

CLINICAL STUDY PROTOCOL

A RANDOMIZED, DOUBLE-BLIND, PLACEBO- CONTROLLED WITH ACTIVE COMPARATOR, 12-WEEK STUDY OF DS-8500a IN SUBJECTS WITH TYPE 2 DIABETES MELLITUS ON METFORMIN

DS8500-A-U202

IND 125,803

VERSION 1.0, 28 OCT 2015

SPONSOR:	Daiichi Sankyo, Inc. 399 Thornall Street Edison, NJ 08837 United States
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Protocol DS8500-A-U202
Version 1.0, 28 OCT 2015

INVESTIGATOR AGREEMENT

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED WITH ACTIVE COMPARATOR, 12-WEEK STUDY OF DS-8500a IN SUBJECTS WITH TYPE 2 DIABETES MELLITUS ON METFORMIN

Sponsor Approval:

This clinical study protocol has been reviewed and approved by the Daiichi Sankyo representative listed below.

_____, MD
Print Name

Signature

Director, Clinical Development
Title

29 OCT 2015
Date (DD MMM YYYY)

Investigator's Signature:

I have fully discussed the objectives of this study and the contents of this protocol with the Sponsor's representative.

I understand that information contained in or pertaining to this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorization from the Sponsor. It is, however, permissible to provide information to a subject in order to obtain consent.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, International Conference on Harmonisation guidelines on Good Clinical Practice (ICH E6), and applicable regional regulatory requirements.

I agree to make available to Sponsor personnel, their representatives and relevant regulatory authorities, my subjects' study records in order to verify the data that I have entered into the case report forms. I am aware of my responsibilities as a Principal Investigator as provided by the Sponsor.

I understand that the Sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to the Sponsor.


Print Name

Signature

Title

Date (DD MMM YYYY)

PROTOCOL SYNOPSIS

IND Number:	125,803
Protocol Number:	DS8500-A-U202
Investigational Product:	DS-8500a, sitagliptin (active comparator), and placebo
Active Ingredient(s)/INN:	
Study Title:	A Randomized, Double-Blind, Placebo-Controlled with Active Comparator, 12-Week Study of DS-8500a in Subjects with Type 2 Diabetes Mellitus on Metformin
Study Phase:	Phase 2
Indication Under Investigation:	Type 2 Diabetes Mellitus (T2DM)
Study Objectives:	<p>The primary objective is to evaluate change in hemoglobin A1c (HbA1c) from baseline to Week 12 with DS-8500a compared with placebo in subjects with T2DM.</p> <p>The secondary objectives are:</p> <ul style="list-style-type: none">• To evaluate changes in lipids [total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-high density cholesterol (non-HDL-C) and triglycerides (TG)] from baseline to Week 12 with DS-8500a compared with placebo.• To evaluate change in 3h area under the curve (AUC_{0-3h}) plasma glucose (PG) in response to a mixed meal tolerance test (MMTT) from baseline to Week 4 and Week 12 with DS-8500a compared with placebo.• To evaluate change in fasting plasma glucose (FPG) from baseline to Weeks 2, 4, 8 and 12 with DS-8500a compared with placebo.• To evaluate the proportion of subjects achieving HbA1c < 7.0% at Week 12 with DS-8500a compared with placebo.• To assess the pharmacokinetics (PK) of DS-

8500a and its metabolite (A209-3952).

The safety objectives are:

- To evaluate the safety and tolerability of DS-8500a in subjects with T2DM assessed by treatment emergent adverse events (TEAEs) and change in vital signs and safety laboratory values.
 - a. The proportion of subjects with TEAE.
 - b. Changes in routine safety laboratory testing (i.e., hematology, chemistry) from baseline to Week 12.
 - c. The proportion of subjects with prospectively adjudicated cardiovascular events including cardiovascular death, non-fatal myocardial infarction, transient ischemic attack and non-fatal stroke, hospitalization for unstable angina, urgent coronary revascularization intervention and hospitalization for congestive heart failure.

The exploratory objectives are:

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

Study Design:

This is a randomized, dose ranging, double-blind, double-dummy, placebo-controlled with active comparator, multi-center, and 12-week study of DS-8500a in subjects with T2DM on a stable metformin dose.

Approximately 260 eligible subjects will be randomized in a 2:2:3:3:3 ratio with 40 subjects per arm in each of the DS-8500a 25 mg and DS-8500a 50 mg treatment groups, and 60 subjects per arm in each of the DS-8500a 75 mg, placebo, and sitagliptin 100 mg treatment groups. The randomization will be stratified on the basis of 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors (statins) treatment at the time of randomization. One stratum will include subjects who have been treated by statins, and the other stratum will include subjects who were not treated by statins at the time of randomization.

The study will include 4 periods for a total of up to 18 weeks:

1. Screening Period (Weeks -4 to -3):

There will be a period up to 2 weeks for subject screening based on medical history, physical examination and clinical labs, and meeting all inclusion and exclusion criteria.

Subjects will receive basic dietary and exercise instruction at the time of screening. Subjects should not embark on aggressive, excessively restrictive or high fat content diets or change their physical activity level during this study.

2. Lead-in Period (Weeks -2 and -1):

During the Lead-in Period, subjects will take single blind DS-8500a matching placebo tablets and a sitagliptin matching placebo capsule to assess compliance with study regimen. Subjects will also be required to continue taking metformin as taken prior to screening. Subjects will be required to perform and record fasting self-monitoring of blood glucose (SMBG) daily.

3. Randomization (Day 1):

At the end of the Lead-in Period, eligible subjects who demonstrate good compliance with study drug (taking $\geq 80\%$ and $\leq 120\%$ of both dispensed DS-8500a placebo tablets and sitagliptin placebo capsules) and an appropriate Lead-in Period fasting glucose (≤ 240 mg/dL, at least 7 days of recorded fasting SMBG required) will be

randomized in a 2:2:3:3:3 ratio to parallel double-blind treatment groups of DS-8500a 25 mg, DS-8500a 50 mg, DS-8500a 75 mg, placebo, or sitagliptin 100 mg. A 3-hour MMTT will be performed on Day 1 (prior to randomization).

4. Treatment Period (Day 2 to Week 12):

The Treatment Period will consist of 12 weeks of randomized double-blind, double dummy treatment with study medication, starting on Day 2 (one day after randomization day). Treatment visits will occur at Weeks 2, 4, 8, and 12 of the randomized Treatment Period. HbA1c will be measured at Weeks 4, 8, and 12 and FPG will be measured at every visit. A 3-hour MMTT will be performed on Week 4 and End-of-Treatment /Early Termination visit (Week 12). Metformin treatment will continue at the same dose taken prior to screening throughout the Treatment Period.

Subjects who meet protocol discontinuation criteria will be asked to return to the clinic for follow-up assessment and confirmation of values prior to discontinuation. Discontinued subjects must complete Early Termination Visit procedures.

5. Post-study Follow-up Period (Weeks 13 and 14):

Subjects who complete the randomized Treatment Period or are discontinued will return to the clinic for a post-study follow-up safety assessment visit approximately 2 weeks after taking the final dose of randomized study medication.

Study Duration:	The study includes 4 periods for a total of up to 18 weeks: a Screening period up to 2 weeks, a 2 week single-blind placebo Lead-in (Weeks -2 and -1), a 12-week double-blind, double-dummy Treatment period (Day 2 to Week 12), and a 2-week post-dosing Follow-up (Weeks 13 and 14).
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Study Centers and Location:	The study will be conducted at approximately 65 study centers in the United States and Canada.
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Subject Eligibility Criteria:	<u>Inclusion Criteria:</u> <ol style="list-style-type: none"> 1. Able to provide written informed consent and adhere to the study visit schedule and treatment 2. Diagnosed with Type 2 diabetes mellitus as defined in the American Diabetes Association Standards of
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Medical Care in Diabetes 2015^{a,6}

3. Male or female ≥ 18 and ≤ 70 years of age
4. Screening fasting C-peptide > 0.5 ng/mL
5. Women of child bearing potential (WOCBP) must be willing to use double-barrier contraception for the entire study
6. WOCBP must have a negative pregnancy test (human chorionic gonadotropin, beta subunit [β hCG]) before entering the Lead-in Period
7. Body mass index ≥ 25 kg/m² and ≤ 45 kg/m² at the Screening Visit
8. On stable (≥ 8 weeks) metformin monotherapy ≥ 1000 mg/day
9. Screening HbA1c $\geq 7.0\%$ and $\leq 10\%$
10. Taking $\geq 80\%$ and $\leq 120\%$ of both dispensed DS-8500a placebo tablets and sitagliptin placebo capsules during the Lead-in Period

Exclusion Criteria:

1. History of type 1 diabetes and/or history of ketoacidosis
 2. History of insulin use for > 2 weeks within 2 months prior to the Screening Visit
 3. Two or more readings of fasting SMBG > 240 mg/dL or worsening symptoms of hyperglycemia with one SMBG level of > 240 mg/dL during the second week of Lead-in Period, confirmed by laboratory measurement
 4. Screening hemoglobin < 12 g/dL for males and < 11 g/dL for females
 5. Blood donation within 2 months prior to the Screening Visit or plans to donate blood or blood products during the study
 6. Subjects after bariatric surgery or any gastric bypass or planning to have such a procedure during the
-

^a HbA1c $\geq 6.5\%$; or FGP ≥ 126 mg/dL; or 2-hour PG ≥ 200 mg/dL during an oral glucose tolerance test (OGTT); or classic symptoms of hyperglycemia with a random PG ≥ 200 mg/dL

study

7. Screening thyroid stimulating hormone (TSH) levels not within normal range (based on reference laboratory values)
8. Screening alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $> 2.0 \times$ upper limit of normal (ULN), and/or total bilirubin $> 1.5 \times$ ULN. If a subject has total bilirubin $> 1.5 \times$ ULN, unconjugated and conjugated bilirubin fractions should be analyzed and only subjects documented to have Gilbert's syndrome may be enrolled
9. Screening Serum creatinine ≥ 1.5 mg/dL for males and ≥ 1.4 mg/dL for females, or creatinine clearance (CrCl) < 50 mL/min for both males and females
10. Screening Creatine kinase (CK) $> 3.0 \times$ ULN
11. History of unstable angina, myocardial infarction, cerebrovascular accident, transient ischemic attack, peripheral arterial event or any revascularization procedure during the 6 months prior to the Screening Visit or planned vascular procedures or surgery during study period
12. History of congestive heart failure (CHF)
13. Exclusionary concomitant medications:
 - a. Eight weeks prior to screening and throughout the duration of the study:
 - Any diabetes medication other than metformin; any prescription or over the counter medication for weight-loss.
 - Systemic corticosteroids (including nasal and inhaled), with the exception of use of topical and ophthalmic corticosteroids.
 - Rosuvastatin > 20 mg daily.
 - b. During treatment periods, additional medications will be prohibited based on potential drug-drug interaction (DDI) (see Section 5.6)
14. Subjects with anticipated interruption in metformin or study drug use during the course of the clinical trial (e.g., due to an imaging procedure involving iodinated contrast media)

15. Subjects in whom treatment with sitagliptin 100 mg is contraindicated (e.g., known hypersensitivity or intolerance to sitagliptin) or may not be medically advisable (e.g., history of pancreatitis)
16. Abuse of or dependence on prescription medications, illicit drugs, or alcohol within the last 1 year
17. Any history of a malignancy other than basal cell carcinoma within the past 5 years
18. Pregnancy or breast-feeding, or intent to become pregnant during the study period
19. Known (or evidence of) infection with human immunodeficiency virus
20. Any condition, laboratory abnormality, or concomitant therapy which, in the opinion of the Investigator, might pose a risk to the subject or make participation not in the subject's best interest
21. Subject is currently enrolled in or has not yet completed at least 30 days since ending another investigational device or drug study or is receiving other investigational agents
22. A direct or familial relationship with the Sponsor, Investigator, or site personnel affiliated with the study

Dosage Form, Dose and
Route of Administration:

Double-blind, double-dummy study medication will be provided in blister cards ("wallets").

DS-8500a is supplied in the form of 25 mg tablets for oral administration. Doses of DS-8500a include 25 mg, DS-8500a 50 mg, and 75 mg once a day (QD). Matching placebo tablets are also used.

Sitagliptin 50 mg tablets will be over-encapsulated to provide a once daily dose of 100 mg. Matching placebo capsules will also be used.

DS-8500a or matching placebo tablets and sitagliptin or matching placebo capsules will be administered orally once daily after breakfast for 12 weeks, except for study visit days. The first dose of randomized study drug will be taken after breakfast on Day 2 after the Day 1 visit. On days of study visits that involve MMTT, study drug will be taken after ingestion of the liquid meal [Day 1 (Lead-in tablets and capsule) and Visits 5 and 7 at Weeks 4 and 12]. On

days of Visits 4 and 6 (Weeks 2 and 8, respectively), study drug should be taken after study laboratory blood draw and after having breakfast.

Study Endpoints:

The primary efficacy endpoint is change from baseline in HbA1c at Week 12.

The secondary endpoints are:

- Changes from baseline in lipids (TC, LDL-C, HDL-C, non-HDL-C and TG) at Week 12.
- Changes from baseline in AUC_{0-3h} and C_{max} of PG in response to MMTT at Weeks 4 and 12.
- Changes from baseline in FPG from baseline to Weeks 2, 4, 8, and 12.
- The proportion of subjects achieving HbA1c < 7.0% at Week 12.

Exploratory endpoints are:

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

Planned Sample Size:

Approximately 260 eligible subjects will be randomized in a 2:2:3:3:3 ratio with 40 subjects per arm in each of the DS-8500a 25 mg and DS-8500a 50 mg treatment groups, and 60 subjects per arm in each of the DS-8500a 75 mg, placebo, and sitagliptin 100 mg treatment groups. Assuming a common standard deviation of 1.0% and an early dropout rate of 10%, with a 2-sided significance level

of 0.1, it will provide at least 90% power to detect a 0.6% difference between DS-8500a 75 mg dose and placebo and at least 80% power to detect a 0.6% difference between each of the DS-8500a 25 mg and 50 mg doses and placebo in mean HbA1c change from baseline to Week 12. No adjustment will be made for multiplicity.

Statistical Analyses:

Primary Endpoint:

The primary estimand is the treatment difference between DS-8500a and placebo for the change in HbA1c from baseline to Week 12 attributable to the initially randomized treatment for all subjects in the modified Intent-To-Treat (mITT) population. The primary estimand will be analyzed using a mixed-effect model with repeated measures (MMRM) with treatment, previous statins stratum, week, and treatment-by-week as fixed effects, week as a repeated factor, and baseline HbA1c as a covariate.

Secondary Endpoints:

Secondary efficacy analyses will include comparisons of each DS-8500a dose level to placebo for the change from baseline to Week 4 and to Week 12 in lipids, 3h AUC PG in response to MMTT, changes in FPG at Weeks 2, 4, 8 and 12 and the proportion of subjects achieving HbA1c < 7.0% at Week 12. A MMRM with treatment, previous statins stratum, week, and treatment-by-week as fixed effects, week as a repeated factor, and baseline value as a covariate will be used for the analyses of changes from baseline in FPG, lipids and 3h AUC PG. A logistic regression model with treatment and previous statins stratum as fixed effects and baseline value as a covariate will be used for the analysis of proportion of subjects achieving HbA1c < 7.0% at Week 12.

Exploratory Endpoints:

[REDACTED]

TABLE OF CONTENTS

INVESTIGATOR AGREEMENT.....	2
PROTOCOL SYNOPSIS	3
TABLE OF CONTENTS.....	13
LIST OF TABLES.....	19
LIST OF FIGURES	20
LIST OF ABBREVIATIONS.....	21
1. INTRODUCTION	24
1.1. Background.....	24
1.1.1. Investigational Product(s).....	24
1.1.1.1. Name.....	24
1.1.1.2. Description.....	24
1.1.1.3. Intended Use Under Investigation	24
1.1.1.4. Nonclinical Studies.....	24
1.1.1.5. Clinical Experience.....	24
1.2. Study Rationale.....	26
2. STUDY OBJECTIVES AND HYPOTHESIS	28
2.1. Study Objectives.....	28
2.1.1. Primary Objectives	28
2.1.2. Secondary Objectives	28
2.1.3. Safety Objectives	28
2.1.4. Exploratory Objectives	29
2.2. Study Hypothesis.....	29
3. STUDY DESIGN	30
3.1. Overall Design	30
3.2. Discussion of Study Design.....	30
4. STUDY POPULATION.....	32
4.1. Inclusion Criteria	32
4.2. Exclusion Criteria	32
4.3. Women of Child-Bearing Potential (WOCBP)	34
5. STUDY TREATMENT(S).....	35
5.1. Assigning Subjects to Treatments and Blinding.....	35

5.1.1.	Treatment during Lead-in Period.....	35
5.1.2.	Treatment Group(s)	35
5.1.3.	Method of Treatment Allocation	36
5.1.4.	Blinding	36
5.1.5.	Emergency Unblinding Procedure.....	37
5.2.	Study Drug(s).....	37
5.2.1.	Description.....	37
5.2.2.	Labeling and Packaging.....	38
5.2.3.	Preparation	38
5.2.4.	Administration	38
5.2.5.	Storage	38
5.2.6.	Drug Accountability	38
5.3.	Control Treatment.....	39
5.4.	Dose Interruptions and Reductions.....	39
5.5.	Method of Assessing Treatment Compliance.....	39
5.6.	Prior and Concomitant Medications	40
5.7.	Subject Withdrawal/Discontinuation.....	41
5.7.1.	Reasons for Withdrawal	41
5.7.2.	Withdrawal Procedures.....	43
5.7.3.	Subject Replacement	43
5.7.4.	Subject Re-screening Procedures	43
6.	STUDY PROCEDURES	44
6.1.	Screening Period.....	44
6.1.1.	Screening Visit (Visit 1; Week -4 to Week -3).....	44
6.2.	Placebo Lead-in (Visit 2, Week -2)	46
6.3.	Randomization (Visit 3, Day 1).....	47
6.4.	Treatment Period (Visit 4 to Visit 7, Week 2 to Week 12, respectively).....	48
6.4.1.	Visit 4 (Week 2).....	48
6.4.2.	Visit 5 (Week 4).....	49
6.4.3.	Visit 6 (Week 8).....	50
6.4.4.	Visit 7 (End-of-Treatment Visit, Week 12) or Early Termination Visit.....	51

6.5.	Follow-Up (Visit 8, Week 14)	52
7.	EFFICACY ASSESSMENTS	53
7.1.	Primary Efficacy	53
7.2.	Secondary Efficacy	53
7.3.	Exploratory Efficacy.....	53
8.	PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS	54
8.1.	Pharmacokinetic (PK) Endpoint(s).....	54
8.2.	Pharmacodynamic (PD) Endpoint(s).....	54
8.3.	Biomarker Endpoint(s)	55
8.4.	Immunogenicity	56
8.5.	Pharmacogenomic Analysis.....	56
9.	SAFETY EVALUATION AND REPORTING	57
9.1.	Adverse Event Collection and Reporting	57
9.2.	Safety Endpoint Event(s).....	58
9.3.	Events of Special Interest	58
9.3.1.	Adjudicated Cardiovascular Events.....	58
9.3.2.	Anemia Monitoring and Stopping Criteria	58
9.3.2.1.	Rules for Anemia Evaluation and Stopping of Study Subjects	58
9.3.2.2.	Anemia Monitoring	59
9.3.3.	Combined Elevations of Aminotransferases and Bilirubin	59
9.4.	Adverse Event.....	59
9.4.1.	Definition of Adverse Event (AE).....	59
9.4.2.	Definition of Serious Adverse Event (SAE).....	60
9.4.3.	Severity Assessment	60
9.4.4.	Causality Assessment	61
9.4.5.	Action Taken Regarding the Study Product	61
9.4.6.	Adverse Event Outcome	61
9.4.7.	Other Action Taken for Event	61
9.5.	Reporting Procedure For Investigators	62
9.6.	Notifying Regulatory Authorities, Investigators, and Institutional Review Board/Ethics Committee	62
9.7.	Exposure In Utero During Clinical Studies	63
9.8.	Clinical Laboratory Evaluations	63

9.8.1.	Hematology.....	63
9.8.2.	Blood Chemistry	64
9.8.2.1.	Estimation of Creatinine Clearance	65
9.8.3.	Urinalysis	65
9.8.4.	Pregnancy Testing	65
9.8.5.	Thyroid Stimulating Hormone (TSH)	65
9.9.	Vital Signs	65
9.10.	Body Height and Weight	66
9.11.	Electrocardiograms	66
9.12.	Physical Examinations	66
9.13.	Other Examinations	66
9.13.1.	Medical History and Demographics	66
9.13.2.	Home Self-Monitoring of Blood Glucose	67
9.13.3.	Study Diary	67
9.14.	Patient Reported Outcomes	67
9.15.	Pharmacoeconomic Assessments	67
10.	OTHER ASSESSMENTS	68
10.1.	Patient Reported Outcomes	68
10.2.	Pharmacoeconomic Assessments	68
11.	STATISTICAL METHODS.....	69
11.1.	Analysis Sets.....	69
11.2.	General Statistical Considerations	69
11.3.	Study Population Data	69
11.4.	Statistical Analysis.....	70
11.4.1.	Efficacy Analyses	70
11.4.1.1.	Primary Efficacy Analyses	70
11.4.1.2.	Secondary Efficacy Analyses	70
11.4.1.3.	Exploratory Efficacy Analyses	71
11.4.1.4.	Subgroup Efficacy Analyses.....	71
11.4.2.	Pharmacokinetic/Pharmacodynamic Analyses	72
11.4.2.1.	Pharmacokinetic Analyses	72
11.4.2.2.	Pharmacodynamic Analyses	72
11.4.2.3.	Biomarker Analyses.....	73

11.4.2.4.	Pharmacogenomic Analyses	73
11.4.3.	Safety Analyses	73
11.4.3.1.	Adverse Event Analyses	73
11.4.3.2.	Clinical Laboratory Evaluation Analyses	73
11.4.3.3.	Vital Sign Analyses	73
11.4.3.4.	Electrocardiogram Analyses	74
11.4.3.5.	Physical Examination Analyses	74
11.4.3.6.	Exploratory Safety Analyses	74
11.4.4.	Other Analysis	74
11.5.	Interim Analyses	74
11.5.1.	Data Monitoring Committee	74
11.6.	Sample Size Determination	74
11.7.	Statistical Analysis Process	74
12.	DATA INTEGRITY AND QUALITY ASSURANCE	76
12.1.	Monitoring and Inspections	76
12.2.	Data Collection	76
12.3.	Data Management	77
12.4.	Study Documentation and Storage	78
12.5.	Record Keeping	78
13.	FINANCING AND INSURANCE	80
13.1.	Finances	80
13.2.	Reimbursement, Indemnity, and Insurance	80
14.	PUBLICATION POLICY	81
15.	ETHICS AND STUDY ADMINISTRATIVE INFORMATION	82
15.1.	Compliance Statement, Ethics and Regulatory Compliance	82
15.2.	Subject Confidentiality	82
15.3.	Informed Consent	82
15.4.	Regulatory Compliance	83
15.5.	Protocol Deviations	84
15.6.	Supply of New Information Affecting the Conduct of the Study	84
15.7.	Protocol Amendments	84
15.8.	Study Termination	85
15.9.	Data and Safety Monitoring Board	85

15.10. Address List85

16. REFERENCES86

17. APPENDICES87

17.1. Cockcroft-Gault Equation.....87

17.2. Schedule of Events88

LIST OF TABLES

Table 5.1: Study Treatment Administration by Treatment Group.....35

Table 5.2: Prohibited Medications during Treatment Periods41

Table 6.1: Screening Laboratory Values45

Table 8.1: PK Sampling for DS-8500a and Its Metabolite (A209-3952)54

Table 8.2: PD Sampling for Plasma Glucose, Insulin, C-peptide, total GLP-1,
active GLP-1, PYY and Glucagon.....55

Table 9.1: Hematology Analytes64

Table 9.2: Blood Chemistry Analytes.....64

Table 9.3: Urinalysis Determinations65

Table 17.1: Schedule of Events89

LIST OF FIGURES

Figure 3.1: Design of Phase 2 study of DS-8500a in Subjects with T2DM30

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Plasma Concentration-Time Curve
AUC _{0-3h}	Area Under Plasma Concentration-Time Curve for 0 to 3.0 hours
AUC _{last}	Area Under the Plasma Concentration-Time Curve from Time 0 to the Time of the Last Quantifiable Concentration
AUC _{tau}	Area Under the Plasma Concentration-Time Curve for a Dosing Interval
BCRP	Breast Cancer Resistance Protein
CBC	Complete Blood Count
CEC	Cardiovascular Endpoints Committee
CHF	Congestive Heart Failure
CI	Confidence Intervals
C _{max}	Maximum Plasma Concentration
eCRF	Electronic Case Report Form
CRO	Contract Research Organization
CrCl	Creatinine Clearance
DDI	Drug-Drug Interaction
DI	Disposition Index
ECG	Electrocardiogram
EDC	Electronic Data Capture
FPG	Fasting Plasma Glucose
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GLP-1	Glucagon-Like Peptide-1
GPR119	G-Protein Coupled Receptor 119
HbA1c	Hemoglobin A1c
HDL-C	High-Density Lipoprotein Cholesterol
HMG-CoA	3-hydroxy-3-methyl-glutaryl-CoA
HOMA-IR	Homeostatic Model Assessment-Insulin Resistance
HOMA-%β	Homeostatic Model Assessment-Beta-Cell Function

ABBREVIATION	DEFINITION
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference On Harmonisation
IEC	Independent Ethics Committee
INN	International Non-Proprietary Name
IRB	Institutional Review Board
ISI	Insulin Sensitivity Index
ITT	Intent-To-Treat
IXRS	Interactive Web/Voice Response System
LDL-C	Low-Density Lipoprotein Cholesterol
MedDRA	Medical Dictionary For Regulatory Activities
mITT	Modified ITT
MMTT	Mixed Meal Tolerance Test
Non-HDL-C	Non-High Density Lipoprotein Cholesterol
OGTT	Oral Glucose Tolerance Test
OTC	Over the Counter
PD	Pharmacodynamic
PG	Plasma Glucose
P-gp	P-Glycoprotein
PIC	Powder in Capsule
PK	Pharmacokinetic
QD	Once a Day
TEAE	Treatment-emergent Adverse Event
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SID	Subject Identifier
SMBG	Self-monitoring of Blood Glucose
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
T2DM	Type 2 Diabetes Mellitus
TC	Total Cholesterol
TG	Triglycerides

ABBREVIATION	DEFINITION
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
WMG	Weighted Mean Glucose
WOCBP	Women of Child-Bearing Potential
βhCG	Human Chorionic Gonadotropin, Beta Subunit

1. INTRODUCTION

1.1. Background

1.1.1. Investigational Product(s)

1.1.1.1. Name

DS-8500a is the compound code for [REDACTED]

1.1.1.2. Description

DS-8500a is a novel [REDACTED] are expected to reduce plasma glucose levels by promoting insulin secretion in a glucose-dependent manner and to improve pancreatic β -cell function over long-term treatment.

1.1.1.3. Intended Use Under Investigation

DS-8500a is being developed for treatment of type 2 diabetes mellitus (T2DM).

1.1.1.4. Nonclinical Studies

In nonclinical pharmacology studies, DS-8500a exerted agonistic activity in Chinese hamster [REDACTED] and improved glucose intolerance in Zucker fatty rats. Administration of DS-8500a to fasted rats showed a low risk of hypoglycemia compared with sulfonylureas.

Data from nonclinical studies of DS-8500a are summarized in the DS-8500a Investigator's Brochure (IB).

1.1.1.5. Clinical Experience

In Phase 1 studies in healthy Japanese adult males, DS-8500a, provided as powder in capsule (PIC), was well tolerated as a single oral dose of up to 600 mg and in multiple oral doses up to 300 mg daily for 7 days and 75 mg daily for 14 days. The area under the plasma concentration-time curve (AUC) and maximum plasma concentration (C_{\max}) increased in less than a dose-proportional manner following single oral administration of ≥ 30 mg and following 7-day multiple oral administration, at all doses studied. When DS-8500a tablets at a dose of 50 mg or 100 mg were administered once daily for 7 days to Japanese healthy adult male subjects under fed condition, C_{\max} and area under the plasma concentration-time curve for a dosing interval (AUC_{τ}) of DS-8500a increased in less than a dose-proportional manner. The ratios of C_{\max} and area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration (AUC_{last}) of subjects who received the tablets to those who received with the PIC were 2.3 and 2.2, respectively.

A Phase 2, randomized, multicenter, double-blind, placebo-controlled, parallel-group study was conducted in Japanese patients with T2DM. Subjects were treated daily with DS-8500a 10 mg (32 subjects), DS-8500a 75 mg (34 subjects) or placebo (33 subjects) for 28 days as monotherapy. After 28 days of treatment weighted mean glucose (WMG) reduction from baseline, compared with placebo, was -13.3 mg/dL ($p=0.0093$) for the 10 mg dose and -18.9 mg/dL ($p=0.0002$) for the 75 mg dose. Subjects treated with DS-8500a also had a reduction in total cholesterol, LDL-C and triglycerides and an increase in HDL-C. The number of reported treatment-emergent adverse events (TEAEs) was small, balanced across treatment groups and none were considered drug related. There were no reports of hypoglycemia.

Based on *in vitro* studies, DS-8500a or its metabolites may affect plasma concentrations of concomitant drugs that act as substrates of [REDACTED] or [REDACTED] by the [REDACTED]. In addition, DS-8500a is a [REDACTED]. A drug-drug interaction (DDI) study assessing DS-8500a's induction potential [REDACTED] showed that the magnitude of the effect on the exposure of [REDACTED] was considered not clinically meaningful (i.e., < 20% change in [REDACTED] AUC). Therefore, it was concluded that DS-8500a is not a moderate or strong [REDACTED]. A DDI study was conducted to assess the effect of DS-8500a on [REDACTED] which is metabolized by [REDACTED] and eliminated through [REDACTED]. Preliminary results showed that following administration of 75 mg of DS-8500a tablets for 15 days, the mean (90% confidence intervals (CI)) change in the ratios of C_{max} and AUC of [REDACTED] were 1.28 (1.12, 1.48) and 0.96 (0.86, 1.00), respectively, for concomitant administration with DS-8500a compared to [REDACTED] alone. These results suggest a modest increase in [REDACTED] exposure. An additional DDI study was conducted in the US to assess the effect of DS-8500a on [REDACTED] a substrate [REDACTED]. Preliminary results showed that following administration of 75 mg of DS-8500a once daily for 16 days, the mean (90% CI) change in the ratios of C_{max} and AUC of [REDACTED] were 1.66 (1.48, 1.88) and 1.32 (1.20, 1.45), respectively, for administration with DS-8500a compared with [REDACTED]. These results suggest that co-administration of [REDACTED] with DS-8500a results in a clinically meaningful increase in exposure, apparently mediated by [REDACTED].

Other concomitant medications with DDI potential for DS-8500a, as determined from *in vitro* studies, will be excluded from this study until additional clinical DDI data are available.

DS-8500a is metabolized to form multiple metabolites [REDACTED] in both animal species and in humans (preliminary data) which have relative abundance > 25% of parent and longer terminal elimination half-lives. [REDACTED] appears to have a higher relative abundance than DS-8500a based on preliminary clinical data. Therefore, plasma concentrations of [REDACTED] will be measured in this study.

In a food effect study, healthy adult subjects were administered a single oral dose of DS-8500a 100 mg tablets either in a fasted state or after a meal. C_{max} and AUC_{last} were greater under fed condition than under fasting condition, in ratios of 1.8 and 1.9 for C_{max}

and AUC_{last} , respectively. Subjects in the present study should take study medication right after having their breakfast.

1.2. Study Rationale

T2DM is a chronic disease with long-term consequences including microvascular complications (nephropathy, neuropathy, and retinopathy), and macrovascular complications such as ischemic heart disease, stroke, and peripheral artery disease. The rapid increase in the number of patients with T2DM worldwide has become a serious challenge for global public health; it is critical to treat the disease early and appropriately in order to prevent long-term complications.¹

At present, there are several classes of oral antidiabetic agents available for the treatment of T2DM: sulfonylureas, short-acting insulin secretagogues, and dipeptidyl peptidase-IV inhibitors to increase insulin secretion; thiazolidinediones to improve insulin resistance; biguanides (metformin) to reduce hepatic glucose production; sodium glucose transporter 2 inhibitors to increase urinary glucose excretion; and α -glucosidase inhibitors to reduce and delay glucose absorption in the gut. Injectable glucagon-like peptide-1 (GLP-1) receptor agonists that slow gastric emptying, reduce appetite, and improve insulin secretion, are also available. Patients with long-term T2DM often require treatment with insulin. Patients with T2DM who have poor glycemic control with monotherapy are treated with a combination of these agents that differ in their mechanisms of action. However, given that [REDACTED] is a major contributor to the progression of T2DM, a new drug with a mechanism that helps improve insulin secretion from [REDACTED] in a mechanism distinct from available drugs may hold great promise as a new addition to conventional antidiabetic therapy.

A novel target for antidiabetic drugs is the G-protein coupled receptor 119 (GPR119), which has been shown to be highly expressed in the human small intestinal L-cells of the gastrointestinal tract and in pancreatic β -cells.^{2,3} GPR119 agonists promote a glucose-dependent insulinotropic effect in isolated pancreatic islets in mice and improve glucose intolerance assessed by oral glucose tolerance test in mice.^{3,4} GPR119 agonists upregulate insulin and genes essential for controlling pancreatic β -cells in a mouse model of T2DM. [REDACTED] agonists dose-dependently increase the concentration of cyclic adenosine monophosphate in cells expressing [REDACTED] and promote [REDACTED] [REDACTED] derived from the large intestinal L-cells in mice. Based on these findings, [REDACTED] are expected to reduce [REDACTED] by promoting insulin secretion in a glucose-dependent manner and to improve [REDACTED] over long-term treatment.

DS-8500a is a novel [REDACTED] discovered by Daiichi Sankyo Co., Ltd. In nonclinical pharmacology studies, DS-8500a exerted [REDACTED] [REDACTED] and improved glucose intolerance in Zucker fatty rats. Furthermore, DS-8500 administered for 4 weeks in Japanese subjects with T2DM provided significant reduction in WMG. Consequently, DS-8500a is being developed as an oral anti-diabetic agent for a novel approach for the treatment of T2DM, and additional clinical studies are being planned.

The present study is designed to assess efficacy and safety of DS-8500a administered in a double-blind, dose ranging, double dummy manner in subjects with T2DM on stable metformin, compared with placebo and sitagliptin 100 mg daily in US and Canada.

2. STUDY OBJECTIVES AND HYPOTHESIS

2.1. Study Objectives

2.1.1. Primary Objectives

The primary objective is to evaluate change in hemoglobin A1c (HbA1c) from baseline to Week 12 with DS-8500a compared with placebo in subjects with T2DM.

2.1.2. Secondary Objectives

The secondary objectives are:

- To evaluate changes in lipids [total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-high density cholesterol (non-HDL-C) and triglycerides (TG)] from baseline to Week 12 with DS-8500a compared with placebo.
- To evaluate change in 3h area under the curve (AUC_{0-3h}) plasma glucose (PG) in response to a mixed meal tolerance test (MMTT) from baseline to Week 4 and Week 12 with DS-8500a compared with placebo.
- To evaluate change in fasting plasma glucose (FPG) from baseline to Weeks 2, 4, 8 and 12 with DS-8500a compared with placebo.
- To evaluate the proportion of subjects achieving HbA1c < 7.0% at Week 12 with DS-8500a compared with placebo.
- To assess the pharmacokinetics (PK) of DS-8500a [REDACTED]

2.1.3. Safety Objectives

- To evaluate the safety and tolerability of DS-8500a in subjects with T2DM assessed by treatment emergent adverse events (TEAEs) and change in vital signs and safety laboratory values.
 - a. The proportion of subjects with TEAE.
 - b. Changes in routine safety laboratory testing (i.e., hematology, chemistry) from baseline to Week 12.
 - c. The proportion of subjects with prospectively adjudicated cardiovascular events including cardiovascular death, non-fatal myocardial infarction, transient ischemic attack and non-fatal stroke, hospitalization for unstable angina, urgent coronary revascularization intervention and hospitalization for congestive heart failure.

2.1.4. Exploratory Objectives

The exploratory objectives are:

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

2.2. Study Hypothesis

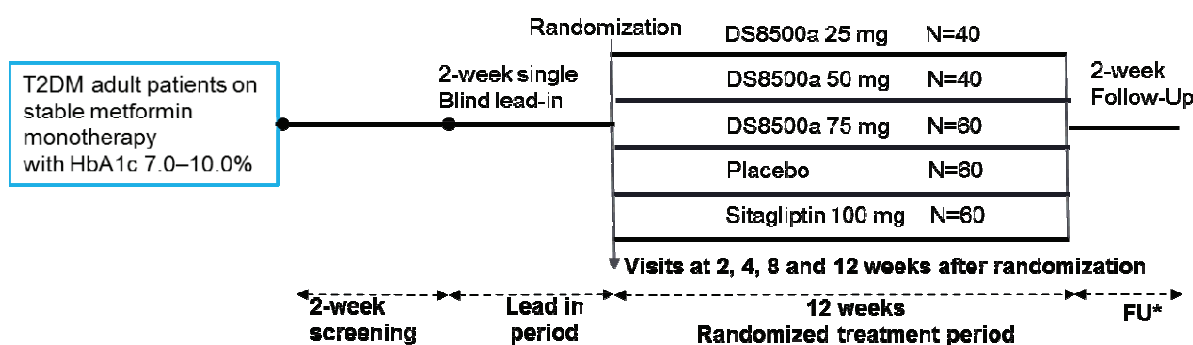
The hypothesis of this Phase 2 study is that DS-8500a will improve glycemic control relative to placebo from baseline to Week 12, based on changes in HbA1c, with an acceptable safety and tolerability profile, in patients with T2DM.

3. STUDY DESIGN

3.1. Overall Design

This is a randomized, dose ranging, double-blind, double-dummy, placebo-controlled with active comparator, multicenter, 12-week study of DS-8500a in subjects with T2DM on a stable metformin dose. The study design is depicted in Figure 3.1.

Figure 3.1: Design of Phase 2 study of DS-8500a in Subjects with T2DM



*FU=Follow-Up

3.2. Discussion of Study Design

This will be a randomized, dose-ranging, double-blind, double-dummy, placebo-controlled with active comparator, multicenter, 12-week study of DS-8500a in subjects with T2DM who are on a stable metformin dose.

Approximately 260 eligible subjects will be randomized in a 2:2:3:3:3 ratio with 40 subjects per arm in each of the DS-8500a 25 mg and DS-8500a 50 mg treatment groups, and 60 subjects per arm in the each of DS-8500a 75 mg, placebo, and sitagliptin 100 mg treatment groups. The randomization will be stratified on the basis of 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors (statins) treatment at the time of randomization. One stratum will include subjects who have been treated by statins, and the other stratum will include subjects who were not treated by statins at the time of randomization. The study will include 4 periods for a total of up to 18 weeks: a screening period of up to 2 weeks, a 2 week single-blind placebo Lead-in (Weeks -2 and -1), a 12-week double-blind, double-dummy treatment period (Day 2 to Week 12), and a 2-week post-dosing follow-up (Weeks 13 and 14). During the treatment period subjects will have clinic visits on Weeks 2, 4, 8, and 12 after randomization.

All subjects who enter the Lead-in Period must be on stable background diabetes treatment of metformin monotherapy ≥ 1000 mg/day and have a screening HbA1c $\geq 7.0\%$ and $\leq 10\%$. All subjects will continue the same metformin dose taken prior to screening throughout the study.

1. Screening Period (Weeks -4 to -3):

There will be a period up to 2 weeks for subject screening based on medical history, physical examination and clinical labs, and meeting all inclusion and exclusion criteria.

Subjects will receive basic dietary and exercise instruction at the time of screening. Subjects should not embark on aggressive, excessively restrictive or high fat content diets or change their physical activity level during this study.

2. Lead-in Period (Weeks -2 and -1):

During the Lead-in Period, subjects will take single blind DS-8500a matching placebo tablets and a sitagliptin matching placebo capsule to assess compliance with study regimen. Subjects will also be required to continue taking metformin as taken prior to screening. Subjects will be required to perform and record fasting self-monitoring of blood glucose (SMBG) daily.

3. Randomization (Day 1):

At the end of the Lead-in Period, eligible subjects who demonstrate good compliance with study drug (taking $\geq 80\%$ and $\leq 120\%$ of both dispensed DS-8500a placebo tablets and sitagliptin placebo capsules) and an appropriate Lead-in Period fasting glucose (≤ 240 mg/dL, at least 7 days of recorded fasting SMBG required) will be randomized in a 2:2:3:3:3 ratio to parallel double-blind treatment groups of DS-8500a 25 mg, DS-8500a 50 mg, DS-8500a 75 mg, placebo, or sitagliptin 100 mg. A 3-hour MMTT will be performed on Day 1 (prior to randomization).

4. Treatment Period (Day 2 to Week 12):

The Treatment Period will consist of 12 weeks of randomized double-blind, double dummy treatment with study medication, starting on Day 2 (one day after randomization day). Treatment visits will occur at Weeks 2, 4, 8, and 12 of the randomized Treatment Period. HbA1c will be measured at Weeks 4, 8, and 12 and FPG will be measured at every visit. A 3-hour MMTT will be performed on Week 4 and at the End-of-Treatment /Early Termination visit (Week 12). Metformin treatment will continue at the same dose taken prior to screening throughout the Treatment Period.

Subjects who meet protocol discontinuation criteria will be asked to return to the clinic for follow-up assessment and confirmation of values prior to discontinuation. Discontinued subjects must complete Early Termination Visit procedures.

5. Post-study Follow-up Period (Weeks 13 and 14):

Subjects who complete the randomized Treatment Period or are discontinued will return to the clinic for a post-study follow-up safety assessment visit approximately 2 weeks after taking the final dose of randomized study medication.

4. STUDY POPULATION

Investigators will maintain a confidential screening log of all potential study candidates that includes limited information of the subjects (initials, age, sex) date and outcome of screening process (e.g., enroll in the study, reason for ineligibility, refused to participate).

Prior to initiation of formal screening procedures, each subject will be asked to review and sign the informed consent form (ICF) provided by the site. All subjects must personally sign and date the ICF before any study-specific activities occur. For additional information on informed consent, see Section 15.3.

4.1. Inclusion Criteria

Subjects must satisfy all of the following criteria to be included in the study:

1. Able to provide written informed consent and adhere to the study visit schedule and treatment
2. Diagnosed with Type 2 diabetes mellitus as defined in the American Diabetes Association Standards of Medical Care in Diabetes 2015^{b,6}
3. Male or female ≥ 18 and ≤ 70 years of age
4. Screening fasting C-peptide > 0.5 ng/mL
5. Women of child bearing potential (WOCBP) must be willing to use double-barrier contraception for the entire study
6. WOCBP must have a negative pregnancy test (human chorionic gonadotropin, beta subunit [β hCG]) before entering the Lead-in Period
7. Body mass index ≥ 25 kg/m² and ≤ 45 kg/m² at the Screening Visit
8. On stable (≥ 8 weeks) metformin monotherapy ≥ 1000 mg/day
9. Screening HbA1c $\geq 7.0\%$ and $\leq 10\%$
10. Taking $\geq 80\%$ and $\leq 120\%$ of both dispensed DS-8500a placebo tablets and sitagliptin placebo capsules during the Lead-in Period

4.2. Exclusion Criteria

Subjects who meet any of the following criteria will be disqualified from entering the study:

1. History of type 1 diabetes and/or history of ketoacidosis
2. History of insulin use for > 2 weeks within 2 months prior to the Screening Visit

^b HbA1c $\geq 6.5\%$; or FGP ≥ 126 mg/dL; or 2-hour PG ≥ 200 mg/dL during an oral glucose tolerance test (OGTT); or classic symptoms of hyperglycemia with a random PG ≥ 200 mg/dL

3. Two or more readings of fasting SMBG > 240 mg/dL or worsening symptoms of hyperglycemia with one SMBG level of > 240 mg/dL during the second week of Lead-in Period, confirmed by laboratory measurement
4. Screening hemoglobin <12 g/dL for males and <11 g/dL for females
5. Blood donation within 2 months prior to the Screening Visit or plans to donate blood or blood products during the study
6. Subjects after bariatric surgery or any gastric bypass or planning to have such a procedure during the study
7. Screening thyroid stimulating hormone (TSH) levels not within normal range (based on reference laboratory values)
8. Screening alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.0 x upper limit of normal (ULN), and/or total bilirubin > 1.5 x ULN. If a subject has total bilirubin > 1.5 x ULN, unconjugated and conjugated bilirubin fractions should be analyzed and only subjects documented to have Gilbert's syndrome may be enrolled
9. Screening Serum creatinine \geq 1.5 mg/dL for males and \geq 1.4 mg/dL for females, or creatinine clearance (CrCl) < 50 mL/min for both males and females
10. Screening Creatine kinase (CK) > 3.0 \times ULN
11. History of unstable angina, myocardial infarction, cerebrovascular accident, transient ischemic attack, peripheral arterial event or any revascularization procedure during the 6 months prior to the Screening Visit or planned vascular procedures or surgery during study period
12. History of congestive heart failure (CHF)
13. Exclusionary concomitant medications:
 - a. Eight weeks prior to screening and throughout the duration of the study:
 - Any diabetes medication other than metformin; any prescription or over the counter medication for weight-loss.
 - Systemic corticosteroids (including nasal and inhaled), with the exception of use of topical and ophthalmic corticosteroids.
 - Rosuvastatin > 20 mg daily.
 - b. During treatment periods, additional medications will be prohibited based on potential drug-drug interaction (DDI) (see Section 5.6)
14. Subjects with anticipated interruption in metformin or study drug use during the course of the clinical trial (e.g., due to an imaging procedure involving iodinated contrast media)
15. Subjects in whom treatment with sitagliptin 100 mg is contraindicated (e.g., known hypersensitivity or intolerance to sitagliptin) or may not be medically advisable (e.g., history of pancreatitis)

16. Abuse of or dependence on prescription medications, illicit drugs, or alcohol within the last 1 year
17. Any history of a malignancy other than basal cell carcinoma within the past 5 years
18. Pregnancy or breast-feeding, or intent to become pregnant during the study period
19. Known (or evidence of) infection with human immunodeficiency virus
20. Any condition, laboratory abnormality, or concomitant therapy which, in the opinion of the Investigator, might pose a risk to the subject or make participation not in the subject's best interest
21. Subject is currently enrolled in or has not yet completed at least 30 days since ending another investigational device or drug study or is receiving other investigational agents
22. A direct or familial relationship with the Sponsor, Investigator, or site personnel affiliated with the study

4.3. Women of Child-Bearing Potential (WOCBP)

For the purposes of this study, all female participants will be considered as WOCBP unless they have undergone surgical sterilization or are postmenopausal and have a documented serum follicle stimulating hormone (FSH) level >35 mIU/mL (with or without hormone replacement therapy) and no menses for at least 12 months.

WOCBP are permitted in the study but must consent to avoid becoming pregnant by using an approved contraception method throughout the study and for up to 2 weeks after completion, as described below.

Study-acceptable methods of birth control are double-barrier methods, which include a combination of any 2 of the following: systemic contraceptives, diaphragm or sponge with spermicide, condom, intrauterine device, or partner's vasectomy.

All WOCBP subjects must have a negative serum pregnancy test (β hCG) at the Screening Visit (Visit 1) in order to continue in the study. A urine pregnancy test will be conducted at all other clinic visits through the Follow-up clinic visit (Visits 2-8) for all WOCBP subjects. If a urine test result is positive, a serum pregnancy test will be performed to confirm the result.

Daiichi Sankyo must be notified of any study subject who becomes pregnant while participating in this clinical study, as described in Section 9.7.

5. STUDY TREATMENT(S)

5.1. Assigning Subjects to Treatments and Blinding

5.1.1. Treatment during Lead-in Period

All subjects will take single-blind DS-8500a placebo matching tablets and a sitagliptin matching placebo capsule (three placebo tablets and 1 placebo capsule) once daily after breakfast for 2 weeks. On Day 1 (randomization day) lead-in DS-8500a placebo tablets and sitagliptin placebo capsules will be taken during MMTT immediately after ingestion of the liquid meal.

5.1.2. Treatment Group(s)

Subjects will be randomly assigned in a 2:2:3:3:3 ratio to 1 of the following 5 treatment arms (Table 5.1):

- DS-8500a 25 mg + sitagliptin placebo
- DS-8500a 50 mg + sitagliptin placebo
- DS-8500a 75 mg + sitagliptin placebo
- DS-8500a placebo + sitagliptin placebo
- DS-8500a placebo + sitagliptin 100 mg

DS-8500a tablets will be provided at strengths of 25 mg. Sitagliptin 50 mg tablets will be over encapsulated to provide once daily dose of 100 mg.

A matching placebo tablet for DS-8500a and a matching placebo capsule for sitagliptin will be utilized to conduct the double-dummy, double-blind treatment period. Three tablets and 1 capsule will be taken once daily.

Table 5.1: Study Treatment Administration by Treatment Group

Treatment Arm	Tablet	Capsule
1	DS-8500a 25 mg	sitagliptin placebo
2	DS-8500a 50 mg	sitagliptin placebo
3	DS-8500a 75 mg	sitagliptin placebo
4	DS-8500a placebo	sitagliptin placebo
5	DS-8500a placebo	sitagliptin 100 mg

DS-8500a or matching placebo tablets and sitagliptin or matching placebo capsules will be administered orally once daily after breakfast for 12 weeks, except for study visit days. The first randomized study drug dose will be taken after breakfast on Day 2 after the Day 1 visit. On days of study visits that involve MMTT study drug will be taken after ingestion of the liquid meal (Visits 5 and 7 at Weeks 4 and 12) (see Section 8.2). On days

of Visits 4 and 6 (Weeks 2 and 8, respectively), study drug should be taken after study laboratory blood draw and after having breakfast (see Section 8.1).

The schedule of events is provided in Section 17.2. Additional information regarding study procedures is provided in Section 6.

5.1.3. Method of Treatment Allocation

Randomization will be performed centrally using an Interactive Web/Voice Response System (IXRS). At the Screening Visit, the investigator, or other site personnel under the direction of the investigator, should contact or access the IXRS to register the subject, obtain the subject identifier (SID). At Lead-in visit (Visit 2), after confirmation of a subject's eligibility, the investigator, or designee, will contact the IXRS to register the subject to obtain the SID of the Lead-in drug carton to be dispensed to this subject. Upon confirmation of a subject's eligibility at the Randomization Visit (Day 1), the investigator, or designee, will contact the IXRS to register the subject as randomized and obtain the SID of the initial study medication carton to be dispensed to this subject. At Treatment Visits 5 and 6, the investigator or designee, should contact the IXRS to record the subject's visit and status and obtain the correct carton number to be dispensed at that visit. Study medication should only be dispensed in accordance with IXRS instructions and carton number assignment. At the End-of-Treatment/Early Termination (Visit 7), the subject's visit and status should also be recorded using the IXRS.

A draft randomization schedule generated by the IXRS vendor will be reviewed by the Daiichi Sankyo study statistician before the start of study. After approval, the live randomization schedule will be generated by the IXRS vendor by varying the randomization seed. The final randomization schedule will be reviewed and approved by an independent statistician at Daiichi Sankyo. Eligible subjects will be randomized in the ratio of 2:2:3:3:3 to receive 12 weeks of double-blind treatment with DS-8500a 25mg QD, DS-8500a 50mg QD, DS-8500a 75mg QD, placebo, or sitagliptin 100 mg QD. The randomization will be stratified on the basis of HMG-CoA reductase inhibitors (statins) treatment at the time of the Randomization Visit.

IXRS and Clinical Supply Operations personnel will have access to medication identification codes. IXRS personnel along with Clinical Supply Operations personnel will be unblinded. All other personnel involved with the conduct and the interpretation of the study, including investigators, investigational site personnel, Daiichi Sankyo employees and designees will be blinded to the treatment until after the database lock.

5.1.4. Blinding

The DS-8500a 25mg tablets and the matching placebo tablets have been manufactured to be identical in size and appearance.

Sitagliptin 50 mg tablets will be over encapsulated to provide a once daily dose of 100 mg and a matching placebo capsule has been manufactured.

Throughout the study, sponsor and designee, the Investigator and the study subject will be blinded to the treatment assignment. The bioanalytical laboratory will be unblinded. The bioanalytical laboratory will protect the randomization schedule in order to maintain

the blind outside of the laboratory. In order to analyze PK samples, and to maintain the study blind, the drug concentration results will be shared outside of the bioanalytical laboratory ONLY AFTER the clinical study database has been unblinded.

The study blind will be broken at the end of the study once all the following prerequisites are met:

- Database locked
- Statistical analysis plan (SAP) finalized
- Subjects and data inclusion in Analysis Sets finalized

Once the decision for unblinding is reached, the study team will prepare an unblinding memo with signatures from at least the study director and sponsor biostatistician.

5.1.5. Emergency Unblinding Procedure

In the case of an emergency where, in the opinion of the Investigator, discontinuation of study drug is not sufficient and the study treatment must be unblinded in order to evaluate further a course of medical treatment, the Investigator can perform the unblinding by directly accessing the IXRS.

In the event of an emergency unblinding, the subject will be informed about their treatment assigned, but not their treatment dose. Information about the treatment assignment **must be** restricted to designated study center staff/ personnel who are providing immediate care to the subject. Any documentation of the treatment assignment **must be** maintained separately (i.e., a secured file). The information **must not be** included in the subject's source files to ensure the treatment assignment will remain blinded to sponsor or designee's Medical Monitor not involved with the subject's immediate care.

When an emergency unblinding has occurred, an automatic notification (via e-mail) will be sent to the investigator and selected Daiichi Sankyo study personnel from the IXRS vendor. The notification will not contain any unblinded information. This will trigger the follow-up process to document the unblinding by completing the Emergency Unblinding by Investigator Form (to be provided by study personnel upon receipt of IXRS notification) and submission to Daiichi Sankyo Clinical Safety and Pharmacovigilance (CSPV). Please refer to the form for completion instructions.

Once the study treatment has been unblinded for a specific subject, the study treatment should be discontinued for the subject, and the subject should leave the study treatment phase. The End-of-treatment/Early termination and Follow-up assessments for the subjects will be performed as defined in the protocol.

5.2. Study Drug(s)

5.2.1. Description

DS-8500a is a novel [REDACTED] expected to reduce PG levels by promoting insulin secretion in a glucose-dependent manner and to improve pancreatic β -cell function over long-term treatment.

5.2.2. Labeling and Packaging

Double-blind study medication will be provided in labeled blister cards (“wallets”) in cartons. The blister label will include all information required by federal and local regulations. Additional details on the investigational drug products can be found in documentation accompanying drug shipment.

Code-break envelopes or scratch-off labels will not be used for unblinding in this study. Unblinding of individual subjects will be controlled using the IXRS (see Section 5.1.5).

5.2.3. Preparation

Study drug will be provided to sites as fully prepared blister cards (wallets) in cartons. All wallets will have 3 tablets and 1 capsule for each day of dosing. Cartons will be individually numbered; only the correctly numbered cartons should be distributed to study subjects in accordance with IXRS instructions.

5.2.4. Administration

DS-8500a or matching placebo tablets and sitagliptin or matching placebo capsules will be administered orally once daily after breakfast for 12 weeks, except for study visit days. The first randomized study drug dose will be taken after breakfast on Day 2 after Day 1 visit. On study visit days that involve MMTT, study drug will be taken after ingestion of the liquid meal [Day 1 (Lead-in tablets and capsule) and Visits 5 and 7 at Weeks 4 and 12, respectively] (see Section 8.2). On the days of Visits 4, and 6 (Weeks 2 and 8, respectively), study drug should be taken after the study laboratory’s blood draw and after having a breakfast meal (see Section 8.1).

5.2.5. Storage

Drug supplies must be stored appropriately in a locked cabinet in a room with limited and controlled access under the labeled storage conditions. The labeled storage conditions are provided on the labeled drug supplies. Temperature measurement will be recorded daily on a temperature log excluding weekends and holidays.

NOTE: If storage conditions go outside of the labeled storage conditions, the site must not dispense the affected supplies (affected supplies should be placed in quarantine) and Daiichi Sankyo personnel or designee must be contacted to determine if the affected supplies can be used.

5.2.6. Drug Accountability

When a drug shipment is received, the investigator or designee will check the amount and condition of the drug, check for appropriate local language in the label, and sign the Receipt of Shipment Form provided. The original will be retained at the site. In addition, the investigator or designee shall contact the sponsor as soon as possible if there is a problem with the shipment.

A Drug Accountability Record will be provided to each site for documenting the use of the investigational product. The record must be kept current and should include the date and quantity of drug (number of cartons) received at each shipment, the SID (and initials)

of each subject for whom the investigational product was dispensed, the carton numbers, date and quantities of investigational product dispensed at each visit, amount of remaining or returned product received at each subject visit (including the number of tablets/capsules inside or outside of returned wallets), and the initials of the dispenser.

At the end of the study, or as directed, all study treatment, including unused, partially used, or empty wallets, and any drug that may have been removed from the wallets (but not taken), will be destroyed on site according to the site's drug handling and disposition standard operating procedures (SOPs). A copy of these SOPs must be available onsite. The certificate of destruction must be provided to Daiichi Sankyo documenting the drug, the quantity (in tablets and capsules), method of destruction, and date of destruction.

If sites are unable to destroy drug, the monitor will make arrangements to return drug to a designated depot for destruction.

Medications provided by the Sponsor will be destroyed (or returned) only after the study monitor has completed an inventory to verify the quantity to be destroyed (or returned). The destruction (or return) of medications provided by the sponsor must be documented and the documentation filed (and if returned, included in the shipment).

All investigational product inventory forms must be made available for inspection by the sponsor's authorized representative (e.g., contract research organization (CRO) site monitor) and any authorized inspector from a regulatory agency. The investigator is responsible for the accountability of all used and unused study supplies at the site.

5.3. Control Treatment

Placebo and sitagliptin will serve as control treatments. Inclusion of placebo is required in light of the known placebo effect in T2DM studies. Inclusion of sitagliptin is intended to generate active comparator data for study reference. Sitagliptin will be initiated at the recommended starting dose for patients with normal renal function or mild renal impairment (administered as 100 mg QD).

5.4. Dose Interruptions and Reductions

Subjects who miss > 7 days of consecutive doses of study medication will be withdrawn from the study and early termination study procedures performed. There will be no dose reduction for DS8500a/sitagliptin/placebo.

5.5. Method of Assessing Treatment Compliance

Records of treatment compliance for each subject will be kept during the study. The identification number of all dispensed and returned study drug wallets should be recorded, along with the SID. The number of tablets/capsules used and remaining in each wallet should be documented at the Lead-in visit and each Treatment visit and the End-of-Treatment/Early Termination visit. If any tablets or capsules have been removed from the wallets (but not taken), these should be counted, documented, and retained.

Treatment compliance will be calculated by dividing the number of tablets and capsules taken by the number of tablets and capsules assigned for the appropriate visit interval

(adjusted for any changes in the visit interval). Compliance for each visit interval is defined as taking at least 80% and no more than 120% of the study drug prescribed for that interval. If a subject is noncompliant, the subject will be counseled by study staff on the importance of taking the correct amount of study medication. As the primary analysis will follow the intent-to-treat (ITT) principle, subjects should not be discontinued from the study for treatment noncompliance unless the subject meets the discontinuation criteria outlined in Section 5.7.1.

5.6. Prior and Concomitant Medications

Subjects should be instructed not to take any diabetes medications (other than metformin) and/or any prescriptions or over the counter medications for weight-loss. No systemic corticosteroids (including nasal and inhaled) can be taken during the study, but topical and ophthalmic corticosteroids are permitted.

Any medication (other than study drug) taken by subjects during the course of the study will be recorded and coded using the World Health Organization (WHO) dictionary. If drug therapy other than that specified by the protocol is taken, a joint decision will be made by the Investigator and Sponsor on whether to continue or discontinue the subject.

Concomitant medications with DDI potential for DS8500a based on the in vitro studies will be excluded from this study until further clinical data is available. These medications can be found in Table 5.2. The highest dose of rosuvastatin will be limited to 20 mg due to the potential for increased rosuvastatin exposure during concomitant administration with DS-8500a.

Table 5.2: Prohibited Medications during Treatment Periods

CYP3A4 substrates with narrow therapeutic windows			
Quinidine		Cyclosporine	
P-gp substrates with narrow therapeutic windows			
Digoxin		Dabigatran	
Strong CYP3A4 inhibitors			
Boceprevir	Itraconazole	Posaconazole	
Clarithromycin	Ketoconazole	Ritonavir	
Conivaptan	Lopinavir	Saquinavir	
Grapefruit	Nefazodone	Telaprevir	
Grapefruit Juice	Nelfinavir	Telithromycin	
Indinavir	Voriconazole		
CYP2C9 substrates with narrow therapeutic windows			
Warfarin	Sulfonylureas	Valproic acid	Phenytoin

*Topical use (if available) is allowed for the prohibited medications in the table.

5.7. Subject Withdrawal/Discontinuation

Data from all randomized subjects are important to achieve study objectives, and subjects should be encouraged to adhere to protocol instructions and visit schedules. However, in accordance with the Declaration of Helsinki and other applicable regulations, a subject has the right to withdraw from the study at any time, and for any reason, without prejudice to his or her future medical care by the study physician or at the study site. The investigator is also free to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants such action. The sponsor or regulatory authorities also may request termination of the study at any time due to safety issues or concerns related to study conduct.

5.7.1. Reasons for Withdrawal

Any subject who discontinues from the study treatment for any reason will have their study treatment discontinuation recorded.

If a subject discontinues from the study treatment for any reason, the reason for discontinuation or withdrawal must be recorded on the electronic case report form (eCRF) using the following criteria:

For subjects withdrawn prior to randomization but after signing informed consent

- Did not satisfy all inclusion/exclusion criteria
- Adverse event
- Lost to follow-up
- Withdrawal by subject (indicate reason)
- Physician decision

For subjects discontinued or withdrawn after randomization but before completing the treatment period

- Persistent hyperglycemia defined as follows:
 - Up to and including Visit 6 (Week 8): two or more readings of fasting SMBG ≥ 240 mg/dL OR 1 reading of fasting SMBG ≥ 240 mg/dL and worsening symptoms of hyperglycemia, confirmed by repeating fasting laboratory glucose.
 - After Visit 6 (Week 8): two or more readings of fasting SMBG ≥ 220 mg/dL OR 1 reading of fasting SMBG ≥ 220 mg/dL and worsening symptoms of hyperglycemia, confirmed by repeating fasting laboratory glucose.
- Severe hypoglycemia^{7,c} requiring assistance
- Anemia (see Section 9.3.2)
- Pregnancy
- Adverse event
- Death
- Lack of efficacy
- Lost to follow-up
- Protocol deviation
- Study terminated by sponsor
- Withdrawal by subject (indicate reason)
- Other (indicate reason)

Reasons recorded under “protocol deviation” may include failure to comply with protocol requirements or study procedures.

^c Severe hypoglycemia is an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration⁷.

A subject may be withdrawn due to non-compliance with any aspect of the protocol, as determined by the investigator and/or the sponsor's medical monitor or designee. Subjects who miss > 7 days of consecutive doses of study medication will be withdrawn from the study and early termination study procedures performed.

All subjects who are withdrawn from the Treatment Period should complete protocol-specified withdrawal procedures (see Section 5.7.2 and Section 6.4.4).

5.7.2. Withdrawal Procedures

If a subject withdraws (or is withdrawn) from the study, the investigator should complete and report all observations as thoroughly as possible up to the date of withdrawal, including the date of last treatment and the reason for withdrawal.

If the subject is withdrawn due to an adverse event (AE), the investigator should follow the subject until the AE has resolved or stabilized.

All subjects who are withdrawn from the study should complete all End-of-treatment/Early termination (Visit 7) procedures as soon as possible after early withdrawal (Section 6.4.4).

If a subject becomes lost to follow-up, the sites will be given instruction on actions to take to try to locate the subject.

5.7.3. Subject Replacement

Subjects removed from the study for any reason will not be replaced.

5.7.4. Subject Re-screening Procedures

Rescreening of subjects will not be permitted.

6. STUDY PROCEDURES

A study visit schedule in tabular format is provided in Section 17.2. Missing visits are strongly discouraged in this study. It is expected that investigator site staff thoroughly explain the visit schedule to potential subjects. Any missed visit that occurs during the double-blind treatment period must be rescheduled within 1 week. Two or more consecutive missed visits are grounds for immediate subject discontinuation from the study.

The study will include 4 periods for a total of up to 18 weeks: a **Screening Period** up to 2 weeks, a 2 week single-blind placebo **Lead-in Period** (Weeks -2 and -1), a 12-week double-blind, double-dummy **Treatment Period** (Day 2 to Week 12), and a 2-week post-dosing **Follow-up** (Weeks 13 and 14). During the Treatment Period, subjects will have clinic visits on Weeks 2, 4, 8, and 12 after randomization. All visits except the Follow-Up Visit should be conducted after at least 8 hours of fasting (no food or drink except water).

6.1. Screening Period

There will be a period up to 2 weeks for subject screening based on medical history, physical examination and screening laboratories, and meeting all inclusion and exclusion criteria.

6.1.1. Screening Visit (Visit 1; Week -4 to Week -3)

The initial Screening Visit should occur 4 to 3 weeks prior to the Randomization Visit (Day 1). At least 8 hours of fasting is required for the Screening Visit. Subjects will be screened for study participation. The initial eligibility will be determined by assessment of the applicable inclusion and exclusion criteria, listed in Section 4.1 and Section 4.2, respectively. The following activities and/or assessments will be performed at/during the Screening Visit (Visit 1):

- Obtain written informed consent
- Confirm the subject fasted overnight. If a subject has not fasted the investigator will reschedule the subject to collect the laboratories within 3 days.
- Assess all applicable inclusion and exclusion criteria
- Record demographics
- Obtain past medical and medication history
- Record prior and concomitant medications
- Record vital signs (see Section 9.9), body height and body weight (see Section 9.10)
- Perform screening full physical examination (see Section 9.12)
- Perform a 12-lead ECG (see Section 9.11)

- Register screened subject in the IXRS.
- Collect urine sample for evaluation of urinalysis (see Section 9.8.3).
- Collect blood samples for the following:
 - Perform serum pregnancy test as applicable (see Section 9.8.4).
 - Standard laboratory safety tests (chemistry, hematology) (see Section 9.8.1 and Section 9.8.2).
 - HbA1c
 - FPG
 - Lipid panel
 - C-peptide
 - TSH (see Section 9.8.5)
 - FSH (in postmenopausal women who are not surgically sterile)
- Subjects will be excluded based on screening laboratory values limits in Table 6.1.

Table 6.1: Screening Laboratory Values

Blood chemistry	TSH	Outside of normal range based on laboratory reference values
	Hemoglobin	<12 g/dL for males and <11 g/dL for females
	AST (SGOT)	> 2.0 × ULN
	ALT (SGPT)	> 2.0 × ULN
	Total bilirubin ^a	> 1.5 × ULN
	Creatine kinase	> 3.0 × ULN
	Serum creatinine	≥ 1.5 mg/dL for males and ≥1.4 mg/dL for females
	Calculated CrCl	< 50mL/min

Abbreviations: TSH = thyroid stimulating hormone, ALT (SGPT) = alanine aminotransferase, AST (SGOT) = aspartate aminotransferase, CrCl = creatinine clearance (determined by the central laboratory using the Cockcroft-Gault equation), ULN = upper limit of normal

^a If a subject has total bilirubin > 1.5 x ULN, unconjugated and conjugated bilirubin fractions should be analyzed and only subjects documented to have Gilbert's syndrome may be enrolled

- Provide instructions on basic dietary and exercise:
 - Don't embark on aggressive, excessively restrictive or high fat content diets
 - Don't change physical activity level during this protocol.
- Schedule Lead-in visit to occur in approximately 1-2 weeks (± 3 days).

6.2. Placebo Lead-in (Visit 2, Week -2)

During the Lead-in Period, subjects will take single-blind DS-8500a-matching placebo tablets and a sitagliptin-matching placebo capsules. Subjects will also be required to continue taking metformin as taken prior to entering the Lead-in Period. Subjects will be required to perform and record fasting SMBG daily. The following activities and/or assessments will be performed at Lead-in Visit:

- Review inclusion/exclusion criteria
- Record vital signs (see Section 9.9) and body weight (see Section 9.10).
- Perform a targeted physical examination (including lungs, heart, and as needed examination, see Section 9.12).
- Assess for and record AEs and concomitant medications.
- Perform urine pregnancy test as applicable (see Section 9.8.4).
- Study Medication:
 - Contact IXRS to register the subject and obtain study medication kit number.
 - Dispense study medication kit (single-blind DS-8500a placebo tablets and sitagliptin placebo capsules) and instruct subject in proper dosing after breakfast each day.
- Dispense blood glucose meter and provide instruction on use and daily recording of SMBG. (see Section 9.13.2).
- Dispense study diary and instruct subject to fill out day and time of study drug dosing and record SMBG readings. (see Section 9.13.3).
- At end of study visit review and remind subject to:
 - Begin using home blood glucose meter to check fasting SMBG each morning prior to eating.
 - Bring study diary and glucose meter to each visit.
 - Record exact time of morning medication doses and SMBG readings in the study diary.
 - Bring study medication to each visit.
 - Fast for at least 8 hours prior to the next visit and arrive at the study site approximately between 6am and 9am.
 - NOT take study medication in the morning prior to each clinic visit until instructed to do so at the site.
- Schedule next clinic visit to occur in approximately 2 weeks (\pm 3 days).

6.3. Randomization (Visit 3, Day 1)

At the end of the Lead-in Period, eligible subjects demonstrating good compliance with study drug (taking $\geq 80\%$ and $\leq 120\%$ of dispensed placebo tablets and placebo capsules) and an appropriate Lead-in Period fasting SMBG (≤ 240 mg/dL, at least 7 days of recorded fasting SMBG required) will be randomized in a 2:2:3:3:3 ratio to 1 of the following parallel double-blind treatment groups: DS-8500a 25 mg, DS-8500a 50 mg, DS-8500a 75 mg, placebo, or sitagliptin 100 mg. The randomization will be stratified on the basis of HMG-CoA reductase inhibitors (statins) treatment at the time of the Randomization Visit.

This is a fasting visit. Subjects should be fasting (no food or drinks except water) for at least 8 hours prior to the visit, and arrive at the study site approximately between 6am and 9am.

The following procedures and assessments will be performed at the Randomization visit (Day1):

- Confirm subject has fasted and has not taken study medication this morning. If subject has not fasted, reschedule this visit to occur within 3 days. All randomization laboratories must be collected on the same day in order to establish the proper baseline of laboratories and MMTT results for each subject.
- Confirm inclusion/exclusion criteria.
- Review study diary.
- Review fasting SMBG records and assess for eligibility criteria based on Exclusion Criterion 3 (see Section 4.2)
- Assess for and record AEs and concomitant medications.
- Record vital signs (see Section 9.9) and body weight (see Section 9.10).
- Perform a targeted physical examination (including lungs, heart, and as needed examination, see Section 9.12).
- Perform urine pregnancy test for WOCBP (see Section 9.8.4).
- Prior to the randomization, conduct the MMTT test and collect a pre-dose blood sample (time 0) for PK analysis (see Section 8.1). Subjects should be fasting for at least 8 hours prior to the MMTT. The standardized meal will be given approximately between 7am and 10am. Study drug from the Lead-in Period will be administered immediately after consuming the liquid meal. (see Section 8.2).
- Collect blood samples for the following during time 0 of MMTT:
 - Standard laboratory safety tests (chemistry, hematology) (see Section 9.8.1 and Section 9.8.2).
 - HbA1c

- FPG
- Lipid panel
- Study Medication:
 - Contact IXRS to obtain new medication kit number.
 - Collect study medication and check study drug adherence.
 - Dispense randomized study medication.
 - Instruct subject to take study drug from the new kit after breakfast on the next day.
- Schedule next clinic visit to occur in approximately 2 weeks (\pm 3 days).
- At end of study visit review and remind subject to:
 - Fast for at least 8 hours prior to the next visit.
 - Record exact time of morning medication doses in the study diary.
 - Bring study medication, study diary and glucose meter to each visit to check drug adherence and SMBG.
 - Not take study medication in the morning prior to next clinic visit until instructed to do so at the site, after morning blood samples have been taken and having breakfast.

6.4. Treatment Period (Visit 4 to Visit 7, Week 2 to Week 12, respectively)

6.4.1. Visit 4 (Week 2)

This is a fasting visit. Subjects should be fasting (no food or drinks except water) for at least 8 hours prior to the visit.

The following procedures and assessments will be performed:

- Confirm subject has fasted for at least 8 hours prior to visit and has not taken study medication this morning. If subject has not fasted, reschedule this visit to occur within 3 days.
- Review study diary.
- Review SMBG records (see Section 9.13.2).
- Check study drug adherence.
- Assess for and record AEs and concomitant medications.
- Record vital signs (see Section 9.9) and body weight (see Section 9.10).
- Perform a targeted physical examination (including lungs, heart, and as needed examination, see Section 9.12).
- Perform urine pregnancy test for WOCBP (see Section 9.8.4).

- Collect blood for the following:
 - Standard laboratory safety tests (chemistry, hematology) (see Section 9.8.1 and Section 9.8.2).
 - A pre-dose blood sample will be collected for PK analysis (see Section 8.1).
 - FPG
- Administer and record date and time of dose taken at this visit.
- Schedule next clinic visit to occur in approximately 2 weeks (\pm 3 days).
- At end of study visit review and remind subject to:
 - Fast for at least 8 hours prior to the next visit and arrive at the study site approximately between 6am and 9am.
 - Record exact time of morning medication doses in the study diary.
 - Bring study medication study diary and glucose meter to each visit to check drug adherence and SMBG.
 - Not take study medication in the morning prior to each clinic visit until instructed to do so at the site.

6.4.2. Visit 5 (Week 4)

This is a fasting visit. Subjects should be fasting (no food or drinks except water) for at least 8 hours prior to the visit, and should arrive at the study site approximately between 6am and 9am.

The following procedures and assessments will be performed:

- Confirm subject has fasted and has not taken study medication this morning. If subject has not fasted, reschedule this visit to occur within 3 days.
- Review study diary.
- Review SMBG records (see Section 9.13.2).
- Assess for and record AEs and concomitant medications.
- Record vital signs (see Section 9.9) and body weight (see Section 9.10).
- Perform a targeted physical examination (including lungs, heart, and as needed examination, see Section 9.12).
- Perform a 12-lead ECG (see Section 9.11).
- Perform urine pregnancy test for WOCBP (see Section 9.8.4).
- Conduct the MMTT test. Subjects should be fasting for at least 8 hours prior to the MMTT. The standardized liquid meal will be given approximately between 7am and 10am. Study drug will be administered immediately after consuming the liquid meal (see Section 8.2). The PK samples for DS-8500a

and its metabolite [REDACTED] evaluation will be collected at the same time points as MMTT, including pre-dose (time 0), 0.5, 1.0, 1.5, 2.0, 2.5 and 3.0 h after initiation of ingesting the liquid meal (see Section 8.1).

- Collect blood for the following during time 0 of MMTT:
 - Standard laboratory safety tests (chemistry, hematology) (see Section 9.8.1 and Section 9.8.2).
 - HbA1c
 - FPG
 - Lipid panel
- Administer and record date and time of dose taken at this visit.
- Study Medication:
 - Collect study medication and check study drug adherence.
 - Contact IXRS to obtain new medication kit number.
 - Dispense new study medication.
- Schedule next clinic visit to occur in approximately 4 weeks (\pm 3 days).
- At end of study visit review and remind subject to:
 - Fast for at least 8 hours immediately prior to the next visit. Fast for at least 8 hours prior to the next visit and arrive at the study site approximately between 6am and 9am.
 - Record exact time of morning medication doses in the study diary.
 - Bring study medication study diary and glucose meter to each visit to check drug adherence and SMBG.
 - Not take study medication in the morning prior to each clinic visit until instructed to do so at the site, after morning blood samples have been taken and having breakfast.

6.4.3. Visit 6 (Week 8)

This is a fasting visit. Subjects should be fasting (no food or drinks except water) for at least 8 hours prior to the visit.

The following procedures and assessments will be performed:

- Confirm subject has fasted and has not taken study medication this morning. If subject has not fasted, reschedule this visit to occur within 3 days.
- Review study diary.
- Review SMBG records (see Section 9.13.2).
- Assess for and record AEs and concomitant medications.
- Record vital signs (see Section 9.9) and body weight (see Section 9.10).

- Perform a targeted physical examination (including lungs, heart, and as needed examination, see Section 9.12).
- Collect blood for the following:
 - Standard laboratory safety tests (chemistry, hematology) (See Section 9.8.1 and Section 9.8.2).
 - HbA1c
 - FPG
 - A pre-dose blood sample will be collected for PK sample (see Section 8.1).
- Perform urine pregnancy test for WOCBP (see Section 9.8.4).
- Administer and record date and time of dose taken at this visit.
- Study Medication:
 - Collect study medication and check study drug adherence.
 - Contact IXRS to obtain new medication kit number.
 - Dispense new study medication.
- Schedule next clinic visit to occur in approximately 4 weeks (\pm 3 days).
- At end of study visit review and remind subject to:
 - Fast for at least 8 hours prior to the next visit and should arrive at the study site approximately between 6am and 9am.
 - Record exact time of morning medication doses in the study diary.
 - Bring study medication study diary and glucose meter to each visit to check drug adherence and SMBG.
 - Not take study medication in the morning prior to next clinic visit until instructed to do so at the site.

6.4.4. Visit 7 (End-of-Treatment Visit, Week 12) or Early Termination Visit

This is a fasting visit. Subjects should be fasting (no food or drinks except water) for at least 8 hours prior to the visit, and should arrive at the study site approximately between 6am and 9am.

The following procedures and assessments will be performed at the End-of-treatment Visit (Week 12 \pm 3 days) or at Early Termination:

- Confirm subject has fasted and has not taken study medication this morning. If subject has not fasted, reschedule this visit to occur within 3 days.
- Review study diary.
- Review SMBG records (see Section 9.13.2).
- Assess for and record AEs and concomitant medications.

- Record vital signs (see Section 9.9), body weight (see Section 9.10)
- Perform full physical examination (see Section 9.12)
- Perform a 12-lead ECG (Section 9.11)
- Perform urine pregnancy test for WOCBP (see Section 9.8.4).
- Collect urine sample for evaluation of urinalysis (see Section 9.8.3).
- Conduct the MMTT test. Subjects should be fasting for at least 8 hours prior to the MMTT. The standardized meal was given approximately between 7am and 10am. Study drug will be administered immediately after consuming the liquid meal (see Section 8.2). The PK samples of DS-8500a and its metabolite [REDACTED] evaluation will be collected at the same time points as MMTT, including pre-dose (time 0), 0.5, 1.0, 1.5, 2.0, 2.5 and 3.0 h after initiation of ingesting the liquid meal (see Section 8.1).
- Collect blood for the following during time 0 of MMTT:
 - Standard laboratory safety tests (chemistry, hematology) (see Section 9.8.1 and Section 9.8.2).
 - HbA1c
 - FPG
 - Lipid panel
- Administer and record date and time of dose taken at this visit.
- Collect study medication and check study drug adherence.
- Contact the IXRS.
- Schedule Follow-up visit to occur in approximately 2 weeks (\pm 3 days)

6.5. Follow-Up (Visit 8, Week 14)

This is a non-fasting visit.

The following procedures and assessments will be performed at the Week 14 (\pm 3 days) visit:

- Assess for and record AEs.
- Record vital signs (see Section 9.9) and body weight (see Section 9.10).
- Perform a targeted physical examination (including lungs, heart, and as needed examination, see Section 9.12).
- Perform urine pregnancy test for WOCBP (see Section 9.8.4)
- Collect urine and blood for the following:
 - Repeat any abnormal results from prior visit.

7. EFFICACY ASSESSMENTS

For all efficacy variables except lipids, baseline is defined as the last measurement prior to the first dose of randomized study medication. Baseline lipid variables will be the average of the screening and Week 0/Day 1 values.

7.1. Primary Efficacy

The primary efficacy endpoint is change from baseline in HbA1c at Week 12.

7.2. Secondary Efficacy

The secondary endpoints are:

- Changes from baseline in lipids (TC, LDL-C, HDL-C, non-HDL-C and TG) at Week 12.
- Changes from baseline in AUC_{0-3h} and C_{max} of PG in response to MMTT at Weeks 4 and 12.
- Changes from baseline in FPG from baseline to Weeks 2, 4, 8, and 12.
- The proportion of subjects achieving HbA1c < 7.0% at Week 12.

7.3. Exploratory Efficacy

Exploratory endpoints are:

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

8. PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS

8.1. Pharmacokinetic (PK) Endpoint(s)

Blood samples for the measurement of DS-8500a and its metabolite [REDACTED] will be collected as shown in Table 8.1. The subject will be instructed not to take study medication prior to the study visit for PK sampling. At Visits 3, 4, and 6 (Day 1, Week 2, and Week 8) only pre-dose PK levels will be obtained. At Visits 5 and 7 (Weeks 4 and 12, respectively), PK sampling will be obtained during the MMTT pre-dose (time 0) and every 30 minutes after MMTT ingestion up to 3 hours (see Section 8.2). The time of last dose and meal prior to the study visit must be recorded.

Table 8.1: PK Sampling for DS-8500a and Its Metabolite (A209-3952)

Week (Visit)	Pre-dose	Post Consumption of Liquid Meal (hour)					
	within 10 min prior to liquid meal ^a	0.5h (± 5 min)	1.0h (± 5 min)	1.5h (± 5 min)	2.0h (± 5 min)	2.5h (± 5 min)	3.0h (± 5 min)
Week 0 (Day 1, Visit 3) ^b	X						
Week 2 (Visit 4)	X						
Week 4 (Visit 5) ^b	X	X	X	X	X	X	X
Week 8 (Visit 6)	X						
Week 12 (Visit 7) ^c	X	X	X	X	X	X	X

^a Only applies to visit 3, 5 and 7

^b Prior to randomization

^c Mixed Meal Tolerance Test

DS-8500a and its metabolite will be measured by a validated Liquid Chromatography Mass Spectrometry (LC-MS)/ Mass Spectrometry (MS) bioanalytical method.

Plasma PK and standard noncompartmental PK parameters (area under the concentration versus time curve [ng•h/mL] from 0 to 3 hours [AUC_{0-3h}] and trough concentrations [C_{trough}]) will be calculated for DS-8500a and its metabolite [REDACTED].

8.2. Pharmacodynamic (PD) Endpoint(s)

Mixed Meal Tolerance Test (MMTT)

The MMTT will be performed in all subjects at randomization visit (Day 1, prior to the randomization), Week 4 and Week 12 (Visits 5 and 7, respectively). On study visit days that involve MMTT, subjects will have fasted (no food or drinks except water) for at least

8 hours prior to the MMTT. The standardized meal will be given approximately between 7am and 10am. The entire liquid meal is to be completed within a 10-minute period. Study drug will be administered immediately after consuming the liquid meal. On day 1 Lead-in tablets and capsules will be taken after the liquid meal and on Week 4 and Week 12 (Visits 5 and 7, respectively) randomized tablets and capsules will be taken.

During the MMTT, blood samples will be collected within 10 min prior to the start of the meal (time 0), and at 0.5, 1, 1.5, 2, 2.5, and 3 hours after initiation of ingesting the liquid meal for the measurement of plasma glucose.

On Day 1, PK sample will be collected at time 0 of the MMTT. On Visits 5 and 7, PK samples will be collected at each time point of the MMTT.

Blood samples will be collected for PD assessment of plasma glucose and biomarkers such as insulin, C-peptide, total GLP-1, active GLP-1, PYY and glucagon as shown in Table 8.2. The mean plasma glucose during the 3 h postprandial period (0–3 h) will be calculated as the AUC for the plasma glucose profile (calculated by the trapezoid rule) divided by the 3 h time interval.

Table 8.2: PD Sampling for

Week (Visit)	Pre-dose (min)	Post-Dose (hour)					
	within 10 min prior to liquid meal	0.5h (± 5 min)	1.0h (± 5 min)	1.5h (± 5 min)	2.0h (± 5 min)	2.5h (± 5 min)	3.0h (± 5 min)
Week 0 (Day 1, Visit 3) ^a	X	X	X	X	X	X	X
Week 4 (Visit 5) ^b	X	X	X	X	X	X	X
Week 12 (Visit 7) ^b	X	X	X	X	X	X	X

^a Prior to randomization, blood samples for plasma glucose and biomarkers at each time point. Plasma PK at pre-dose only

^b Blood samples for plasma glucose, biomarkers. Plasma PK at all-time points.

Content of standardized meal for the MMTT:

The standardized meal consists of two servings of liquid supplement containing approximately 100 g of total carbohydrates and approximately 2930 kJ (700 kcal). (i.e., Ensure Plus[®] – each bottle contains 50 g carbohydrates, 11 g fat, 13 g protein for a total 350 calories).

Instructions for specimen collection, storage, and shipping will be provided in the lab manual.

8.3. Biomarker Endpoint(s)

Blood samples for biomarker evaluation will be collected during MMTT test (see Section 8.2).

8.4. Immunogenicity

Not applicable.

8.5. Pharmacogenomic Analysis

Not applicable.

9. SAFETY EVALUATION AND REPORTING

9.1. Adverse Event Collection and Reporting

All clinical AEs (see Section 9.4.1 for definitions) occurring after the subject signs the Informed Consent Form and through the Follow-up Visit, whether observed by the investigator or reported by the subject, will be recorded on the AE CRF page. Medical conditions (including laboratory values/vital signs that are out of range) that were diagnosed or known to exist prior to Informed Consent will be recorded as part of medical history.

All AEs, serious adverse events (SAEs), and Adverse Events of Special Interest are to be reported according to the procedures in Section 9.5.

All laboratory results, vital signs, physical examination and ECG findings should be appraised by the Investigator to determine their clinical significance. Isolated abnormal laboratory results, vital sign findings, or ECG findings (i.e., not part of a reported diagnosis) should be reported as AEs if they are symptomatic, lead to study drug discontinuation, dose reduction, require corrective treatment, or constitute an AE in the investigator's clinical judgment.

At each visit, the investigator will determine whether any AEs have occurred by evaluating the subject. Adverse events may be directly observed, reported spontaneously by the subject or by questioning the subject at each study visit. Subjects should be questioned in a general way, without asking about the occurrence of any specific symptoms. The Investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 9.4. The Investigator's assessment must be clearly documented in the site's source documentation with the Investigator's signature.

Always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the SAE narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report as individual entries of AE or SAE.

For events that are serious due to hospitalization, the reason for hospitalization must be reported as the SAE (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Preplanned (prior to signing the ICF) procedures or hospitalizations for pre-existing conditions which do not worsen in severity should not be reported as SAEs. For deaths, the underlying or immediate cause of death should always be reported as an SAE.

In addition, any serious, untoward event that may occur subsequent to the reporting period that the investigator assesses as related to study drug should also be reported and managed as an SAE.

Any serious, untoward event that may occur subsequent to the reporting period that the Investigator assesses as related to study drug should also be reported and managed as an SAE.

Investigators should follow subjects with AEs until the event has resolved or the condition has stabilized. Unresolved AEs, including significant abnormal laboratory values at the end of the study, should be followed up until resolution or until no longer clinically relevant.

9.2. Safety Endpoint Event(s)

Not applicable.

9.3. Events of Special Interest

9.3.1. Adjudicated Cardiovascular Events

A Cardiovascular Endpoints Committee (CEC) consisting of independent external experts in the field of cardiovascular medicine will blindly review and adjudicate any event that is potentially a cardiovascular event including cardiovascular death, non-fatal myocardial infarction, transient ischemic attack and non-fatal stroke, hospitalization for unstable angina, urgent coronary revascularization intervention and hospitalization for congestive heart failure.

The CEC will need to verify that the event meets pre-specified definitions. The definitions for each of these cardiovascular events and the process of identifying events that require adjudication will be detailed in the CEC Charter.

9.3.2. Anemia Monitoring and Stopping Criteria

In toxicology studies anemia was observed in 3 monkeys in (see data in Investigator Brochure). All cases of anemia improved or tended to improve after drug withdrawal. The mechanism of anemia development was not identified. No anemia or reduction in hemoglobin has been observed in any human studies with DS-8500a. To ensure subjects' safety, complete blood count and reticulocytes count will be measured at every study visit and anemia will be closely monitored throughout the study.

9.3.2.1. Rules for Anemia Evaluation and Stopping of Study Subjects

- If Hemoglobin decreases more than 1.5 g/dL but less than or equal to 2.0 g/dL compared to baseline level, the test should be repeated within a week. Additional tests should be conducted to evaluate the potential cause of anemia (see Section 9.3.2.2). The subject should be followed until labs return to baseline.
- If Hemoglobin decreased more than 2.0 g/dL compared to baseline level and/or Hemoglobin level is lower than 10.0 g/dL for males and 9.5 g/dL for females, the test should be repeated within 3 days. Additional tests should be conducted to evaluate the potential cause of anemia (see Section 9.3.2.2). If any of the above changes in hemoglobin are confirmed, the subject should stop taking study drug and discontinue from the study (see Section 5.7). Subject should be followed until

labs return to baseline. All early termination procedure (see Section 6.4.4) should be conducted except MMTT. This event should always be reported to the Sponsor using a SAVER form, with the investigator's assessment of seriousness, causality, and a detailed narrative. This event should be reported within 24 hours of Investigator's awareness of the event.

- Additional tests and/or a referral to hematology consult may be done based on investigator's discretion.

9.3.2.2. Anemia Monitoring

The hematology test for CBC and reticulocytes count should be measured at each visit (see Section 9.8.1). The following tests are recommended for the subjects who are developing anemia or having the reduction in Hemoglobin as described in Section 9.3.2.1:

- CBC and Reticulocytes
- Blood smear
- Chemistry including lactate dehydrogenase, total bilirubin, direct bilirubin
- Ferritin
- Haptoglobin
- Hemocult test

9.3.3. Combined Elevations of Aminotransferases and Bilirubin

Combined elevations of aminotransferases and bilirubin, either serious or non-serious and whether or not causally related, meeting the laboratory criteria of a potential Hy's Law case [ALT or $AST \geq 3 \times ULN$ with simultaneous total bilirubin $\geq 2 \times ULN$] should always be reported to the Sponsor using a SAVER form, with the investigator's assessment of seriousness, causality, and a detailed narrative. These events should be reported within 24 hours of Investigator's awareness of the event.

9.4. Adverse Event

9.4.1. Definition of Adverse Event (AE)

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

It is the responsibility of Investigators, based on their knowledge and experience, to determine those circumstances or abnormal laboratory findings which should be considered adverse events.

9.4.2. Definition of Serious Adverse Event (SAE)

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

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect, or
- Is an important medical event.

Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require treatment to prevent one of the other outcomes listed in the definition above. Examples include allergic bronchospasm, convulsions, and blood dyscrasias or development of drug dependency or drug abuse.

Note:

- Procedures are not AEs or SAEs, but the reason for the procedure may be an AE or SAE.
- Pre-planned (prior to signing the Informed Consent Form) procedures or treatments requiring hospitalizations for pre-existing conditions that do not worsen in severity are not SAEs.

9.4.3. Severity Assessment

The following definitions should be used to assess intensity of adverse events:

- Mild: Awareness of sign or symptom, but easily tolerated (i.e., does not interfere with subject’s usual function).
- Moderate: Discomfort enough to cause interference with usual activity.
- Severe: Incapacitating with inability to work or do usual activity (i.e., interferes significantly with subject’s usual function).

Severity vs. Seriousness: Severity is used to describe the intensity of a specific event while the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as “seriousness,” which is based on patient/event outcome at the time of the event.

9.4.4. Causality Assessment

The Investigator should assess causal relationship between an AE and the study product on the basis of his/her clinical judgment and the following definitions. The causality assessment should be made based on the available information and can be updated as new information becomes available.

- 1 = Related:
 - The AE follows a reasonable temporal sequence from study drug administration, and cannot be reasonably explained by the subject's clinical state or other factors (e.g., disease under study, concurrent diseases, and concomitant medications).
 - The AE follows a reasonable temporal sequence from study drug administration, and is a known reaction to the drug under study or its chemical group, or is predicted by known pharmacology.
- 2 = Not Related:
 - The AE does not follow a reasonable sequence from study product administration, or can be reasonably explained by the subject's clinical state or other factors (e.g., disease under study, concurrent diseases, and concomitant medications).

9.4.5. Action Taken Regarding the Study Product

- 1 = Dose Not Changed: No change in study drug dosage was made.
- 2 = Drug Withdrawn: The study product was permanently stopped.
- 3 = Drug Interrupted: The study product was temporarily stopped.

9.4.6. Adverse Event Outcome

- 1 = Recovered/Resolved
 - The subject fully recovered from the adverse event with no residual effect observed.
- 2 = Recovered/Resolved with Sequelae
 - The residual effects of the adverse event are still present and observable.
 - Include sequelae/residual effects.
- 3 = Not Recovered/Not Resolved
 - The AE itself is still present and observable.
- 4 = Fatal

9.4.7. Other Action Taken for Event

- 1 = None.

- No treatment was required.
- 2 = Medication required.
 - Prescription and/or over the counter (OTC) medication was required to treat the AE.
- 3 = Other.

9.5. Reporting Procedure For Investigators

All AEs and SAEs will be reported in the eCRF.

In addition, the following events should be reported on a SAVER (Serious Adverse Event Report) form within 24 hours of awareness.

- SAEs (see Section 9.4.2 for definition)
- Hepatic events meeting combination abnormalities [ALT or AST $\geq 3 \times$ ULN with simultaneous TBL $\geq 2 \times$ ULN] (potential Hy's Law case), both serious and non-serious (see Section 9.3.3 for additional details).
- Hemoglobin decrease of > 2.0 g/dL from baseline level, and/or Hemoglobin < 10.0 g/dL for males or < 9.5 g/dL for females, both serious and non-serious (see Section 9.3.2.1 for additional details).

All events (serious and non-serious) must be reported with Investigator's assessment of the event's seriousness, severity, and causality to the blinded study drug. A detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome should be provided. Specific or estimated dates of event onset, treatment, and resolution should be included when available. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the narrative. For fatal events, the narrative should state whether an autopsy was or will be performed, and include the results if available. Source documents will be retained in site's files and should not be submitted to the Sponsor for SAE reporting purposes.

Urgent safety queries must be followed up and addressed promptly. Follow-up information and response to non-urgent safety queries should be combined for reporting via the eCRF to provide the most complete data possible within each follow-up.

Please call the local SAE Hotline or your study monitor for any questions on SAE reporting.

9.6. Notifying Regulatory Authorities, Investigators, and Institutional Review Board/Ethics Committee

Daiichi Sankyo and/or CRO will inform Investigators, central Institutional Review Boards (IRBs), and regulatory authorities of any Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring in other study centers or other studies of the investigational drug, as appropriate per local reporting requirements. Daiichi Sankyo and/or CRO will comply with any additional local safety reporting requirements.

In the US and Canada, upon receipt of the Sponsor's notification of SUSARs that occurred with the study drug, unless delegated to the Sponsor, it is the Investigator's responsibility to inform the IRB per Sponsor's instruction.

9.7. Exposure In Utero During Clinical Studies

Daiichi Sankyo must be notified of any subject who becomes pregnant while receiving or the study drug through the Follow-up Visit.

Although pregnancy is not technically an adverse event, all pregnancies must be followed to conclusion to determine their outcome. This information is important for both drug safety and public health concerns. It is the responsibility of the Investigator, or designee, to report any pregnancy in a female subject via using the Exposure In Utero (EIU) Reporting form. Please contact your study monitor to receive the EIU Reporting Form upon learning of a pregnancy. The investigator should make every effort to follow the subject until completion of the pregnancy and complete the EIU Reporting Form with complete pregnancy outcome information, including normal delivery and induced abortion. The adverse pregnancy outcome, either serious or non-serious, should be reported in accordance with study procedures. If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., post-partum complications, spontaneous or induced abortion, stillbirth, neonatal death, or congenital anomaly, including that in an aborted fetus), the Investigator should follow the procedures for reporting SAEs outlined in Section 9.5.

9.8. Clinical Laboratory Evaluations

Blood and urine samples for clinical laboratory evaluations will be shipped to a central laboratory for analysis. Results of all laboratory tests will be reported in the subject's eCRF or merged electronically with the clinical database.

9.8.1. Hematology

Ethylenediamine tetraacetic acid (EDTA) tube of blood will be drawn for the hematology assessments and HbA1c listed in Table 9.1. These will be measured from samples obtained at the Screening Visit, Randomization Visit, Treatment visits and End-of-treatment/Early termination visit. All abnormal results from prior visit will be repeated at Follow-up Visit.

Table 9.1: Hematology Analytes

Complete Blood Count (CBC) ^a	Hemoglobin
	Hematocrit
	Red blood cell (RBC) count (with indices)
	White blood cell (WBC) count (with differential)
	Platelet count
Reticulocytes count ^b	
HbA1c ^c	

^a CBC counts will be measured at each visit.

^b Reticulocytes counts will be measured at each visit.

^c HbA1c will only be measured at Screening Visit, Randomization Visit, Treatment Visits (Week 4 and Week 8) and End-of-treatment/Early Termination Visit (Week 12).

9.8.2. Blood Chemistry

A serum separating tube of blood will be drawn for the blood chemistry assessments listed in Table 9.2. These will be measured from samples obtained at the Screening Visit, Randomization Visit, Treatment visits and End-of-treatment/Early Termination visit. All abnormal results from prior visit will be repeated at Follow-up Visit.

Table 9.2: Blood Chemistry Analytes

Sodium	Lactate Dehydrogenase
Potassium	Creatinine
Magnesium	Blood urea nitrogen
Bicarbonate	Total protein
Calcium	Albumin
Inorganic phosphorus	Uric acid
AST	Creatine kinase
ALT	Fasting blood glucose
Alkaline phosphatase	C-peptide ^a
Total bilirubin ^b	Lipid Panel ^c - Total cholesterol (TC), - Low-density lipoprotein cholesterol (LDL-C) - High-density lipoprotein cholesterol (HDL-C) - Triglycerides (TG)

^a C-peptide will be measured at the Screening Visit.

^b Total bilirubin should be fractionated whenever total bilirubin > 1.5 x ULN. Unconjugated and conjugated bilirubin fractions should be analyzed and only subjects documented to have Gilbert's syndrome may be enrolled.

^c Lipid panel will only be measured at Screening Visit, Randomization Visit, Treatment Visit 5 (Week 4) and End-of-treatment/Early Termination Visit (Week 12).

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal

9.8.2.1. Estimation of Creatinine Clearance

Creatinine clearance will be estimated from serum creatinine and subject demography by the central laboratory using the Cockcroft-Gault equation ([Appendix 17.1](#)).

9.8.3. Urinalysis

Standard urinalysis including a microscopic examination will be conducted for all subjects at the Screening Visit and End-of-treatment/Early Termination visit (Table 9.3). All abnormal results from prior visit will be repeated at Follow-up Visit.

Table 9.3: Urinalysis Determinations

Specific gravity	Blood
pH	RBC
Protein	WBC
Glucose	Bilirubin
Ketones	Urobilinogen

Abbreviations: RBC = red blood cell; WBC = white blood cell.

For samples with findings on macroscopic analysis, microscopic examination for red blood cells, white blood cells, bacteria, and casts should be performed.

9.8.4. Pregnancy Testing

All WOCBP must have a negative serum pregnancy test at the Screening Visit. A urine pregnancy test will also be performed for all WOCBP subjects at all clinic visits through the Follow-up Visit (as defined in Section 4.3). If a urine test result is positive, a serum pregnancy test will be performed to confirm the result.

9.8.5. Thyroid Stimulating Hormone (TSH)

A serum TSH test will be performed at the Screening Visit (Visit 1) for all subjects. Subjects with TSH not within normal range are excluded.

9.9. Vital Signs

Vital signs will be recorded at all clinic visits and will include temperature, heart rate, and sitting blood pressure.

Measurement of blood pressure should be conducted using a calibrated manometer or automatic inflatable cuff monitor.

Blood pressure should be measured using the same arm and measuring device throughout the study. At the Screening Visit (Visit 1) only, a blood pressure reading should be taken in both arms (unless there is a medical reason not to use a particular arm). The arm with the higher systolic reading should then be used throughout the rest of the study.

Blood pressure should be recorded to the nearest 2 mmHg mark on the manometer or to the nearest whole number on an automatic device.

After all blood pressures have been obtained; measure the subject's heart rate using the same arm.

9.10. Body Height and Weight

Measurement of height will be performed only at the Screening Visit (Visit 1) with the subject in a standing position and with shoes removed. The subject's knees should be straightened, head held erect, with eyes forward.

Measurement of weight should be performed at all clinic visits with the subject dressed in indoor clothing, shoes removed and bladder empty. Subjects should be weighed on the same scale at all clinic visits.

9.11. Electrocardiograms

A 12-lead ECG will be conducted at the Screening Visit, Visit 5 (Week 4) and at the End-of-treatment/Early termination visit (Visit 7). ECG recordings should be assessed as normal or abnormal, and any abnormal findings should be assessed as not clinically significant or clinically significant. Clinically significant abnormal findings should be reported as medical history (if pre-existent). Refer to Section 9.1 for general guidance on when to report abnormal findings as AEs. If new abnormal findings in ECG are identified in Visit 5 or Visit 7, assessment should be made whether these changes meet criteria for event requiring review by CEC.

9.12. Physical Examinations

A full physical examination, with the exception of pelvis, breast, and rectum in women and the genitourinary system and prostate in men, will be performed at the Screening Visit (Visit 1) and End-of-treatment/Early termination visit (Visit 7). The full physical examination should minimally include clinical evaluations of the head, neck, thyroid, eyes, ears, nose, throat, chest, heart, lungs, lymph nodes, abdomen, skin, extremities, musculoskeletal and neurological.

A targeted physical examination will be performed at Visits 2, 3, 4, 5, 6, and Follow-up Visit (Visit 8). The abbreviated physical examination should minimally include clinical evaluations of the heart and lungs. Additional systems may be examined based on any symptoms exhibited by the subject.

9.13. Other Examinations

9.13.1. Medical History and Demographics

Demographic information including month and year of birth, race, sex, weight, and height will be collected on all subjects at screening. Medical history, including details regarding all illnesses and allergies, date(s) of onset, whether condition currently persist(s), and smoking and alcohol use, will be collected on all subjects. Additional

information to be collected includes past surgical and medical procedures as well as medications.

9.13.2. Home Self-Monitoring of Blood Glucose

All subjects enrolled will be provided with home blood glucose monitor to measure blood glucose levels throughout the study. Subjects will be instructed to obtain blood glucose levels every morning, before having breakfast and taking study medication. Subjects may also obtain blood glucose measurements, as instructed by the investigator, at any other time and specifically should be encouraged to measure and record if they experience symptoms of hypoglycemia or hyperglycemia. Subjects will be instructed to call the clinic if the monitoring device indicates a fasting blood glucose level <70 mg/dL or >240 mg/dL, or blood glucose <70 mg with or without symptoms at any time. Subjects will receive appropriate medical advice based on their blood glucose level and, if deemed necessary by the investigator, a clinic visit will be scheduled within 3 days for a follow-up laboratory evaluation of fasting glucose.

At the Randomization Visit, subjects will report their fasting SMBG obtained during the Lead-in Period. If a subject reports 2 or more values during Lead-in Period that were greater than 240 mg/dL, or 1 value greater than 240 mg/dL and worsening polyuria, polydipsia, dizziness, vision changes, or other symptoms of hyperglycemia, subject should have their FPG measured and if values are confirmed by the laboratory should be discontinued prior to randomization.

Throughout the study, subjects should use provided glucose monitor to perform SMBG. Results, along with any symptoms of either hyper or hypoglycemia should be recorded in their study diary. For SMBG meeting discontinuation criteria please see Section [5.7.1](#).

9.13.3. Study Diary

Subjects will be provided with a paper diary to help them to record their home SMBG, the time of study drugs taken, and any new symptoms.

9.14. Patient Reported Outcomes

Not applicable.

9.15. Pharmacoeconomic Assessments

Not applicable.

10. OTHER ASSESSMENTS

10.1. Patient Reported Outcomes

Not applicable.

10.2. Pharmacoeconomic Assessments

Not applicable.

11. STATISTICAL METHODS

11.1. Analysis Sets

The following analysis sets will be used to summarize the data from this study:

- The Randomized Analysis Set will include all subjects who signed the ICF and were randomized into the study.
- The Safety Analysis Set will include all subjects who received at least 1 dose of randomized study drug.
- The modified Intent-To-Treat (mITT) analysis set will include all subjects in the Safety Analysis Set who have a baseline measurement and at least 1 post-baseline measurement.
- The Per-protocol Analysis Set will include all subjects in the Safety Analysis Set and who were sufficiently compliant with the protocol, according to pre-specified criteria which will be finalized prior to database unblinding.
- The PK Analysis Set will include all subjects who received at least 1 dose of DS-8500a and have at least 1 PK concentration measured.

11.2. General Statistical Considerations

Unless otherwise specified, hypothesis testing will be performed at the 0.1 significance level (2-sided) and 2-sided 90% CI will be provided.

Raw data will be presented with the same precision with which they were collected.

For summary statistics, means and medians will be displayed to 1 more decimal place than was determined for raw data, dispersion statistics will have 2 more decimal places, and the minimum and maximum will be displayed to the same number of decimal places as the raw data.

Quantitative data will be tabulated with descriptive summary statistics: arithmetic mean, standard deviation (SD), median, minimum and maximum values, and number of observations. For categorical data, frequency tables will be provided.

For variables expressed as percent, the denominators for the calculations of percentages will be the number of subjects who had that variable assessed.

11.3. Study Population Data

Demographic characteristics will be summarized for the randomized subject population according to treatment assignment. Continuous demographic variables (age [calculated from date of birth to the date of signed informed consent], weight, height, and body mass index) for all randomized subjects will be summarized with descriptive statistics. Categorical demographic variables (sex, race, ethnicity, and age group) will be summarized with frequency counts and corresponding percentages.

Subject disposition will be summarized as the number of subjects screened, the number randomized, and the number and percent of those who completed treatment or withdrew (with the latter summarized by reason for withdrawal).

Prior and concomitant medications will be summarized by number and percent of subjects for each WHO-Drug preferred base name and Anatomical Therapeutic Chemical category.

11.4. Statistical Analysis

11.4.1. Efficacy Analyses

For all efficacy variables except lipids, baseline is defined as the last measurement prior to the first dose of randomized study medication. Baseline lipid variables will be the average of the screening and Week 0/Day 1 values.

11.4.1.1. Primary Efficacy Analyses

The primary estimand is the treatment difference between DS-8500a and placebo for the change in HbA1c from baseline to Week 12 attributable to the initially randomized treatment for all subjects in the mITT Analysis Set. The primary estimand will be analyzed using a mixed-effect model with repeated measures (MMRM) with treatment group, previous statins stratum, week, and treatment-by-week as the fixed effects, week as a repeated factor, and baseline HbA1c as a covariate to compare each DS-8500a dose vs. placebo. No adjustment will be made for multiple comparisons.

The between-treatment group effects at Week 12 will be tested at 2-sided 10% level of significance. Point estimates and corresponding 90% CIs for the differences in least-square mean changes between each DS-8500a dose and placebo will be calculated.

To establish the assay sensitivity of the study, the comparison of sitagliptin and placebo will be carried out using the same method as that for the primary estimand. The point estimate and corresponding 90% CI for the difference in least-square mean change between sitagliptin and placebo will be calculated.

Graphical presentations of change from baseline in HbA1c will be provided for each treatment group over 12 weeks.

Similar analyses will be performed for the change in HbA1c from baseline to Week 12 for the Per-protocol Analysis Set.

11.4.1.2. Secondary Efficacy Analyses

The secondary efficacy variables will be analyzed for the mITT Analysis Set.

The secondary efficacy variables are:

- The change and percent change from baseline at Weeks 4 and 12 in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-high density cholesterol (non-HDL-C), and triglycerides (TG).

- The change from baseline in HbA1c at Weeks 4 and 8.
- The change from baseline in FPG at Weeks 2, 4, 8, and 12.
- The proportion of subjects achieving HbA1c<7% at Week 12.

For the change and percent change from baseline in lipid variables, a MMRM with treatment group, previous statins stratum, week, and treatment-by-week as the fixed effects, week as a repeated factor, and baseline value as a covariate will be applied to compare each DS-8500a dose vs. placebo and sitagliptin vs. placebo.

For the change from baseline in HbA1c at Week 4 and Week 8, comparisons of each DS-8500a dose vs. placebo and sitagliptin vs. placebo will be performed using the MMRM applied for the analysis of the primary estimand.

For the change from baseline in FPG, the MMRM with treatment, previous statins stratum, week, and treatment-by-week as fixed effects, week as a repeated factor, and baseline FPG as a covariate will be used to compare each DS-8500a dose vs. placebo and sitagliptin vs. placebo.

The responder analysis for the proportion of subjects achieving HbA1c<7% at Week 12 will be carried out using a logistic regression model with treatment group and previous statins stratum as factors and baseline HbA1c as a covariate.

The difference in changes from baseline in TG vs. placebo will be estimated using Hodges-Lehmann estimator and the corresponding non-parametric 2-sided 90% CI will be constructed using Moses' method.

All comparisons will be tested at a 2-sided significance level of 0.1 for all variables. There will be no adjustment for multiplicity.

11.4.1.3. Exploratory Efficacy Analyses

[REDACTED]

11.4.1.4. Subgroup Efficacy Analyses

Descriptive summaries will be provided for the change from baseline in HbA1c at Week 12 for each subgroup factor by treatment group. The following subgroup factors will be used:

- Age (≤ 65 or > 65 years),
- Sex
- Race
- Baseline HbA1c level (< 8.5 , ≥ 8.5),

- Body mass index ($<30 \text{ kg/m}^2$, $\geq 30 \text{ kg/m}^2$).

11.4.2. Pharmacokinetic/Pharmacodynamic Analyses

11.4.2.1. Pharmacokinetic Analyses

(A209-3952) will be assessed. The

11.4.2.2. Pharmacodynamic Analyses

The PD parameters will include 3h area under the curve (AUC_{0-3h}), C_{max} and mean for plasma glucose (PG) in response to MMTT. The analyses will be performed, using a MMRM with treatment group, previous statins stratum, week, and treatment-by-week as the fixed effects, week as a repeated factor, and baseline value as a covariate, for the following PD variables:

- The change in body weight from baseline at each scheduled visit.

For the beta-cell function, insulin sensitivity and disposition index data, the assumptions of normality and homogeneity of variance will be examined prior to fitting the models. If a significant departure from the assumption is observed, an appropriate non-parametric method will be applied.

The time-course of the PD measures will be plotted.

11.4.2.3. Biomarker Analyses

11.4.2.4. Pharmacogenomic Analyses

Not applicable.

11.4.3. Safety Analyses

Safety assessments include adverse events, clinical laboratory measurements (hematology, blood chemistry, and urinalysis and vital signs. The Safety Analysis Set will be used for all safety analyses.

11.4.3.1. Adverse Event Analyses

Adverse events will be grouped by system organ class and by preferred term within system organ class according to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Treatment-emergent adverse events are defined as adverse events that first occurred or worsened in severity after initiation of double-blind treatment. Tables summarizing subject incidence of all TEAEs, serious adverse events, severe adverse events, study drug-related TEAEs, study drug-related serious adverse events, study drug-related severe adverse events, and TEAEs leading to early withdrawal from study and/or death will be provided.

Adverse events collected from the Screening Period and the Lead-in Period will be presented separately.

11.4.3.1.1. Cardiovascular Event Adjudication

Selected cardiovascular events will be adjudicated by an independent board. Tables summarizing subject incidence of the cardiovascular events will be provided by treatment group. A subject listing of the cardiovascular events will be provided.

11.4.3.2. Clinical Laboratory Evaluation Analyses

Tables summarizing baseline, post baseline, and change from baseline for each scheduled collection time point will be provided for hematology and blood chemistries.

The number and percentage of subjects with “markedly abnormal” laboratory values will be tabulated. The clinical laboratory data will be listed, and values outside the normal ranges will be flagged.

11.4.3.3. Vital Sign Analyses

For vital signs, descriptive summary statistics for baseline and change from baseline values will be presented by treatment group.

11.4.3.4. Electrocardiogram Analyses

Clinically significant abnormal 12-lead ECG findings will be reported as AEs. Data from ECG findings will be listed. Shift tables for ECG results (normal or abnormal) will be presented by treatment group.

11.4.3.5. Physical Examination Analyses

Clinically significant abnormal physical examination findings will be reported as AEs. Data from physical examinations will be listed and summarized by treatment group.

11.4.3.6. Exploratory Safety Analyses

Not applicable

11.4.4. Other Analysis

Not applicable

11.5. Interim Analyses

Not applicable

11.5.1. Data Monitoring Committee

A data monitoring committee will not be formed for this study.

11.6. Sample Size Determination

Approximately 260 eligible subjects will be randomized in a 2:2:3:3:3 ratio with 40 subjects per arm in each of the DS-8500a 25 mg and DS-8500a 50 mg treatment groups, and 60 subjects per arm in each of the DS-8500a 75 mg, placebo, and sitagliptin 100 mg treatment groups. Assuming a common SD of 1.0% and an early (prior to first post-baseline assessment) dropout rate of 10%, with a 2-sided t-test at a significance level of 0.1, it is estimated the sample size will provide at least 90% power to detect a 0.6% difference between DS-8500a 75 mg dose and placebo and at least 80% power to detect a 0.6% difference between each of the DS-8500a 25 mg and 50 mg doses and placebo in mean HbA1c change from baseline to Week 12. No adjustment will be made for multiplicity.

11.7. Statistical Analysis Process

The clinical study data will be analyzed by the CRO.

The SAP will provide the statistical methods and definitions for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other clinical study information such as subject disposition, demographic and baseline characteristics, study drug exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused, and spurious data will be addressed.

The SAP will be finalized prior to unblinding to preserve the integrity of the statistical analysis and clinical study conclusions. Any deviations from the planned statistical analyses in the protocol will be fully described in the SAP.

All statistical analyses will be performed using SAS® Version 9.3 or higher (SAS Institute, Cary, NC 27513).

12. DATA INTEGRITY AND QUALITY ASSURANCE

The investigator/investigational site will permit study-related monitoring, audits, IRB/Independent Ethics Committee (IEC) review, and regulatory inspections by providing direct access to source data/documents. Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of a clinical study.

12.1. Monitoring and Inspections

The sponsor or designee's monitor and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (e.g., CRFs, source data, and other pertinent documents).

The verification of adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to ICH GCP and local regulations on the conduct of clinical research will be accomplished through a combination of onsite visits by the monitor and review of study data remotely. The frequency of the monitoring visit will vary based on the activity at each study site. The monitor is responsible for inspecting the CRFs and ensuring completeness of the study essential documents. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the CRFs. Detailed information is provided in the monitoring plan.

The monitor will communicate deviations from the protocol, SOPs, GCP and applicable regulations to the Investigator and will ensure that appropriate action (s) designed to prevent recurrence of the detected deviations is taken and documented.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are addressed to the satisfaction of the sponsor and documented.

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor. Audit of study center facilities (e.g., pharmacy, drug storage areas, laboratories) and review of study related records will occur in order to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements. The investigator should respond to audit findings. In the event that a regulatory authority informs the investigator that it intends to conduct an inspection, the Sponsor shall be notified immediately.

12.2. Data Collection

All relevant observations and data related to the study, as per the study protocol, will be recorded on eCRF pages. A representative of Daiichi Sankyo or their designee will provide instruction for completing the eCRF. Adequate and accurate case records should be maintained, including the evaluation of inclusion and exclusion criteria, medical history, physical examinations, clinical assessments, a record of clinical safety laboratory sample collection, drug administration, AEs, and final evaluation.

The eCRFs must be completed for each subject who signs the ICF and undergoes screening procedures. For subjects who are screened but not randomized, minimal data will be recorded on the eCRF, including demography, subject status, and AEs. All study related data for these subjects will be maintained in the medical records at the site.

The eCRF data entry shall be completed on the day of the visit or as soon as possible thereafter. The investigator must electronically sign and date the eCRF. The signature shall indicate that the investigator has reviewed the data and data queries recorded on eCRFs and the site notifications, and agrees with the content. After the completion of the study, eCRFs including audit trail will be returned to Daiichi Sankyo and stored in the archives.

12.3. Data Management

Each subject will be identified in the database by a unique SID as defined by the sponsor.

To ensure the quality of clinical data across all subjects and study centers, a Clinical Data Management review will be performed on subject data according to specifications given to the sponsor or designee. Data will be vetted both electronically and/or manually for CRFs and the data will be electronically vetted by programmed data rules within the application. Queries generated by rules and raised by reviewers will be generated within the electronic data capture (EDC) application. During this review, subject data will be checked for consistency, completeness and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. For eCRFs, the data will be electronically vetted by programmed data rules within the application. Queries generated by rules and raised by reviewers will be generated within the EDC application and also resolved within the EDC application.

Data received from external sources such as central labs will be reconciled to the clinical database.

Serious Adverse Events in the clinical database will be reconciled with the safety database.

All Adverse Events (except terms pre-specified on the eCRF) will be coded using MedDRA. All prior and concomitant medications will be coded using WHO Drug Dictionary.

12.4. Study Documentation and Storage

The Investigator will maintain a Signature List of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Signature List.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, X-rays, and correspondence.

Records of subjects, source documents, monitoring visit logs, data correction forms, CRFs, inventory of study drug, regulatory documents (e.g., protocol and amendments, IRB/IEC correspondence and approvals, approved and signed informed consent forms, Investigator's Agreement, clinical supplies receipts, distribution and return records), and other sponsor correspondence pertaining to the study must be kept in appropriate study files at the study center (Trial Master File). Source documents include all recordings and observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. These records will be retained in a secure file for the period required by the institution or study center policy. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

12.5. Record Keeping

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system (Trial Master File) of all study-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. Essential documents include:

- Subject files containing completed CRFs, informed consent forms, and supporting copies of source documentation (if kept).
- Study files containing the protocol with all amendments, IB, copies of relevant essential documents required prior to commencing a clinical study, and all correspondence to and from the EC/IRB and the Sponsor.
- Records related to the study drug(s) including acknowledgment of receipt at study center, accountability records and final reconciliation and applicable correspondence.

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

All essential documentation will be retained by the institution until told otherwise by the sponsor.

No study document should be destroyed without prior written agreement between the sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, he/she must notify the sponsor in writing of the new responsible person and/or the new location.

All investigators and site personnel must ensure subject confidentiality as outlined in Section [15.2](#).

13. FINANCING AND INSURANCE

13.1. Finances

Prior to starting the study, the Principal Investigator and/or institution will sign a clinical study agreement with the sponsor or designee. This agreement will include the financial information agreed upon by the parties.

13.2. Reimbursement, Indemnity, and Insurance

The Sponsor provides insurance for study subjects to make available compensation in case of study-related injury.

Reimbursement, indemnity and insurance shall be addressed in a separate agreement on terms agreed upon by the parties.

14. PUBLICATION POLICY

A study center may not publish results of a study until after a coordinated multicenter publication has been submitted for publication or until one year after the study has ended, whichever occurs first. Therefore, the study center will have the opportunity to publish the results of the study, provided that Daiichi Sankyo has had the opportunity to review and comment on the study center's proposed publication prior to its being submitted for publication with the prior advice of Daiichi Sankyo Legal Affairs (intellectual property council) and with proper regard to the protection of subjects' identities.

15. ETHICS AND STUDY ADMINISTRATIVE INFORMATION

15.1. Compliance Statement, Ethics and Regulatory Compliance

This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the ICH consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), and applicable regulatory requirement(s) including the following:

- US Food and Drug Administration (FDA) GCP Regulations: Code of Federal Regulations (CFR) Title 21, parts 11, 50, 54, 56 and 312 as appropriate and/or;
- Other applicable local regulations.

15.2. Subject Confidentiality

The Investigators and the Sponsor will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP and local regulations.

The Investigator must ensure that the subject's anonymity is maintained. On the CRFs or other documents submitted to the Sponsor or the CRO, subjects should be identified by a unique SID as designated by the Sponsor. Documents that are not for submission to the Sponsor or the CRO (e.g., signed ICF) should be kept in strict confidence by the Investigator.

In compliance with ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/EC direct access to review the subject's original medical records for verification of study-related procedures and data. The Investigator is obligated to inform the subject that his/her study-related records will be reviewed by the above named representatives without violating the confidentiality of the subject.

15.3. Informed Consent

Before a subject's participation in the study, it is the Investigator's responsibility to obtain freely given consent, in writing, from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific procedures or any study drugs are administered. Subjects should be given the opportunity to ask questions and receive satisfactory answers to their inquiries, and should have adequate time to decide whether or not to participate in the study. The written ICF should be prepared in the local language(s) of the potential subject population.

In obtaining and documenting informed consent, the Investigator should comply with the applicable regulatory requirements, and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The consent form and any revision(s) should be approved by the EC or IRB prior to being provided to potential subjects.

The subject's written informed consent should be documented in the subject's medical records. The ICF should be signed and personally dated by the subject and by the person who conducted the informed consent discussion (not necessarily the Investigator). The original signed ICF should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject. The date and time (if applicable) that informed consent was given should be recorded on the CRF.

Suggested model text for the ICF for the study and any applicable subparts (genomic, PK, etc.) are provided in the Sponsor's ICF template for the Investigator to prepare the documents to be used at his or her study center. Updates to applicable forms will be communicated via letter from the Sponsor.

For studies in the US, an additional consent is required for the Health Insurance Portability and Accountability Act (HIPAA). Also, a separate special consent will be required for Pharmacogenomic testing for this protocol.

15.4. Regulatory Compliance

The study protocol, subject information and consent form, the Investigator Brochure, any subject written instructions to be given to the subject, available safety information, subject recruitment procedures (e.g., advertisements), information about payments and compensation available to the subjects, and documentation evidencing the Investigator's qualifications should be submitted to the EC or IRB for ethical review and approval according to local regulations, prior to the study start. The written approval should identify all documents reviewed by name and version.

Changes in the conduct of the study or planned analysis will be documented in a protocol amendment and/or the SAP.

The Investigator must submit and, where necessary, obtain approval from the EC or IRB for all subsequent protocol amendments and changes to the ICF. The Investigator should notify the EC or IRB of deviations from the protocol or SAEs occurring at the study center and other AE reports received from the Sponsor/CRO, in accordance with local procedures.

As required by local regulations, the Sponsor's local Regulatory Affairs group or representative to whom this responsibility has been delegated will ensure all legal aspects are covered, and approval from the appropriate regulatory bodies obtained, prior to study initiation, and that implementation of changes to the initial protocol and other relevant study documents happen only after approval by the relevant regulatory bodies.

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable Regulatory Authorities 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 drug, the Sponsor should be informed immediately.

In addition, the investigator will inform the Sponsor immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any suspected/actual serious GCP non-compliance that the investigator becomes aware of.

15.5. Protocol Deviations

The investigator should conduct the study in compliance with the protocol agreed to by Sponsor and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the IRBs/ECs.

A deviation to any protocol procedure or waiver to any stated criteria will not be allowed in this study except where necessary to eliminate immediate hazard(s) to the subject. Sponsor must be notified of all intended or unintended deviations to the protocol (e.g., inclusion/exclusion criteria, dosing, missed study visits) on an expedited basis.

The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

If a subject was ineligible or received the incorrect dose or study treatment, and had at least 1 administration of study drug, data should be collected for safety purposes.

If applicable, the Investigator should notify the IRB/IEC of deviations from the protocol in accordance with local procedures.

15.6. Supply of New Information Affecting the Conduct of the Study

When new information becomes available that may adversely affect the safety of subjects or the conduct of the study, the Sponsor will inform all Investigators involved in the clinical study, ECs/IRBs, and regulatory authorities of such information, and when needed, will amend the protocol and/or subject information.

The Investigator should immediately inform the subject whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue participation in the study. The communication should be documented on medical records, for example, and it should be confirmed whether the subject is willing to remain in the study.

If the subject information is revised, it must be re-approved by the IEC/IRB. The Investigator should obtain written informed consent to continue participation with the revised written information even if subjects were already informed of the relevant information. The Investigator or other responsible personnel who provided explanations and the subject should sign and date the revised ICF.

15.7. Protocol Amendments

Any amendments to the study protocol that seem to be appropriate as the study progresses will be communicated to the Investigator by Daiichi Sankyo or the CRO. Also, the Sponsor will ensure the timely submission of amendments to regulatory authorities.

A global protocol amendment will affect study conduct at all study centers in all regions of the world. Such amendments will be incorporated into a revised protocol document. Changes made by such amendments will be documented in a Summary of Changes document. These protocol amendments will undergo the same review and approval process as the original protocol.

A local protocol amendment will affect study conduct at a particular study center(s) and/or in a particular region/country. Sponsor approval of local amendments will be clearly documented.

A protocol amendment may be implemented after it has been approved by the IRB/EC and by regulatory authorities where appropriate, unless immediate implementation of the change is necessary for subject safety.

15.8. Study Termination

Circumstances under which the study may be stopped based upon independent Data and Safety Monitoring Board (DSMB) recommendation are specified in Section 15.9. In addition, the study may be terminated at any time at the sponsor's discretion.

15.9. Data and Safety Monitoring Board

Not applicable.

15.10. Address List

A list of key study personnel (including personnel at the sponsor, CRO, laboratories, and other vendors) and their contact information (address, telephone, fax, email) will be kept on file and updated in the Study Operations Manual.

16. REFERENCES

1. International Diabetes Federation. IDF Diabetes Atlas, sixth edition; 2013.
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3. Chu ZL, Carroll C, Alfonso J, et al. A role for intestinal endocrine cell-expressed G protein-coupled receptor 119 in glycemic control by enhancing glucagon-like peptide-1 and glucose-dependent insulinotropic Peptide release. *Endocrinology.* 2008;149(5):2038-47.
4. Chu ZL, Jones RM, He H, et al. A role for beta-cell-expressed G protein-coupled receptor 119 in glycemic control by enhancing glucose-dependent insulin release. *Endocrinology.* 2007; 148 (6):2601-9
5. Yoshida S, Ohishi T, Matsui T, et al. The role of small molecule GPR119 agonist, AS1535907, in glucose-stimulated insulin secretion and pancreatic β -cell function. *Diabetes Obes Metab.* 2011;13(1):34-41
6. American Diabetes Association. Classification and diagnosis of diabetes. Sec. 2. In *Standards of Medical Care in Diabetes 2015.* *Diabetes Care* 2015;38(Suppl. 1):S8–S16
7. Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *J Clin Endocrinol Metab.* 2013 May;98(5):1845-59.

17. APPENDICES

17.1. Cockcroft-Gault Equation

The estimated creatinine clearance rate (CrCl; mL/min) will be calculated using the Cockcroft-Gault equation based on weight kilograms (1 kilogram = 2.2 pounds):

Conventional units – serum creatinine in mg/dL:

Male:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in mg/dL)} \times 72}$$

$$\frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in mg/dL)} \times 72}$$

Female:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in mg/dL)} \times 72}$$

$$\frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in mg/dL)} \times 72} \times 0.85$$

International System of Units (SI) – serum creatinine in μmol/L:

Male:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in } \mu\text{mol/L)} \times 72 \times 0.0113}$$

$$\frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in } \mu\text{mol/L)} \times 72 \times 0.0113}$$

Female:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in } \mu\text{mol/L)} \times 72 \times 0.0113}$$

$$\frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in } \mu\text{mol/L)} \times 72 \times 0.0113} \times 0.85$$

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.

17.2. Schedule of Events

Table 17.1: Schedule of Events

	Screening*	Lead-in	Randomization	Treatment				End-of-treatment/ Early Termination	Follow-Up
				4	5	6	8		
Visit number	1	2	3					7	8
Week number	-4 to -3	-2	0	2	4	8		12 or E/T	14
Days		-14	1	14	28	56		84	98
Visit Window (days)		±3	±3	±3	±3	±3		±3	±3
Signed informed consent	X								
Inclusion/exclusion criteria	X	X	X						
Demographic information, medical/surgical history	X								
Height ^a Vital signs and weight	X	X	X	X	X	X		X	X
Full ^b physical examination assessment	X							X	
Targeted ^c physical examination assessment		X	X	X	X	X			X
Electrocardiogram(s) (12-lead)	X			X	X			X	
Pregnancy test (if WOCBP) ^d	X	X	X	X	X	X		X	X
TSH and serum FSH screening ^e	X								
HbA1c	X		X		X	X		X	
FPG	X		X	X	X	X		X	
Lipid panel	X		X	X	X			X	
C-peptide	X								
Safety laboratory (Chemistry, Hematology) ^f	X		X	X	X	X		X	X ^g
Urinalysis: dipstick and microscopy	X							X	X ^g
Pharmacokinetics sampling ^h			X	X	X	X		X	
MMTT			X	X	X			X	
Adverse events		X	X	X	X	X		X	X
Concomitant medications	X	X	X	X	X	X		X	
Dispense blood glucose meter and study diary		X							
Review glucose meter reading and study diary ⁱ			X	X	X	X		X	
Contact IXRS	X	X	X	X	X	X		X	
Study Drug dispensing		X	X		X	X		X	
Drug adherence check			X	X	X	X		X	

^a Height measured only at Screening Visit.

^b Includes head, neck, thyroid, eyes, ears, nose, throat, chest, lungs, heart, lymph nodes, abdomen, skin, extremities, musculoskeletal and neurological (see Section 9.12).

^c Includes lungs, heart, and as needed examination (see Section 9.12).

^d All WOCBP subjects must have a negative serum pregnancy test (βhCG) at the Screening Visit (Visit 1). Urine pregnancy tests will be conducted at all other clinic visits through the Follow-up clinic visit (Visits 2-8) for all WOCBP subjects. If a urine test result is positive, a serum pregnancy test will be performed to confirm the result. (see Section 4.3).

^e Screen serum FSH in postmenopausal women who are not surgically sterile (see Section 4.3). TSH = Thyroid-stimulating hormone; FSH = follicle stimulating hormone.

^f CBC and reticulocytes counts will be measured at each visit. (see Section 9.8.1).

^g Repeat any abnormal results from prior visit.

^h Visits 3, 4, and 6 - Trough levels (time 0) only. Visits 5 and 7, - 3h sampling during the MMTT (see Section 8.1).

ⁱ Subjects should record exact time of morning medication doses and SMBG in the study diary and bring study diary to randomization and all treatment visits (Visit 3 to Visit 7).

* Rescreening of subjects will not be permitted. If laboratory test is failed due to technological error, the test would be repeated.