie, ≤3 X baseline), or if glucagon remains above baseline, no further visits are necessary if the glucagon has stabilized at consecutive visits with no related adverse events. The 3 X baseline limit was set based on the variability of glucagon levels in the subjects that received placebo in the ongoing SAD study. In this study, of the six placebo subjects, glucagon maximum to minimum ratio varied from 1.5 to 3.5 within a subject.

7.4.1.2. Mixed meal tolerance test

A mixed meal tolerance test (MMTT) will be performed at times in the protocol following an overnight fast of at least 10 hours. The standardized MMTT protocol is as follows:

- An intravenous catheter may be placed in a patent vein in the subject's arm for the collection of blood samples
- A liquid meal consisting of 700 kcal (473 mL; 16 fluid ounces) of Ensure Plus® (Homemade Vanilla; 54% carbohydrate, 29% fat, and 17% protein) will be administered (**as breakfast**) on the following days:
  - SAD SC Cohorts
    - Day -1, Day 4 ,Day 15 and Day 29.
  - SAD IV Cohort
    - Day -1, Day 1**,** Day 15 and Day 29.
  - MAD Cohorts
    - Day -1, Day 8 and Day 64.
- The liquid meal will be **consumed within 10 minutes**. Timing of blood samples for MMTT assessment of glucose AUC(0-4) will begin at the **start of the meal** such that the 15 minute time point is collected 5 minutes after the liquid meal ends.

Additional blood samples will be drawn at 15 to 240 minutes (for measurement of plasma glucose, insulin, GLP-1, C-peptide and glucagon) post-meal challenge (time points correspond to minutes after the first swallow of the mixed meal).

All efforts will be made to obtain the MMTT samples at the exact nominal time relative to meal administration. However, samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60 minute sample) will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (eg, CRF).

Instructions for sample collection, processing, storage and shipment will be provided in the laboratory manual.

7.4.1.3. 24 Hour Blood Glucose Profile (fingersticks)

A 24 hour blood glucose profile obtained by the assessment of fingerstick glucose will be obtained at times specified in the protocol. Finger-stick blood samples will be taken for the determination of glucose concentration at the following time points: prior to breakfast (fasting), 2 hours post-breakfast, pre-lunch, 2 hours post lunch, pre-dinner, 2 hours post dinner, 10 pm (prior to snack), and on the following day at 0300 and fasting before breakfast (same time as fasting when study initiated previous day).

Instructions for sample collection, processing, storage and shipment will be provided in the laboratory manual.

7.4.1.4. Mean Daily Glucose

A 24 hour venous blood glucose profile obtained. Venous blood samples will be taken for the determination of glucose concentration at the following time points: 30 minutes and immediately prior to AM meal, 30, 60, 90, 120 and 180 after the AM meal; immediately prior to the midday meal, 60, 120 and 180 minutes after the midday meal; immediately prior to the evening meal, 60, 120 and 180 minutes after the evening meal; approximately 11:00 PM; and on the following day fasting at approximately 0300 and 0730 (immediately before breakfast).

Instructions for sample collection, processing, storage and shipment will be provided in the laboratory manual.

Meals and snacks will be provided as described in Section 4.4.1. Within each subject, the same meals and snacks must be provided during every MDG profile.

7.4.2. Shipment of Pharmacodynamic Samples

The shipment address and assay lab contact information will be provided to the investigator site prior to initiation of the study.

7.5. Banked Biospecimens

7.5.1. Markers of Drug Response

Variation in genetic markers and other biomarkers may help to explain some of the variability in response seen with some drugs among different individuals. This is referred to as pharmacogenomic/biomarker research. Comparing the Deoxynucleic Acid (DNA), Ribonucleic Acid (RNA), protein, and metabolite variation patterns of subjects who respond well and those who respond poorly to treatment may help to better define the most appropriate group of subjects in which to target a given treatment. Collecting biospecimens for exploratory pharmacogenomic/biomarker analyses and retaining them in the Pfizer BioBank makes it possible to better understand the drug's mechanism of action and to seek explanations for differences in, for example, exposure, efficacy, tolerability, or safety not anticipated prior to the beginning of the study. Providing these biospecimens is a required study activity for study sites and subjects, unless prohibited as such by local regulations or ethics committee decision

To protect subjects' confidentiality, the banked biospecimens and data generated from them will be coded with the subject's study identification number. Samples will be kept in a facility accessible only by badge-swipe. Data will be stored on password-protected computer systems. The key between the code and the subject's personal identifiers will be held at the study site; the researchers using the biospecimens and data generated from them will not have access to the key nor any personally identifying information. Biospecimens will only be used for the purposes described here and in the informed consent document/subject information sheet; any other uses require additional ethical approval. Unless a time

limitation is required by local regulations or ethical requirements, biospecimens will be stored indefinitely to allow for future research on the topics described here, including research conducted during the lengthy drug development process and also post-marketing research. Subjects can withdraw their consent for the use of their biospecimens at any time by making a request to the investigator, in which event any remaining biospecimen will be destroyed; data already generated from the biospecimens will continue to be stored to protect the integrity of existing analyses. It is very unlikely that results generated from the biospecimens will have any clinical, diagnostic, or therapeutic implications for the individual study participants. Subjects are notified in the informed consent document/subject information sheet that their results will not be given to them, unless required by local laws or regulations, in which case results will be returned via the investigator. Results will not be provided to family members or other physicians; nor will they be recorded in the subject's medical record. There is no intention to contact subjects after completion of the clinical study.

A 4 mL blood biospecimen **Prep D1 (K_2 EDTA whole blood collection optimized for DNA analysis)** will be collected at the Day-1visit to be retained for potential pharmacogenomic/biomarker analyses related to drug response, unless prohibited by local regulations or ethics committee decision. For example, putative safety biomarkers, drug metabolizing enzyme genes, drug transport protein genes, or genes thought to be related to the mechanism of drug action may be examined.

The banked biospecimens will be collected from all subjects unless prohibited by local regulations or ethics committee decision. Detailed collection, processing, storage and shipment instructions are provided in the central laboratory manual.

It is possible that the use of these biospecimens may result in commercially viable products. Subjects will be advised in the informed consent document/subject information sheet that they will not be compensated in this event.

7.5.2. Additional Research

Unless prohibited by local regulations, subjects will be asked to indicate on the consent form whether they will allow the banked biospecimens to also be used for the following research:

Investigations of the disease under study in the clinical study, and related conditions.

Biospecimens may be used as controls. This includes use in case-control studies of diseases for which Pfizer is researching drug therapies; use in characterizing the natural variation amongst people in genes, RNA, proteins, and metabolites; and use in developing new technologies related to pharmacogenomics/biomarkers.

Subjects need not provide additional biospecimens for the uses described in this section; the samples specified in the Markers of Drug Response section will be used. Subjects may still participate in the clinical study if they elect not to allow their banked biospecimens to be used for the additional purposes described in this section.

7.6. Triggered Requirements

Condition	Action
Management of Hypoglycemia	Obtain plasma glucose level (inpatient)
Symptoms or blood glucose levels ≤70 mg/dl	Outpatient- subject should contact site for appropriate clinical management

In the inpatient setting, a plasma glucose level should be obtained prior to intervention for any suspected hypoglycemic episodes. In the outpatient setting, if the subject experiences any symptoms of hypoglycemia, they will be instructed to contact the site immediately for appropriate clinical management. All episodes of suspected or confirmed hypoglycemia should be reported to the study team (Sponsor) as soon as possible.

Any episode of hypoglycemia must be captured in the source documents and on the Hypoglycemic Adverse Event Form in the Case Report Form. For definition of hypoglycemic episode and severity categorization, refer to Section 7.6.1 below.

7.6.1. Definition and Severity Categorization of Hypoglycemic Events

If subjects experience hypoglycemia, the investigator must assess the glucose values as well as any symptoms documented.

Hypoglycemia is defined as **one** of the following:

- Characteristic symptoms of hypoglycemia with no home glucose monitoring performed. Clinical picture must include prompt resolution with food intake, subcutaneous glucagon, or intravenous glucose; **or**
- Characteristic symptoms of hypoglycemia with blood glucose value of ≤70 mg/dL; **or**
- Any blood glucose value ≤49 mg/dL the following criterion with or without accompanying symptoms

Each hypoglycemic event must be characterized with respect to severity. In order to characterize the event as severe, **all three (3) criteria** below must be met:

a. The subject was unable to treat him/herself. Neurologic impairment, and not the age of the subject, is the explanation for why the subject could not treat him/herself and required the assistance of another person.

b. The subject exhibited at least one of the following neurological symptoms:

   - Memory Loss.
   - Confusion.
   - Uncontrollable behavior.
   - Irrational behavior.

- Unusual difficulty in awakening.
- Suspected seizure.
- Seizure.
- Loss of consciousness.

c. Either:

- If blood glucose was measured and was ≤49 mg/dL; **or**
- If blood glucose was **not** measured, the clinical manifestations were reversed by oral carbohydrates, subcutaneous glucagon, or intravenous glucose.

Events that do **not** meet **all** the criteria above for severe hypoglycemia are characterized as mild or moderate in severity.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

Adverse events will be collected from the time a subject signs consent to the last visit. All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an serious adverse event (SAE) requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the Sponsor, any non-serious adverse event that is determined by the Sponsor to be serious will be reported by the Sponsor as a SAE. To assist in the determination of case seriousness further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. Serious adverse events occurring to a subject after the active reporting period has ended should be reported to the Sponsor if the investigator becomes aware of them; at a minimum, all serious events that the investigator

believes have at least a reasonable possibility of being related to investigational product are to be reported to the Sponsor.

Treatment emergent AEs (serious and non-serious) should be recorded on the CRF/DCT from the time the subject has taken at least one dose of study treatment through last subject visit.

8.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

8.4. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.
    - Per the sponsor, ALT or AST results ≥3xULN are to be reported as AEs along with any clinically relevant/associated symptoms.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

8.5. Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.5.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections and will be handled as SAEs in the safety database (see Section 8.13.1 SAE Reporting Requirements).

8.5.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 times the upper limit of normal (X ULN) concurrent with a total bilirubin value ≥2 X ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 X ULN or not available.

- For subjects with preexisting ALT **OR**, AST **OR** total bilirubin values above the upper limit of normal, the following threshold values should be used in the definition mentioned above:

    - For subjects with pre-existing AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values and ≥3 X ULN, or ≥8 X ULN (whichever is smaller).

- **Concurrent with**

    - For subjects with pre-existing values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of a least one time the upper limit of normal or if value reaches ≥3 times the upper limit of normal (whichever is smaller).

The subject should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment. In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/ international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual

history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as SAEs.

8.6. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute an hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for work-up of persistent pre-treatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);

- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Pre-planned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.7. Severity Assessment

Adverse events occurring during this study will be graded in accordance with the Grade 1 to Grade 5 scale presented below. The detailed definitions are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Event (CTCAE) Version 4.03. Documentation of AE grading in the source documents and CRF must be consistent with provided definitions.

GRADE	Clinical Description of Severity
0	No Change from Normal or Reference Range (This grade is not included in the Version 4.03 CTCAE document but may be used in certain circumstances).
1	MILD Adverse Event
2	MODERATE Adverse Event
3	SEVERE Adverse Event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO Adverse Event

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.8. Causality Assessment

The investigator’s assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF/DCT, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An investigator’s causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal

relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor (see Section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF/DCT, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.9. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products , an Exposure During Pregnancy (EDP) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes, or is found to be pregnant after discontinuing and/or being exposed to the investigational product.

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational product, the investigator must submit this information to the Pfizer Drug Safety Unit on a Serious Adverse Event (SAE) Report Form and Exposure During Pregnancy (EDP) supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EDP Supplemental Form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination and notify Pfizer of the outcome as a follow up to the initial EDP supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the

terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born baby, a terminated fetus, an intrauterine fetal demise or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- "Spontaneous abortion" includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as serious adverse events when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study subject with the Pregnancy Partner Release of Information Form to deliver to his partner. The Investigator must document in the source documents that the subject was given the Pregnancy Partner Release of Information Form to provide to his partner.

8.10. Occupational Exposure

An occupational exposure occurs when during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an adverse event.

An occupational exposure is reported to the drug safety unit within 24 hours of the Investigator's awareness, using the SAE Report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a subject enrolled in the study, the information is not reported on a Case Report Form (CRF), however a copy of the completed SAE Report form is maintained in the investigativesite file.

8.11. Withdrawal Due to Adverse Events

Withdrawal due to AE should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF/DCT page.

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.12. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs.

8.13. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.13.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event.

In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy, exposure via breastfeeding and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

For all SAE, the investigator is obligated to pursue and provide information to Pfizer in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF/DCT. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.13.2. Non-Serious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF/DCT. It should be noted that the form for collection of SAE information is not the same as the AE CRF/DCT. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AE should be reported using concise medical terminology on the CRFs/DCTs as well as on the form for collection of SAE information.

8.13.3. Sponsor's Reporting Requirements to Regulatory Authorities

Adverse event reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan, which will be maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

9.1. Sample Size Determination

This study is exploratory in nature; no pre-planned hypothesis testing is to be performed. The sample size determination is not based on statistical power considerations. Dose cohort size in the SAD portion is generally 8 subjects with a 6:2 ratio of active drug to placebo in a randomized manner and generally 10 subjects with a 8:2 ratio of active drug to placebo in a randomized manner in the MAD portion. Additional subjects may be added at a dose level to further evaluate safety and/or tolerability after discussions between the Pfizer study team and the investigators.

The table below provides the probability of observing 2 or more SAEs under various SAE rates giving the number of subjects to be treated in a cohort in a single ascending dose cohort, and multiple-dose cohort, respectively.

Table 10. Probability of Observing 2 or More SAEs

SAE rate	Prob(X >= 2 SAEs| SAE Rate, n=6)	Prob(X >= 2 SAEs | SAE Rate, n=8)
0.10	0.11	0.19
0.15	0.22	0.34
0.20	0.34	0.50
0.25	0.47	0.63
0.30	0.58	0.74
0.33	0.65	0.80
0.4	0.77	0.89

9.2. Efficacy Analysis

Efficacy analysis is not applicable to this study.

9.3. Pharmacokinetic Analysis

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

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

9.3.1. Derivation of Pharmacokinetic Parameters

PK parameters following single and multiple-dose administration will be derived from the concentration-time profiles as appropriate as follows:

Single Dose PK Parameters

Parameter	Definition	Method of Determination
AUC_{last}	Area under the serum concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last})	Linear/Log trapezoidal method
AUC_{inf}[a]	Area under the serum concentration-time profile from time zero extrapolated to infinite time	$AUC_{last} + (C_{last}*/k_el)$, where $C_{last}*$ is the predicted serum concentration at the last quantifiable time point estimated from the log-linear regression analysis.
C_{max}	Maximum serum concentration	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
t½[a]	Terminal elimination half-life	$Ln(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression.
CL/F[a,b]	Apparent clearance	Dose / AUC_{inf}
V_z/F[a,b]	Apparent volume of distribution	Dose / (AUC_{inf} * k_{el})
CL[a,c]	Clearance	Dose / AUC_{inf}
V_{ss}[a,c]	Steady-state volume of distribution	CL • MRT, where MRT is the mean residence time calculated as ($AUMC_{inf}/AUC_{inf}$ - Infusion duration/2); $AUMC_{inf}$ is area under the moment curve from time 0 extrapolated to infinity
$AUC_{last}(dn)$	Dose normalized AUC_{last}	AUC_{last} / Dose
$AUC_{inf}(dn)$[a]	Dose normalized AUC_{inf}	AUC_{inf} / Dose
$C_{max}(dn)$	Dose normalized C_{max}	C_{max} / Dose

[a] If data permit
[b] SC cohorts only
[c] IV cohort only

Multiple Dose PK Parameters

Parameter	Day(s)	Definition	Method of Determination
AUC_{τ}	1, 57	Area under the concentration-time profile from time zero to time tau (τ), the dosing interval, where τ = 4 weeks (672 hours)	Linear/Log trapezoidal method
C_{max}	1, 57	Maximum serum concentration	Observed directly from data
C_{av}	1, 57	Average concentration	AUC_{τ}/τ
T_{max}	1, 57	Time for C_{max}	Observed directly from data as time of first occurrence
CL/F	1, 57	Apparent clearance	Dose / AUC_{τ}
C_{min}	57	Lowest concentration observed during the dosing interval	Observed directly from data
$t_{½}$[a]	57	Terminal elimination half-life	$Ln(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression.
V_z/F[a]	57	Apparent volume of distribution	Dose / (AUC_{τ} / k_{el})
R_{ac}	57	Observed accumulation ratio based on AUC	AUC_{τ} Day 57 / AUC_{τ} Day 1
$R_{ac,Cmax}$	57	Observed accumulation ratio based on Cmax	C_{max} Day 57 / C_{max} Day 1
AUC_{τ}(dn)	1, 57	Dose normalized AUC_{τ}	AUC_{τ} / Dose
C_{max}(dn)	1, 57	Dose normalized C_{max}	C_{max} / Dose
C_{min}(dn)	57	Dose normalized C_{max}	C_{min} / Dose

[a] If data permit

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

9.3.2. Statistical Methods of PK Analysis

The serum PK parameters for RN909 (PF-06293620) will be summarized descriptively by dose and route of administration. Serum concentrations will be listed and summarized descriptively by dose, nominal PK sampling time and route of administration. Individual subject, summary profiles (mean and median plots) of the serum concentration-time data will be plotted by treatment and PK sampling time. For summary statistics and summary plots, the nominal PK sampling time will be used. For individual subject plots, the actual PK sampling time will be used, whilst the pre-dose time will be set to zero. Summary plots will be presented on both linear-linear and log-linear scales.

Dose normalized parameters for RN909 (PF-06293620) will be plotted against dose and route of administration and will include individual subject values and the geometric means for each dose. For SAD, AUC_{inf}, AUC_{last}, and C_{max} will be plotted; for MAD, AUC_{τ} and C_{max} (Day 1 and Day 57) and C_{min} (Day 57) will be plotted. These plots will be used to help understand the relationship between the PK parameters and dose.

Absolute bioavailability (F) will be estimated as the ratio of dose-normalized adjusted geometric means for SC and IV for AUC_{last} and AUC_{inf}. Dose-normalized natural log transformed AUC_{inf} (data permitting) and AUC_{last} 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 doses are the Test treatments, and IV is the Reference treatment.

Subjects having positive ADAs will be analyzed separately to assess the effects of ADAs on RN909 (PF-06293620) concentrations. If there is no effect on the concentration versus time profiles, then these subjects will be included in the descriptive statistics of concentrations and PK parameters.

9.4. Pharmacodynamic Analysis

PD biomarker data will include fasting plasma glucose, fasting glucagon, fasting GLP-1, 24-hr glucose profile (finger-stick), HbA1c, fructosamine, 1,5-anhydroglucitol, post prandial glucose, insulin, C-peptide, glucagon and GLP-1 AUC after mixed meal tolerance test (MMTT, 4 hr) as well as mean daily glucose (MDG).

The relationship between changes in the values of these biomarkers with the pharmacokinetics of RN909 (PF-06293620) will be explored.

In order to minimize the impact of a single aberrant measurement to the baseline, where feasible, the baseline is defined as the average of at least two measrements prior to the first study drug administration as outlined in the statistical analysis plan.

9.5. Safety Analysis

All safety data analysis will be performed on the safety analysis set, which includes all enrolled subjects who receive at least one dose of study medication.

Adverse events, ECGs, blood pressure, pulse rate, continuous cardiac monitoring (SAD only), ambulatory blood pressure monitoring (MAD cohorts only), and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of subjects. Any clinical laboratory, ECG, BP, and PR abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history and physical exam information collected during the course of the study will be captured for inclusion into the study database, unless otherwise noted. Any untoward findings identified on physical exam conducted after the administration of the first dose of study medication will be captured as an adverse event, if those findings meet the definition of an adverse event. Data collected at Screening that is used solely for inclusion/exclusion criteria, such as laboratory data, ECGs and vital signs will be considered source data, and

will not be captured for inclusion into the study database, unless otherwise noted (note: screening physical exam is a comprehensive exam and will be captured in the study database as the baseline exam). Demographic data collected at Screening will be included in the study database.

Summary statistics and data listings will be provided for the following endpoints:

- Incidence of dose limiting or intolerable treatment related adverse events (AEs).
- Incidence, severity and causal relationship of treatment emergent AEs (TEAEs).
- Incidence of abnormal laboratory findings (clinical chemistry, hematology and urinalysis).
- Changes from baseline in safety laboratory assessments.
- Abnormal and clinically relevant changes in vital signs, BP, and ECG parameters.
- Incidence of anti-drug-antibodies (ADA).

9.5.1. Electrocardiogram (ECG) Analysis

ECG results will be reviewed by investigators in both the SAD and MAD portion of the study. In addition, all ECGs in the MAD portion will undergo central review. The analysis of ECG results will be based on subjects with baseline (Day 1 pre-dose) and on-treatment ECG data. ECG data will be summarized for heart rate (HR) and RR, PR, QRS and QT intervals by dose.

Post dose ECGs will be compared to the Day 1 pre-dose ECG for each subject, and any clinically significant changes will be recorded as adverse events and evaluated further, as clinically warranted.

Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute QTcF value and changes from baseline in QTcF after treatment by treatment group (each RN909 dose and placebo), and by time point. For each subject and dose, the maximum change from baseline will be calculated as well as the maximum post-baseline value across time-points. Outlier analysis of the QTcF data will be conducted and summarized as follows:

- The number of subjects with maximum change from baseline in QTcF (<30, 30-60, and ≥60 ms).
- The number of subjects with maximum post-dose (post-baseline) QTcF (<450, 450-<480, 480-<500, and ≥500 ms).
- Changes from baseline for the ECG parameters QT interval, heart rate, QTc interval, PR interval and QRS interval will be summarized by treatment and time.

- The number (%) of subjects with maximum post dose QTc values and maximum increases from baseline in the following categories will be tabulated by treatment:

Safety QTc

	Borderline (msec)	Prolonged (msec)
Absolute Value	≥450 - <480	≥480
Absolute Change	30-<60	≥60

Shift tables will be provided for baseline vs. worst on study QTcF) using the maximum CTCAE Grade as well as tables of ECG abnormality at baseline (yes, no, not done: (n, %)). Subjects experiencing clinically-relevant morphological ECG changes will be summarized (including frequency and percentage).

The effect of drug concentrations on QTcF change from baseline may be explored graphically. Additional concentration-QTcF analyses may be performed.

In addition, the number of subjects with corrected and uncorrected QT values ≥500 msec will be summarized.

If more than one ECG is collected at a nominal time post dose (for example, triplicate ECGs), the mean of the replicate measurements will be used to represent a single observation at that time point. If any of the three individual ECG tracings has a QTc value ≥500 msec, but the mean of the triplicates is not ≥500 msec, the data from the subject's individual tracing will be described in a safety section of the study report in order to place the ≥500 msec value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are ≥500 msec will not be included in the categorical analysis unless the average from the triplicate measurements is also ≥500 msec.

In addition, an attempt will be made to explore and characterize the relationship between plasma concentration and QT interval length using a PK/PD modeling approach. If a PK/PD relationship is found, the impact of subject factors (covariates) on the relationship will be examined.

9.6. Exploratory Analyses

Exploratory analyses will be conducted for SAD and MAD, respectively. The individual subject's change and percentage change from baseline for PD biomarkers over the period of the study will be tabulated by individual subject. The mean change from baseline values over time per dose group will also be tabulated. Data will be presented in tabular and/or graphical format and summarized descriptively. Placebo subjects will be pooled across all dose cohorts for the respective stages of the study, ie, SAD placebo subjects and MAD placebo subjects. To explore the treatment effect16, the mean change and percentage change from baseline over time with active treatment will be compared to the mean change and percent change from baseline over time with placebo treated subjects. Descriptive statistics on change and percentage change from baseline in fasting plasma glucose, post prandial glucose, insulin, C-peptide and glucagon AUC after mixed meal tolerance test (MMTT, 4 hr), 24-hr glucose profile (finger-stick), HbA1c, fructosamine, 1,5-anhydroglucitol; fasting

glucagon, total and active GLP-1 will be provided separately for each treatment and the pooled placebo group.

Exploratory PK/PD analyses may be conducted on relevant safety and PD endpoints as permitted by the data.

Data listings will be produced by study portion (SAD or MAD), subject, dose cohorts, visit date, and time.

9.7. Interim Analysis

A planned interim analysis may be performed at the completion of the SAD portion of the study. The interim analysis result 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 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**.**

9.8. Data Monitoring Committee

This study will not use a Data Monitoring Committee (E-DMC) or Internal Review Committee.

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or its agent will conduct periodic monitoring visits for studies conducted outside of Pfizer Clinical Research Units, to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs/DCTs is accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

For studies conducted at Pfizer Clinical Research Units, the Clinical Research Unit staff will perform quality control checks regularly during the study to ensure the protocol and Good Clinical Practices (GCPs) are being followed.

The study site may be subject to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

For studies conducted outside of the Pfizer Clinical Research Units, it is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Data Collection Tools/Electronic Data Record

As used in this protocol, the term CRF/DCT should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study, and for studies conducted at Pfizer Clinical Research Units the term CRF/DCT will also refer to the use of PIMS (Phase 1 Management System).

A CRF/DCT is required and should be completed for each included subject. The completed original CRFs/DCTs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs/DCTs and any other data collection forms (source documents) and ensuring that they are accurate, authentic / original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs/DCTs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs/DCTs is true. Any corrections to entries made in the CRFs/DCTs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases the source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs/DCTs must match those charts.

In some cases, the CRF/DCT may also serve as the source document. In these cases, a document should be available at the investigator's site as well as at Pfizer and clearly identify those data that will be recorded in the CRF/DCT, and for which the CRF/DCT will stand as the source document. For studies conducted at Pfizer Clinical Research Units, the CRF/DCT is the source document, and will remain at the Clinical Research Unit. If other source documents are utilized at the CRUs, those documents will be retained per Pfizer requirements.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e.g. CRFs/DCTs and hospital records), all original signed informed consent documents, copies of all CRFs/DCTs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to International Conference on Harmonisation (ICH), local regulations, or as specified in the Clinical Study Agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The

study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/IEC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws.

Subject names, address, birth date and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify study subjects. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subject personal data.

The informed consent document must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The informed consent document(s) used during the informed consent process must be reviewed by the sponsor, approved by the IRB/IEC before use, and available for inspection.

The investigator must ensure that each study subject, or his/her legal representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legal representative before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

12.4. Subject Recruitment

Advertisements approved by ethics committees and investigator databases may be used as recruitment procedures.

12.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable Competent Authority in any area of the World, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in United States

Last subject last visit is defined as the date the investigator reviews the last subject’s final safety data and determines that no further evaluation is required for the subject to complete the trial.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 7 days. As directed by Pfizer, all study materials must be collected and all CRFs/DCTs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or, www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US basic results on www.clinicaltrials.gov for all Pfizer-sponsored interventional studies conducted in patients that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary Completion Date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the pre-specified protocol or was terminated.

EudraCT

Pfizer posts EU Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

www.pfizer.com

Pfizer posts public disclosure synopses (clinical study report synopses in which any data that could be used to identify individual patients have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer has no objection to publication by Investigator of any information collected or generated by Investigator, whether or not the results are favorable to the Investigational Drug. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, Investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

Investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

Investigator will, on request, remove any previously undisclosed Confidential Information (other than the Study results themselves) before disclosure.

If the Study is part of a multi-centre study, Investigator agrees that the first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the Study at all participating sites, Investigator is free to publish separately, subject to the other requirements of this Section.

For all publications relating to the Study, Institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the Clinical Study Agreement between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

16. REFERENCES

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