CLINICAL STUDY PROTOCOL

COLESEVELAM ORAL SUSPENSION AS MONOTHERAPY OR ADD-ON TO METFORMIN THERAPY IN PEDIATRIC SUBJECTS WITH TYPE 2 DIABETES MELLITUS

WEL-A-U307

VERSION: 2.0, 30 AUG 2011

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INVESTIGATOR AGREEMENT

COLESEVELAM ORAL SUSPENSION AS MONOTHERAPY OR ADD-ON TO METFORMIN THERAPY IN PEDIATRIC SUBJECTS WITH TYPE 2 DIABETES MELLITUS

Sponsor Approval:

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

PPD	PPD
Print Name	**Signature**
Executive Director, Clinical Development	30 August 2011
Title	**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 DSPD. 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 Harmonization 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

EudraCT/IND Number:	IND 68,466
Protocol Number:	WEL-A-U307
Investigational Product:	Welchol® (colesevelam hydrochloride) for Oral Suspension
Active Ingredient(s)/INN:	Colesevelam hydrochloride
Study Title:	Colesevelam Oral Suspension as Monotherapy or Add-on to Metformin Therapy in Pediatric Subjects with Type 2 Diabetes Mellitus
Study Phase:	Phase 3b/4
Indication Under Investigation:	Pediatric type 2 diabetes mellitus
Study Objectives:	The primary objective of the study is to demonstrate the effects of colesevelam hydrochloride (HCl) oral suspension as monotherapy or as an add-on therapy to metformin on mean change in hemoglobin HbA1c from baseline over a 6-month double-blind treatment period in pediatric subjects with type 2 diabetes mellitus. The secondary objectives of the study are: • To demonstrate the safety and tolerability of colesevelam HCl oral suspension as an anti-diabetic treatment in pediatric subjects with type 2 diabetes mellitus; • To assess the effect of colesevelam HCl oral suspension on HbA1c over 12 months; • To assess the effect of colesevelam HCl oral suspension on fasting plasma glucose (FPG) over 12 months; • To assess glycemic response to colesevelam HCl oral suspension therapy over time. Response to therapy will be analyzed by the percentage of subjects with a decrease in HbA1c ≥0.7% and ≥0.5%, final HbA1c <7.0% and <6.5%, and/or a decrease in FPG ≥30 mg/dL; and • To assess the effects of colesevelam HCl oral suspension on changes in plasma lipids including total cholesterol (TC), low-density lipoprotein cholesterol

	(LDL-C), high-density lipoprotein cholesterol (HDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), triglycerides (TG), apolipoprotein A-1 (apo A-1), and apolipoprotein B (apo B). • To assess the proportion of subjects requiring rescue and the time from randomization to initiation of rescue medication.
Study Design:	This is a multi-center, randomized, double-blind, 2-group study in pediatric subjects with type 2 diabetes mellitus with suboptimal glycemic control with or without metformin. The study will consist of: • A screening visit, • A 2-week single-blind lead-in/stabilization period, • A 12-month double-blind treatment period, and • A follow-up visit approximately 2 weeks after the end of treatment. Subjects may either be on metformin monotherapy or be currently untreated with antidiabetic agents. "Untreated" includes subjects who have either • never received antidiabetic therapy (naïve) or • received antidiabetic medications for less than 14 days within 3 months prior to screening but no insulin therapy within 14 days of screening. The prior type 2 diabetes mellitus treatment status will be used as a stratification factor at randomization. All subjects will enter a 2-week, single-blind lead-in/stabilization period after being confirmed as eligible to participate in this study. Subjects on metformin monotherapy will remain on the same dose as at screening throughout the stabilization period. A blinded once-daily medication (low-dose colesevelam HCl) will be provided to all subjects. Approximately 220 subjects will be randomized in a 3:2 ratio of high-dose colesevelam HCl oral suspension (3.75 g) once daily to low-dose colesevelam HCl oral suspension (0.625 g) once daily for the treatment period. After randomization, subjects must continue on the same dose of metformin as during lead-in/stabilization, unless and until the subject meets the criteria for glycemic rescue.

	In the event that the subject's HbA1c level cannot be controlled below 8.5% after 3 months or below 7.5% (confirmed persistent hyperglycemia) after 6 months of study medication, as measured by the central laboratory, glycemic rescue must be started with metformin (by initiating or optimizing doses to a maximally tolerated dose up to 2 g/d), and if this is not adequate, with once-daily insulin such as insulin glargine. Those low-dose subjects who complete Month 6 and are switched to the high dose prior to the approval of protocol version 2.0 and its Informed Consent will continue on the high-dose to the end of the study, according to the original protocol. Glucometers will be provided for self-monitoring of blood glucose levels, which will be recorded during the lead-in period and throughout the two 6-month treatment periods.
Study Duration:	The study will consist of a screening visit, a 2-week, single-blind lead-in/stabilization period, a double-blind 12-month treatment period, and a follow-up visit 2 weeks after the end of treatment. The total duration of participation for an individual subject will be approximately 58 weeks.
Study Sites and Location:	Approximately 20 to 30 sites in the United States will participate.
Planned Sample Size:	Approximately 220 subjects will be randomized in this study: approximately 132 to the high-dose colesevelam HCl group and 88 to the low-dose colesevelam HCl group.
Subject Eligibility Criteria:	Individuals who are eligible for this study are males and females, 10 to 17 years of age at randomization, with a diagnosis of type 2 diabetes mellitus, as defined by the American Diabetes Association. At screening, subjects must have an HbA1c between 7.0% and 10.0%, inclusive, and a fasting C-peptide >0.6 ng/mL. Subjects must be on metformin monotherapy, or currently untreated with antidiabetic pharmacotherapy as defined above. Individuals are to be excluded from participation in the study if, at screening, they have an FPG >270 mg/dL, diagnosis of type 1 diabetes, or history of more than 1 episode of ketoacidosis after the initial diagnosis of type 2 diabetes mellitus. Subjects must not have a creatinine clearance <70 mL/min or an alanine transaminase or aspartate aminotransferase elevation

	>2.5 × the upper limit of normal at screening.
Dosage Form, Dose and Route of Administration:	During the 2-week, single-blind lead-in/stabilization period, all subjects will receive low-dose colesevelam HCl oral suspension 0.625 g to be mixed in 4 to 8 ounces of water, fruit juice or diet soft drink for oral administration once daily with a dinner meal. Colesevelam HCl oral suspension will be provided in identically appearing packets of 3.75 g (high dose, 6-tablet equivalent) and packets of 0.625 g (low dose, 1-tablet equivalent) to be mixed in 4 to 8 ounces of water, fruit juice or diet soft drink for oral administration once daily with a dinner meal.
Study Endpoints:	The primary efficacy endpoint is the change in HbA1c from baseline to Month 6 with last observation carried forward (LOCF). The secondary endpoints include the following: • The change in HbA1c from baseline at each scheduled visit up to Month 12; • The change in FPG from baseline to Month 6 and Month 12; • Percentage of subjects achieving a response to therapy at Month 6 and Month 12, defined as HbA1c <7.0% and 6.5%, reduction in HbA1c ≥0.7% and ≥0.5% from baseline, and/or reduction in FPG ≥30 mg/dL from baseline; and • The changes in plasma lipids (including TC, LDL-C, HDL-C, non-HDL-C, TG, apo A-1, and apo B) at each timepoint where measured. • Proportion of subjects requiring rescue and time from randomization to initiation of rescue medication. Safety variables for assessment include adverse events, vital signs, and chemistry and hematology laboratory parameters.
Statistical Analyses:	The primary efficacy analysis is to compare high-dose (3.75 g/day) to low-dose (0.625 g/day) colesevelam HCI oral suspension for change in HbA1c from baseline to Month 6 using the Intent-To-Treat (ITT) population with LOCF. For subjects who received rescue therapy, the last post-baseline HbA1c value observed prior to rescue will be

	carried forward. The treatment difference will be tested at a 2-sided significance level of 0.05, using an analysis of covariance (ANCOVA) model with treatment group and previous T2DM treatment stratum as fixed effects and baseline HbA1c as a covariate. P-value obtained from between-treatment comparison will be presented. The LS mean, standard error, and 95% CI for each treatment as well as for the difference between high- and low-dose colesevelam HCl groups will be estimated. The analyses of the continuous secondary efficacy variables will be carried out using the same method as for the primary efficacy variable, unless otherwise stated. The between-treatment comparison for change in TG will be carried out using a non-parametric ANCOVA. The glycemic control rates will be compared between treatments using Fisher's exact test. Safety assessments include evaluations of adverse events, clinical laboratory measurements (hematology, blood chemistry, and urinalysis), vital signs, physical examinations, prior and concomitant medications, and vitamin D level.

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ANCOVA	Analysis of Covariance
apo A-1	Apolipoprotein A-1
apo B	Apolipoprotein B
BMI	Body mass index
CI	Confidence interval
CFR	Code of Federal Regulations
CRF	Case Report Form
CRL	Central Reference Laboratory
CRO	Contract Research Organization
DSPD	Daiichi Sankyo Pharma Development
EDC	Electronic Data Capture
FDA	Food and Drug Administration
FPG	Fasting plasma glucose
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HCl	Hydrochloride
HDL-C	High-density lipoprotein cholesterol
HMG-CoA	Hydroxyl-methyl-coenzyme A
IAF	Informed Assent Form
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
ITT	Intent-to-treat
IVRS	Interactive voice response system
LDL-C	Low-density lipoprotein cholesterol
LOCF	Last observation carried forward
LS	Least-squares
non-HDL-C	Non-high-density lipoprotein cholesterol
OAD	Oral anti-diabetic
SAE	Serious Adverse Event
SAVER	Serious Adverse Event Report
SOP	Standard operating procedure
TC	Total cholesterol
TG	Triglycerides

1. INTRODUCTION AND BACKGROUND INFORMATION

1.1. Data Summary

Supporting details, data, and study references for the following summary information can be found in the Prescribing Information for Welchol® (colesevelam HCl).[1]

The name of the investigational product is colesevelam hydrochloride (HCl) oral suspension (Welchol for Oral Suspension).

Colesevelam is a bile acid sequestrant initially marketed as an adjunct to diet and exercise to reduce elevated low-density lipoprotein cholesterol (LDL-C) in patients with primary hyperlipidemia as monotherapy or in combination with a hydroxyl-methyl-coenzyme A (HMG-CoA) reductase inhibitor. The indication for pediatric use in lipid reduction has been approved.

Welchol has recently been approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. This indication is based on results of 3 separate double-blind, placebo-controlled pivotal clinical studies in which colesevelam HCl was used in combination with metformin, sulfonylureas, or insulin for the treatment of type 2 diabetes mellitus. These studies enrolled a total of 1018 subjects with baseline hemoglobin HbA1c levels 7.5% to 9.5%. Subjects were enrolled and maintained on their pre-existing, stable, background, anti-diabetic regimen. Colesevelam HCl and placebo were administered either as 3 tablets twice daily with lunch and dinner or as 6 tablets with dinner alone. In all 3 pivotal add-on therapy trials, treatment with Welchol resulted in a statistically significant reduction in HbA1c of 0.5% compared to placebo.

The Food and Drug Administration (FDA) has also approved Welchol for Oral Suspension, providing an alternative to the current tablet formulation.

This present study is being conducted to evaluate the effect of colesevelam HCl oral suspension as monotherapy or as add-on therapy to metformin on the change in HbA1c in pediatric subjects with type 2 diabetes mellitus.

1.1.1. Intended Use Under Investigation

This study will provide support for the use of colesevelam HCl oral suspension as monotherapy or as add-on therapy to metformin to improve glycemic control in pediatric subjects with type 2 diabetes mellitus.

1.1.2. Nonclinical Studies

Nonclinical studies are summarized in the product label.[1]

1.1.3. Clinical Experience

Clinical experience is summarized in the product label.[1]

1.2. Study Rationale

The prevalence of type 2 diabetes mellitus in pediatric subjects has been increasing in recent years, due in part to a rapid rise in childhood obesity. In the United States, Welchol has been approved as a treatment for LDL-C lowering in adults and children with primary hyperlipidemia and for glucose lowering in adults with type 2 diabetes mellitus. The large tablet size and the high number of tablets per day (6) can present challenges to medication compliance in some patients treated with Welchol. Colesevelam HCl oral suspension was developed as an alternative formulation that is conveniently mixed with water, fruit juice or diet soft drink and ingested. This oral suspension formulation can be more acceptable to pediatric subjects who might have difficulty swallowing several large-sized tablets. Thus, the current study evaluates the clinical efficacy and safety of colesevelam HCl oral suspension as an anti-diabetic agent in pediatric subjects with type 2 diabetes mellitus.

1.3. Risks and Benefits for Study Subjects

In this study, subjects will receive colesevelam HCl oral suspension, an alternative formulation of Welchol, which has been shown to benefit adults with type 2 diabetes through improvements in glycemic control and reduction of LDL-C.

Indirect benefits for all subjects in this study include clinically relevant diabetes-specific baseline evaluations with the opportunity to discuss and review results with study physicians. All study participants will be provided with home glucose monitoring supplies and appropriate instruction. In addition, the cornerstones of diabetes therapy, diet and exercise, will be reviewed and reinforced with frequent study visits.

The risk of prolonged hyperglycemia may be higher for subjects randomized to low-dose colesevelam HCl oral suspension, a presumed sub-therapeutic dose. To minimize and mitigate this risk, all subjects are monitored for elevated blood glucose at home and at each study visit. Glycemic rescue medications will be provided to subjects if they meet elevated HbA1c levels after 3 months on study therapy. Stricter glycemic rescue criteria will be used after 6 months on study therapy to minimize prolonged elevations of HbA1c and provide subjects with adequate medical care.

Those subjects randomized to the low-dose group who complete Month 6 prior to the approval of this amended protocol and its Informed Consent will complete the study on the high-dose to which they were switched at Month 6 according to the original protocol.

Colesevelam HCl can increase triglyceride (TG) levels, particularly when used with sulfonylureas. Marked hypertriglyceridemia can cause acute pancreatitis. The effect of hypertriglyceridemia on the risk of coronary artery disease is uncertain. Lipid levels, including TG, will be measured during the study for all subjects.

Bile acid sequestrants, including colesevelam HCl, may also decrease absorption of fat-soluble vitamins; therefore, caution should be used in subjects susceptible to fat-soluble vitamin deficiencies. Colesevelam HCl reduces the absorption of some drugs. Drugs that have a known interaction with colesevelam HCl should be administered at least 4 hours prior to colesevelam HCl. If a drug or drug class has not been tested for an

interaction with colesevelam HCl, particularly those with a narrow therapeutic index, the drug should be given 4 hours prior to colesevelam HCl.

Colesevelam HCl is not absorbed systemically from the gastrointestinal tract, so colesevelam HCl is not expected to be excreted in human milk. Nevertheless, the safety of colesevelam HCl in nursing mothers and children has not yet been established. Precautions are implemented to ensure that women of childbearing potential are not pregnant when they enroll in the study and do not become pregnant during or immediately after the completion of the study. Pregnant or nursing women are not to be enrolled. If a subject becomes pregnant despite appropriate precautions, she is to be discontinued from the study. Follow-up will be required as described in this protocol.

This study is designed to yield scientifically valid and clinically useful information. The risks associated with the deferral of standard therapy are reasonable and appropriately proportional to the magnitude of potential benefit from study participation.

1.4. Population, Route, Dosage, Dosage Regimen, Treatment Period

Approximately 220 pediatric subjects, 10 to 17 years of age at randomization, with a diagnosis of type 2 diabetes mellitus will be randomized.

During the 2-week, single-blind lead-in/stabilization period, all subjects will receive low-dose colesevelam HCl oral suspension 0.625 g to be mixed in 4 to 8 ounces of water, fruit juice or diet soft drink for oral administration once daily with a dinner meal.

During the 12-month blinded treatment period, colesevelam HCl oral suspension will be provided in identically appearing packets of 3.75 g (high dose, 6-tablet equivalent) and packets of 0.625 g (low dose, 1-tablet equivalent) to be mixed in 4 to 8 ounces of water, fruit juice or diet soft drink for oral administration once daily with a dinner meal.

1.5. 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 International Conference on Harmonization (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), and applicable regulatory requirement(s) including FDA GCP Regulations: Code of Federal Regulations (CFR) Title 21, Parts 11, 50, 54, 56 and 312 as appropriate.

1.5.1. 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 Case Report Forms (CRFs) or other documents submitted to Daiichi Sankyo Pharma Development (DSPD) or its designee, subjects should be identified by a unique subject identifier as designated by the Sponsor. Documents that are not for submission to DSPD or its designee (eg, signed Informed Consent Forms [ICFs]) should be kept in strict confidence by the Investigator.

In compliance with Federal regulations/ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the Institutional Review Board (IRB) 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.

1.5.2. Informed Consent and Assent Procedure

Before a minor subject's participation in the study, it is the Investigator's responsibility to obtain freely given consent, in writing, from the subject's parent or legal guardian (consent) and from the subject (assent) after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any study drugs are administered. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study (proof of status must be provided). The written Informed Assent Form (IAF) and ICF should be prepared in the local language(s) of the potential subject population. The forms include consents for the Health Insurance Portability and Accountability Act.

In obtaining and documenting informed consent and assent, 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 ICF, IAF, and any revision(s) should be approved by the IRB prior to being provided to potential subjects.

The legally acceptable representative's informed consent and the subject's written assent should be obtained prior to the subject's participation in the study and should be documented in the subject's medical records, as required by 21 CFR Part 312.62. The ICF should be signed and personally dated by the subject's legally acceptable representative and by the person who conducted the informed consent discussion (not necessarily the Investigator), and the IAF should be personally signed and dated by the subject. The original signed ICF and IAF should be retained in accordance with institutional policy, and a copy of the signed ICF and IAF should be provided to the subject and legal representative. The date and time (if applicable) that informed consent was given should be recorded on the CRF.

If the subject or legally acceptable representative cannot read, then according to ICH GCP Guideline, Section 4.8.9, an impartial witness should be present during the entire informed consent and/or assent discussion. This witness should sign and date the ICF and/or IAF after the subject or the legally acceptable representative has orally consented to the subject's participation and, if possible, signed the ICF. By signing the ICF, the witness attests that the information in the ICF and any other written information was adequately explained to and apparently understood by the subject or the legally acceptable representative and that informed consent was freely given by the subject or the legally acceptable representative.

Suggested text for the ICF and IAF will be provided for the Investigator to prepare site-specific documents. Updates to applicable forms will be communicated via letter from the Clinical Study Manager.

1.5.3. Regulatory Compliance

The study protocol, subject information and ICF/IAF, the Investigator brochure, any subject diary card or written instructions to be given to the subject, available safety information, subject recruitment procedures (eg, advertisements), information about payments and compensation available to the subjects, and documentation evidencing the Investigator's qualifications should be submitted to the 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 Statistical Analysis Plan.

The Investigator must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent and assent documents or changes in the investigational site, facilities, personnel, promotional information, or subject materials. The Investigator should notify the IRB of deviations from the protocol or serious adverse events (SAEs) occurring at the site and other adverse event reports received from DSPD or its designee, in accordance with local procedures.

As required by local regulations, the Sponsor's local Regulatory Affairs group will insure all legal aspects are covered, and approval of 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 the appropriate notification of or approval by the relevant regulatory bodies.

2. STUDY OBJECTIVES AND HYPOTHESES

2.1. Study Objectives

2.1.1. Primary Objectives

The primary objective of the study is to demonstrate the effects of colesevelam HCl oral suspension as monotherapy or as an add-on therapy to metformin on change in HbA1c from baseline over the first 6-month treatment period in pediatric subjects with type 2 diabetes mellitus.

2.1.2. Secondary Objectives

The secondary objectives of the study are:

- To demonstrate the safety and tolerability of colesevelam HCl oral suspension as an anti-diabetic treatment in pediatric subjects with type 2 diabetes mellitus;
- To assess the effect of colesevelam HCl oral suspension on HbA1c over 12 months in pediatric subjects with type 2 diabetes mellitus;
- To assess the effect of colesevelam HCl oral suspension on fasting plasma glucose (FPG) over 12 months;
- To assess glycemic response to colesevelam HCl oral suspension therapy over time. Response will be analyzed by the percentage of subjects with a decrease in HbA1c $\geq$0.7% or $\geq$0.5%, final HbA1c <7.0% and <6.5%, and/or a decrease in FPG $\geq$30 mg/dL; and
- To assess the effects of colesevelam HCl oral suspension on changes in plasma lipids including total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), TG, apolipoprotein A-1 (apo A-1), and apolipoprotein B (apo B).
- To assess the proportion of subjects requiring rescue and the time from randomization to initiation of rescue medication.

2.2. Study Hypothesis

Colesevelam HCl oral suspension for pediatric subjects with type 2 diabetes mellitus is safe, well tolerated, and demonstrates glycemic efficacy (as evidenced by a statistically significant change in HbA1c from baseline at 6 months).

3. STUDY DESIGN

3.1. Overall Plan

3.1.1. Study Type

This is a multi-center, randomized, double-blind, 2-group study in pediatric subjects with type 2 diabetes mellitus with suboptimal glycemic control with or without metformin. The study will consist of a screening visit, a 2-week single-blind lead-in/stabilization period, a 12-month double-blind treatment period, and a follow-up visit approximately 2 weeks after the end of treatment.

Subjects may either be on metformin monotherapy or currently untreated with antidiabetic agents. "Untreated" is defined as either never having received antidiabetic therapy or received antidiabetic medications for less than 14 days within 3 months prior to screening but no insulin therapy within 14 days of screening

All subjects will enter a 2-week, single-blind lead-in/stabilization period after being confirmed as eligible to participate in this study. A blinded once-daily medication (low-dose colesevelam HCl) will be provided to all subjects.

For the 12-month treatment period, approximately 220 subjects will be randomized in a 3:2 ratio to high-dose colesevelam HCl oral suspension (3.75 g) once daily or to low-dose colesevelam HCl oral suspension (0.625 g) once daily with a dinner meal.

Subjects on metformin monotherapy will remain on the same dose as at the time of screening, unless and until the subject meets the criteria for glycemic rescue. The investigator will be blind to HbA1c values through the study. Laboratory reports will alert the investigator to abnormal values. In the event that a subject's HbA1c level cannot be controlled below 8.5% after 3 months or below 7.5% after 6 months (confirmed persistent hyperglycemia) of study medication, as measured by the central laboratory, (see Section 3.1.6), open-label glycemic rescue with metformin must be initiated or optimized, and if this is not adequate, with a once-daily insulin preparation such as insulin glargine.

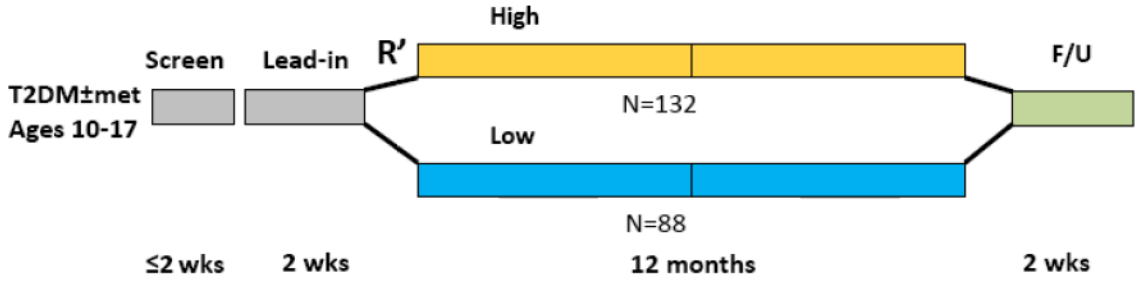
Those low-dose subjects who complete Month 6 and are switched to the high dose prior to the approval of protocol version 2.0 and its Informed Consent will continue on the high-dose to the end of the study, according to the original protocol.

Glucometers will be provided for self-monitoring of blood glucose levels, which will be recorded during the lead-in period and throughout the two 6-month treatment periods.

3.1.2. Treatment Groups

The study design is illustrated in Figure 3.1.

Figure 3.1: Study Schematic



F/U = follow-up; met = metformin; R' = randomization; T2DM = type 2 diabetes mellitus.

3.1.3. Study Endpoints

The primary efficacy endpoint is the change in HbA1c from baseline to Month 6 with last observation carried forward (LOCF).

The secondary endpoints include the following:

- The change in HbA1c from baseline to Month 12 at each scheduled visit where measured;
- The change in FPG from baseline to Month 12 at each scheduled visit where measured;
- Percentage of subjects achieving a response to therapy at Month 6 and Month 12, defined as HbA1c <7.0% or <6.5%, reduction in HbA1c ≥0.7% or ≥0.5% from baseline, and/or reduction in FPG ≥30 mg/dL from baseline;
- The change and percent change in plasma lipids at each scheduled visit where measured, specifically TC, LDL-C, HDL-C, non-HDL-C, TG, apo A-1, and apo B.; and
- Proportion of subjects requiring rescue and time from randomization to initiation of rescue medication

Safety variables for assessment include adverse events, vital signs, and chemistry and hematology laboratory parameters.

3.1.4. Duration of the Study

It is expected that the first subject will be enrolled into the study in November 2010 and that the last subject will complete follow-up before May 2015.

3.1.5. Duration of Subject Participation

The total duration of participation for an individual subject will be approximately 58 weeks.

3.1.6. Glycemic Rescue

In the event that a subject's HbA1c level cannot be controlled below 8.5% after 3 months or below 7.5% (confirmed persistent hyperglycemia) after 6 months of study medication treatment, as measured by the central laboratory, open-label glycemic rescue must be initiated.

Glycemic Rescue first with metformin: When glycemic rescue is needed, all subjects who are not on the maximally tolerated dose of metformin must first have their metformin monotherapy up-titrated to 2 g/d or the maximally tolerated dose, including initiation and dose titration to the maximally tolerated dose up to 2 g/d for those subjects not on metformin therapy at the time of screening.

Glycemic Rescue with insulin: If a subject has been on 2 g or the maximally tolerated doses of metformin monotherapy and requires rescue, a once-daily insulin preparation such as insulin glargine (Lantus®) will be added. Subjects and clinicians will remain blinded to the study treatment assignment, but will be unblinded to HbA1c levels. The recommended initial insulin glargine treatment is 0.2 U/kg to 0.4 U/kg each evening, which can be increased to 1.0 U/kg/d (maximum 100 U).

Subjects may require temporary use of acute insulin (non-basal) due to hospitalization, intercurrent illness, or conditions leading to metabolic decompensation. In these circumstances, any type or dose of insulin can be used at the discretion of the treatment team. However, inability to discontinue acute insulin within 8 weeks without decompensation (ketonuria and symptomatic hyperglycemia) is to be considered as primary treatment failure, and the subject will be discontinued from the study.

3.2. Selection of Doses

3.2.1. Experimental Treatments

This study will evaluate the clinical efficacy and safety of colesevelam HCl oral suspension 3.75 g (high dose, 6-tablet equivalent) once daily with a dinner meal, as an anti-diabetic agent in pediatric subjects with type 2 diabetes mellitus. This is the currently approved dose in adults.

3.2.2. Control Treatments

A placebo oral suspension (powder) product with matching characteristics to the active colesevelam HCl oral suspension product (3.75 g) is not available. Therefore, the low-dose colesevelam HCl oral suspension (0.625 g) is used instead of a placebo as the reference comparison treatment for this study.

4. STUDY POPULATION

Approximately 220 pediatric subjects, 10 to 17 years of age at randomization, with a diagnosis of type 2 diabetes mellitus will be randomized.

4.1. Enrollment

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

Investigators will be expected to maintain an Enrollment Log of all subjects enrolled in the study indicating their assigned study number.

Investigators will maintain a confidential subject identification code list. This confidential list of names of all subjects allocated to study numbers on enrolling in the study allows the Investigator to reveal the identity of any subject when necessary.

A subject is considered to be participating in the study upon the Investigator's (or Investigator's designee) obtaining written informed consent from the subject's legally acceptable representative and assent from the subject. Before the subject is screened to be in the study, the IAF and the ICF provided by the site must be personally signed and dated by the subject and the subject's legally acceptable representative and by the person who conducted the informed consent discussions (not necessarily the Investigator). For more information on informed consent and assent, refer to Section 1.5.2.

4.1.1. Inclusion Criteria

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

1. Diagnosis of type 2 diabetes mellitus, as defined by the American Diabetes Association[2];
2. Understand study procedures and agree to participate by giving written assent and obtaining written consent from a parent or legal guardian at screening (Week ≤ -4);
3. Males and females aged 10 to 17 years, inclusive, at randomization (randomization must occur before 18th birthday);
4. HbA1c at screening between 7.0% and 10.0%, inclusive;
5. Fasting C-peptide >0.6 ng/mL; and
6. Anti-diabetic treatment at screening:
    - On metformin monotherapy: Metformin monotherapy has been initiated prior to screening; or
    - On no antidiabetic treatment (currently untreated), defined as:
        - Naïve, never received antidiabetic therapy or

- Untreated, received anti-diabetic medications for less than 14 days within 3 months prior to screening but no insulin therapy within 14 days of screening.

4.1.2. Exclusion Criteria

Subjects who meet any of the following criteria at screening are not eligible to enter the study:

1. Fasting plasma glucose >270 mg/dL;
2. Diagnosis of type 1 diabetes;
3. History of more than one episode of ketoacidosis after the initial diagnosis of type 2 diabetes mellitus;
4. Positive autoimmune markers including anti-islet cell antigen 512 (anti-ICA 512) or anti-glutamic acid decarboxylase (anti-GAD);
5. Creatinine clearance <70 mL/min;
6. Alanine transaminase or aspartate aminotransferase elevation >2.5 × the upper limit of normal;
7. Use of inhaled glucocorticoids at dose >1 mg of daily fluticasone equivalent or any oral glucocorticoids within the last 60 days or >20 days during the past year;
8. Use of the following medication:
   - Insulin for ≥14 days in the preceding 3 months or insulin within 14 days of screening;
   - Medication(s) (other than metformin) known to affect insulin sensitivity or secretion within the last 30 days (oral contraceptive pill excepted);
   - Medications(s) known to cause weight gain or taken for weight loss within the last 30 days;
   - Growth hormones/somatotropin; or
   - Anabolic steroids within the last 60 days;
9. Participation in a formal weight-loss program (current or planned);
10. Participation in another interventional research study protocol in the past 60 days;
11. Abnormal reticulocyte count or HbA1c chromatogram indicating abnormal hemoglobin variants other than heterozygosity for S and C;
12. Genetic syndrome or disorder known to affect glucose;
13. Female subjects who are lactating, pregnant, or plan to become pregnant within 1 year of screening;
14. Female subjects who are sexually active and unwilling to use appropriate contraception for the duration of the study. Study-acceptable methods of birth control are at least single-barrier methods, which include any of the following:

systemic hormonal regimens, diaphragm, condom, copper intrauterine device, sponge, or spermicide;

15. History of bowel obstruction;
16. Other significant organ system illness or condition (including psychiatric or developmental disorder) that, in the opinion of the Investigator, would prevent full participation;
17. Systolic blood pressure ≥150 mmHg or diastolic blood pressure ≥95 mmHg, despite appropriate medical therapy;
18. Triglycerides >500 mg/dL; or
19. Hematocrit <30% or hemoglobin <10 gm/dL, despite appropriate medical therapy.

4.2. Removal of Subjects From Therapy

4.2.1. Reasons for Withdrawal/Early Discontinuation

Data from all randomized subjects to the study are important to the objectives of this clinical investigation. Every study subject is encouraged to adhere to protocol instructions and visit schedules. However, the subject is free to withdraw from the study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The Investigator is also free to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants it. It is also possible for the Sponsor or the regulatory authorities to request termination of the study if there are concerns about conduct or safety.

For any of the following reasons, study medication and study participation should be discontinued for a subject:

- Persistent Hemoglobin A1c >11.0%;
- Inability to discontinue acute insulin therapy within 8 weeks without decompensation;
- Occurrence of a medical condition or circumstance that exposes the subject to substantial risk;
- Any SAE, clinically significant adverse event, or severe laboratory abnormality which in the opinion of the Investigator indicates that continued participation in the study is not in the best interest of the subject; or
- Pregnancy.

If a subject withdraws from the study, the Investigator will 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, the Investigator will follow the subject until the adverse event has resolved or stabilized.

All subjects who are withdrawn from the study should complete protocol-specified withdrawal procedures (Section 4.2.2).

4.2.2. Withdrawal Procedures for Early Termination

Subjects who discontinue from the study prior to Visit 8 (Month 12) should have all possible End of Treatment visit procedures performed (See Section 6.5).

All subjects, if possible, should be scheduled to return for a follow-up visit 2 weeks after stopping treatment with study medication (See Section 6.6 for a description of procedures performed at the follow-up visit).

4.2.3. Subject Replacement

Subjects withdrawn from the study will not be replaced.

4.2.4. Subject Re-screening Procedures

Subjects will not be re-screened for this study, unless a laboratory error is suspected.

5. TREATMENTS ADMINISTERED

5.1. Investigational Products

The Investigator must ensure that the investigational product will be used only in accordance with the protocol.

According to ICH GCP Guideline, Section 1.33, an investigational product is a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study. This includes products with marketing authorizations when used or assembled (formulated or packaged) in a way different from the approved form or when used for an unapproved indication, or when used to gain further information about an approved use.

The investigational product that will be used for this study is colesevelam HCl oral suspension. Colesevelam HCl oral suspension is a citrus-flavored, white to pale yellow powder containing yellow granules packaged in single-dose packets of either 0.625 g or 3.75 g colesevelam HCl. In addition, each packet contains the following inactive ingredients: lemon flavor, orange flavor, propylene glycol alginate, simethicone, aspartame, citric acid, medium chain triglycerides, and magnesium trisilicate.

5.1.1. Method of Assigning Subjects to Treatments and Blinding

5.1.1.1. Identification Numbers

At screening, each subject will be assigned a unique identification number by the site (via the interactive voice response system [IVRS]), in sequential order according to the following formula: subject identification number will consist of 8 digits; the first 4 digits will reflect the site number assigned to the investigator, and the last 4 digits will reflect the subject number. The subject number will be used to identify the subject throughout the study and will be entered on all documentation.

The unique subject identification number will be entered into the IVRS in order to obtain the kit number to dispense at the enrollment, randomization, and all other dispensing visits.

5.1.1.2. Drug Randomization

Approximately 220 subjects will be randomly assigned in a 3:2 ratio to receive either high-dose colesevelam HCl oral suspension 3.75 g to be taken once daily with a dinner meal or low-dose colesevelam HCl oral suspension 0.625 g to be taken once daily with a dinner meal.

Randomization will be stratified based on prior type 2 diabetes mellitus treatment status (naïve or metformin monotherapy).

Those low-dose subjects who complete Month 6 and are switched to the high dose prior to the approval of protocol version 2.0 and its Informed Consent will continue on the high-dose to the end of the study, according to the original protocol.

5.1.1.3. Blinding

Both high-dose and low-dose colesevelam HCl oral suspension will be provided in identically appearing packets.

The study blind may be broken for individual subjects in the event of a SAE or other safety concern when knowledge of the study medication may provide important clinical information. Emergency unblinding will take place using the IVRS. In case of an emergency, the Investigator must make every effort to contact and consult with the Medical Monitor or DSPD prior to breaking the blind. If the blind is broken without consulting the Medical Monitor, a full explanation for this event must be provided within 24 hours. Contact information is listed in Section 15.2.

During the single-blind placebo lead-in period, only the study subject will be blinded to the treatment assignment. During the 12-month treatment period, DSPD, the Contract Research Organization (CRO), the Investigator, and the study subject will be blinded to the treatment assignment. The study blind will be broken at the end of the study once the study database has been locked.

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.

5.1.2. Method of Assessing Treatment Compliance

Study medication (high-dose and low-dose colesevelam HCl oral suspension) will be dispensed in amounts exceeding the minimum amount required for the period of time until the next clinic visit. Subjects will be instructed to return all unused study medication and used empty packets at the next clinic visit. Compliance to the study medication will be evaluated by the number of study medication packets used.

During the active treatment period, if compliance is not between 80% and 120%, inclusive, the subject will be counseled about the importance of adherence to the mandated regimen.

5.1.3. Labeling and Packaging

Study medication will be packaged in boxes for distribution labeled with the following information, at a minimum: study number, subject number, kit number, contents and quantity, directions, storage statement, and Sponsor information along with CAUTION and WARNING statements. The packet labels will not have subject number, kit number or quantity information, but will have all other label elements.

5.1.4. Preparation

To prepare colesevelam HCl oral suspension, empty the entire contents of 1 packet into a glass or cup. Add ½ to 1 cup (4 to 8 ounces) of water, fruit juice or diet soft drink. Stir well and drink (have the subject drink). Colesevelam HCl oral suspension should not be taken in its dry form.

In this study, colesevelam HCl oral suspension should be taken with a dinner meal.

5.1.5. Storage

Drug supplies must be stored at 25°C (77°F) and protected from moisture; excursions are permitted to 15°–30°C (59°–86°F).

Drug supplies must be stored in a secure, limited access storage area under the recommended storage conditions. The key to the storage area is to be kept by the Investigator or another person responsible for the medication. The storage area will be accessible only to those persons authorized by the Investigator to dispense investigational product. The Investigator will be responsible for the dispensing of medication according to the dosage scheme.

5.1.6. 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 drug expiration date, and sign the Receipt of Shipment Form provided. The Receipt of Shipment Form should be faxed as instructed on the form. The original will be retained at the site. In addition, the Investigator or designee shall contact DSPD as soon as possible if there is a problem with the shipment.

A Drug Accountability Record will be provided for the investigational product. The record must be kept current and should contain the dates and quantities of drug received, subject's identification number and/or initials or supply number as applicable for whom the investigational product was dispensed, the date and quantity of investigational product dispensed and remaining, if from individual subject drug units, as well as the initials of the dispenser.

At the end of the study, or as directed, all investigational products, including unused, partially used, or empty containers, will be returned to a designee as instructed by DSPD. Investigational product will be returned only after the study monitor has completed a final inventory to verify the quantity to be returned. The return of investigational product must be documented and the documentation included in the shipment. At the end of the study, a final investigational product reconciliation statement must be completed by the

Investigator or designee and provided to the Sponsor. Unused drug supplies may be destroyed by the Investigator when approved in writing by DSPD and DSPD has received copies of the site's drug handling and disposition standard operating procedures (SOPs).

All investigational product inventory forms must be made available for inspection by a Sponsor-authorized representative or designee and regulatory agency inspectors. The Investigator is responsible for the accountability of all used and unused study supplies at the site.

5.1.7. Retention Samples

Not applicable.

5.2. Concomitant Medications

Subjects must not have taken any pharmacologic therapy for diabetes within 3 months of the screening visit, with the exception of metformin, which may have been initiated as monotherapy prior to screening. Administration of all concomitant medications, including the name of each medication, the dosage, and date and time of administration is to be documented on the Concomitant Medication page of the CRF. Permitted concomitant medications should remain at a stable dose throughout the study.

If medications are issued or altered due to an adverse event, the change in therapy or dosage must be recorded on the CRF. If a change in dose is medically indicated, the change must be recorded on the CRF.

In the event that a subject's HbA1c level cannot be controlled below 8.5% after 3 months or below 7.5% after 6 months of study medication treatment, open-label glycemic rescue must be initiated. See Section 3.1.6.

Subjects may require temporary use of acute insulin (non-basal) due to hospitalization, intercurrent illness, or conditions leading to metabolic decompensation. In these circumstances, any type or dose of insulin can be used at the discretion of the treatment team. However, inability to discontinue acute insulin within 8 weeks without decompensation (ketonuria and symptomatic hyperglycemia) is to be considered as primary treatment failure, and the subject will be discontinued from the study.

5.3. Restricted Medications

The use of any other investigational drug is prohibited. The following medications are specially excluded from this study:

- Inhaled glucocorticoids at dose >1 mg of daily fluticasone equivalent or any oral glucocorticoids within 60 days;
- Medication(s) known to affect insulin sensitivity or secretion (oral contraceptive pill excepted);
- Medications(s) known to cause weight gain or taken for weight loss; and
- Anabolic steroids.

6. STUDY PROCEDURES

A study visit schedule in tabular format is provided in Table 17.2.

6.1. Screening (Visit 1)

The subject should arrive in a **fasted state** for this visit. The following activities and/or assessments will be performed at/during screening (Visit 1, ≤1 month prior to baseline):

- A parent or legal guardian must sign an IRB-approved ICF. The subject must assent to the study as per the IRB regulations. The original signed ICF and IAF will be kept on file in the Investigator's office and a copy will be given to the subject.
- Assess subject eligibility will be assessed using the study's inclusion/exclusion criteria.
- Record demographic data (including age, sex, and race) and other baseline characteristics.
- Record medical and surgical history.
- Record prior and concomitant medications (including antidiabetic, antihypertensive, and renal medications taken over the past 3 months).
- Record vital signs, height, and weight.
- Collect fasted blood samples for evaluation of efficacy parameters, including FPG, HbA1c, TC, HDL-C, LDL-C, non-HDL-C, TG, apo A-1, and apo B.
- Collect fasted blood and urine samples for evaluation of standard laboratory safety tests (chemistry, hematology, and urinalysis). Clinical safety and diagnostic assessments will include vitamin D, C-peptide, Anti-GAD and Anti-ICA512.
- Perform a urine pregnancy test on all female subjects (serum test also done).
- Perform a physical examination.
- Assess development with Tanner Staging.
- Contact IVRS/IWRS to register the subject.
- Provide counseling on diet and exercise.

6.2. Lead-in/Stabilization Period (Week -2; Visit 2)

There is no fasting requirement for this visit. All subjects will complete a full 2-week, single-blind lead-in period after being confirmed as eligible to participate in this study. All subjects will receive single-blind low-dose colesevelam HCl oral suspension to be taken once daily with a dinner meal. Glucometers will be provided for daily self-monitoring of blood glucose levels, which will be recorded during this period.

The following activities and/or assessments will be performed at the lead-in visit (Visit 2, 2 weeks prior to baseline):

- Assess subject eligibility using the study's inclusion/exclusion criteria.
- Record vital signs, height, and weight.
- Perform a urine pregnancy test on all female subjects and confirm negative.
- Determine and record adverse events and prior and concomitant medications.
- Perform a physical examination.
- If the Screening Vitamin D assessment (25-OH D) is low (<30 ng/ml [75 nmol/L]), cholecalciferol (D3) supplementation is recommended and should be continued through the study.
- Update IVRS/IWRS information and obtain study medication kit number.
- Dispense study medication kit and instruct subject on proper dosing.
- Dispense glucometers and related supplies and instruct subject on use.
- Provide counseling on diet and exercise.

6.3. Treatment Period

Sites will maintain frequent communication with subjects between visits for motivation and information about the study. Visit dates are calculated from Randomization.

6.3.1. Randomization (Day 1; Visit 3)

The subject should arrive in a **fasted state** for this visit. All subjects should have completed a full two week lead-in prior to randomization. If from that lead-in a subject reports **≥ 2 home glucometer readings** of fasting blood glucose (FBG) >240 mg/dL (or 1 value >240 mg/dL and worsening symptoms of hyperglycemia) a clinic visit should be scheduled for a follow up laboratory evaluation of fasting glucose. If confirmed, **discontinue** the subject; do not randomize. If a subject is discontinued based on a local measurement, a sample should still be sent to the central laboratory. The following activities and/or assessments will be performed at the randomization visit (Day 1, Visit 3):

- Assess subject eligibility using the study's inclusion/exclusion criteria.
- Record vital signs, height, and weight.
- Collect fasted blood samples for evaluation of efficacy parameters, including FPG, HbA1c, TC, HDL-C, LDL-C, non-HDL-C, TG, apo A-1, and apo B.
- Collect fasted blood and urine for evaluation of standard laboratory safety tests (chemistry, hematology, and urinalysis).
- Perform a urine pregnancy test on all female subjects and confirm negative.
- Determine and record adverse events and prior and concomitant medications.

- Review home glucose record and perform onsite fingerstick glucose check for comparison; dispense additional supplies as needed.
- Perform a physical examination.
- Collect study medication and review compliance (at least 80%, no more than 120%).
- Update IVRS/IWRS and obtain new study medication kit number.
- Dispense one study medication kit and review dosing instructions.
- Provide counseling on diet and exercise.

6.3.2. Month 1 (Visit 4)

There is no fasting requirement for this visit. The following activities and/or assessments will be performed at Month 1:

- Record vital signs, height, and weight.
- Collect blood sample for evaluation of standard laboratory safety tests (chemistry and hematology).
- Perform a urine pregnancy test on all female subjects and confirm negative.
- Determine and record adverse events and prior and concomitant medications.
- Review home glucose record and perform onsite fingerstick glucose check for comparison; dispense additional supplies as needed.
- Collect study medication and review compliance.
- Update IVRS/IWRS and obtain new study medication kit numbers.
- Dispense two study medication kits and review dosing instructions.
- Provide counseling on diet and exercise.

6.3.3. Month 3 (Visit 5)

There is no fasting requirement for this visit. The following activities and/or assessments will be performed at Month 3:

- Record vital signs, height, and weight.
- Collect blood samples for evaluation of standard safety tests (chemistry and hematology) and efficacy parameters, including HbA1c, TC, HDL-C, LDL-C, non-HDL-C, TG, apo A-1, and apo B.
- Perform a urine pregnancy test on all female subjects and confirm negative.
- Determine and record adverse events and prior and concomitant medications.
- Review home glucose record and perform onsite fingerstick glucose check for comparison; dispense additional supplies as needed.
- Perform a physical examination.

- Collect study medication and review medication compliance.
- Update IVRS/IWRS and obtain new study medication kit numbers.
- Dispense three study medication kits and review dosing instructions.
- Provide counseling on diet and exercise.

6.3.4. Month 6 (Visit 6)

The subject should arrive in a **fasted state** for this visit. The following activities and/or assessments will be performed at Month 6:

- Record vital signs, height, and weight.
- Collect fasted blood samples for evaluation of efficacy parameters, including FPG, HbA1c, TC, HDL-C, LDL-C, non-HDL-C, TG, apo A-1, and apo B.
- Collect fasted blood and urine samples for evaluation of standard laboratory safety tests (chemistry, hematology, and urinalysis).
- Perform a urine pregnancy test on all female subjects and confirm negative.
- Determine and record adverse events and prior and concomitant medications.
- Perform a physical examination.
- Assess Tanner Staging of pubertal development.
- Review home glucose record and perform onsite fingerstick glucose check for comparison; dispense additional supplies as needed.
- Collect study medication and review medication compliance.
- Update IVRS/IWRS and obtain new study medication numbers.
- Dispense three study medication kits and review dosing instruction.
- Provide counseling on diet and exercise.

6.3.5. Month 9 (Visit 7)

There is no fasting requirement for this visit. The following activities and/or assessments will be performed at Month 9:

- Record vital signs, height, and weight.
- A physical examination will be performed.
- Collect blood samples for evaluation of HbA1c and standard laboratory safety tests (chemistry and hematology).
- Perform a urine pregnancy test on all female subjects and confirm negative.
- Determine and record adverse events and prior and concomitant medications.
- Review home glucose record and perform onsite fingerstick glucose check for comparison; dispense additional supplies as needed.

- Collect study medication and review medication compliance.
- Update IVRS/IWRS and obtain new study medication kit numbers. Those low-dose subjects who complete Month 6 and are switched to the high dose prior to the approval of protocol version 2.0 and its Informed Consent will continue on the high-dose to the end of the study, according to the original protocol.
- Dispense three study medication kits and review dosing instruction.
- Provide counseling on diet and exercise.

6.4. End of Treatment/Early Termination* Visit

The subject should arrive in a **fasted state** for this visit. The following activities and/or assessments will be performed at the End of Treatment visit (Month 12, Visit 8 or Early Termination): *EarlyTermination procedures to be done, even if fasting is not possible

- Record vital signs, height, and weight.
- Collect fasted blood samples for evaluation of efficacy parameters, including FPG, HbA1c, TC, HDL-C, LDL-C, non-HDL-C, TG, apo A-1, and apo B.
- Collect fasted blood and urine samples for evaluation of standard laboratory safety tests (chemistry, hematology, and urinalysis). Clinical safety assessments will include vitamin D.
- Perform a urine pregnancy test on all female subjects and confirm negative (serum test also done).
- Determine and record adverse events and prior and concomitant medications.
- A physical examination will be performed.
- Assess development with Tanner Staging.
- Review home glucose record and perform onsite fingerstick glucose check for comparison.
- Collect study medication and review medication compliance.
- Update IVRS/IWRS with subject status (treatment complete or terminated).

6.5. Rescue Visit

Subjects whose HbA1c level cannot be controlled below 8.5% after 3 months or below 7.5% (confirmed persistent hyperglycemia) after 6 months, as measured by the central laboratory, of study medication treatment will undergo open-label glycemic rescue. A pharmacy card will be provided for filling metformin or insulin prescriptions, as necessary (see Section 3.1.6). If at all possible, the rescue visit should be scheduled to allow the patient to arrive in a **fasted state**. The following activities or assessments will be performed for the Rescue Visit, even though subject will continue in the study and even if fasting is not possible:

- Record vital signs, height, and weight.
- Collect fasted blood samples for evaluation of efficacy parameters, including FPG, HbA1c, TC, HDL-C, LDL-C, non-HDL-C, TG, apo A-1, and apo B.
- Collect fasted blood and urine samples for evaluation of standard laboratory safety tests (chemistry, hematology, and urinalysis).
- Perform a urine pregnancy test on all female subjects and confirm negative.
- Review home glucose record and perform onsite fingerstick glucose check for comparison; dispense additional supplies as necessary.
- Perform a physical examination.
- Assess development with Tanner Staging.
- Determine and record adverse events and prior and concomitant medications.
- Collect study medication and review medication compliance.
- Update IVRS/IWRS with subject status RESCUED. If at a regularly scheduled visit, obtain new study medication kit numbers.
- Prescribe metformin as needed, in accordance with metformin label.
- Instruct subject to take metformin as prescribed and to continue taking study medication as instructed per protocol.
- If the subject's dose of metformin has been up-titrated to 2gms/day or the subjects maximally tolerated dose, prescribe insulin as needed, in accordance with insulin label.
- Instruct subject to take insulin as prescribed and to continue taking study medication as instructed per protocol.
- Subject will continue with normally scheduled study visits.
- If rescue has occurred at a scheduled visit, dispense new study medication kits as prescribed for that visit and review dosing.
- Provide counseling on diet and exercise.

6.6. Follow-up

There is no fasting requirement for this visit. The following activities and/or assessments will be performed at the 2-week follow-up visit (Visit 9):

- Record vital signs, height, and weight.
- Determine and record adverse events and prior and concomitant medications.
- Perform a urine pregnancy test on all female subjects and confirm negative.
- Update IVRS/IWRS with subject status complete.

6.7. Protocol Deviations

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

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. DSPD must be notified of all intended or unintended deviations to the protocol (eg, 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.

Any data recorded on the study CRF will be collected and included in the database according to Clinical Data Interchange Standards Consortium standards and subjected to the same procedures as other data. If a subject was ineligible or received the incorrect dose or investigational treatment, and had at least one administration of investigational product, data should be collected for safety purposes.

The Investigator should notify the IRB of deviations from the protocol in accordance with local procedures.

7. EFFICACY ASSESSMENTS

Laboratory evaluations of HbA1c, FPG, and other secondary efficacy parameters will be performed by a certified clinical pathology laboratory. Laboratory certification (including expiration date) and normal reference ranges for all laboratory parameters used during the study will be on file at DSPD prior to study initiation.

The Investigator must review, sign, and date all laboratory test reports.

During the treatment period, the Investigator will be notified in the event of laboratory values outside the normal range and for alert values. In this case, the Investigator will be required to conduct clinically appropriate follow-up procedures. Glycemic-related parameters, HbA1c and FPG, will be blinded to the Investigator. Only alert value status will be conveyed. The Investigator may be given unblinded values as needed to evaluate a potential adverse experience, or in any situation where safety monitoring of an individual subject might require access to actual laboratory values. All such circumstances must be reviewed with the Medical Monitor. At the screening, Month 6 and Month 12 clinic visits, blood specimens must be obtained under fasting conditions (ie, after the subject has fasted overnight for at least 8 hours). If a subject has not fasted, the Investigator will reschedule the subject within 3 days.

7.1. Primary Efficacy Variable

The primary efficacy variable is HbA1c at Month 6. For subjects who discontinue treatment or receive rescue therapy prior to Month 6, the last post-Month 1 visit value observed prior to discontinuation or rescue will be carried forward (LOCF).

7.2. Secondary Efficacy Variables

The secondary efficacy variables are assessed by clinical laboratory evaluations.

The secondary efficacy variables for the study include:

- Change in FPG from baseline to Months 6 and 12;
- Change in HbA1c from baseline to Months 3, 6 and 12;
- Percentage of subjects achieving HbA1c targets of <7.0% and <6.5% at Month 6;
- Percentage of subjects at Months 6 and 12 achieving a changes in HbA1c from baseline ≥0.7% and 0.5%;
- Percentage of subjects achieving a reduction in FPG ≥30 mg/dL at Month 6;
- Changes and percent changes in TC, LDL-C, HDL-C, non-HDL-C, TG, apo A-1, and apo B from baseline to Months 3, 6 and 12; and
- Proportion of subjects requiring rescue and time from randomization to initiation of rescue medication.

8. PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS

8.1. Pharmacokinetic Variables

Not applicable.

8.2. Pharmacodynamic Variables

Not applicable.

8.3. Biomarker and Exploratory Variables

Not applicable.

9. SAFETY ASSESSMENTS

9.1. Adverse Events

All clinical adverse events occurring after the subject signs the ICF and up to the end of the study assessment and follow-up period, whether observed by the Investigator or reported by the subject, parent or legal guardian, will be recorded on the Adverse Event CRF page. Any findings noted during baseline assessment will be recorded as part of medical history. All SAEs are to be reported according to the procedures in Section 9.2 SAE Reporting-Procedure for Investigators. In addition, any 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 adverse event. Pre-planned (prior to signing the ICF) procedure/hospitalization for pre-existing conditions which do not worsen in severity should not be reported as SAEs (see Section 9.1.1 for Definitions).

At each visit, the Investigator will determine whether any adverse events have occurred by evaluating the subject. Adverse events may be directly observed, reported spontaneously by the subject, parent, or legal guardian, or by questioning the subject, parent or legal guardian at each study visit. Subjects should be questioned in a general way, without asking about the occurrence of any specific symptoms. All laboratory values must be appraised by the Investigator as to clinical significance. All post-baseline abnormal laboratory values considered clinically significant by the Investigator must be recorded in the adverse event page of the CRF.

Investigator should follow subjects with adverse events until the event has resolved or the condition has stabilized. In case of unresolved adverse events including significant abnormal laboratory values at the end of study assessment, these events will be followed up until resolution or until they become clinically not relevant.

9.1.1. Definitions

9.1.1.1. Adverse Event

Any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (eg, abnormal laboratory finding), 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.

9.1.1.2. Serious Adverse Event

An SAE is defined as 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 intervention 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: A procedure is not an adverse event or SAE, but the reason for the procedure may be an adverse event. Pre-planned (prior to signing the ICF) surgeries or hospitalizations for pre-existing conditions which do not worsen in severity are not SAEs.

9.1.1.3. Adverse Event Severity

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

- Mild: Awareness of sign or symptom, but easily tolerated (ie, 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 (ie, interferes significantly with subject's usual function).

9.1.1.4. Causality Assessment

The relationship between an adverse event and the study medication will be determined by the Investigator on the basis or his/her clinical judgment and the following definitions:

- 1 = Related:
  - The adverse event follows a reasonable temporal sequence from study drug administration, and cannot be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).
  - The adverse event 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 adverse event does not follow a reasonable sequence from study product administration, or can be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).

9.1.1.5. Action Taken Regarding the Study Medication

Actions taken regarding study medication may include the following:

- 1 = None: No change in study medication dosage was made.
- 2 = Discontinued permanently: The study medication was permanently stopped.
- 3 = Interrupted: The study medication was temporarily stopped.

9.1.1.6. Adverse Event Outcome

The adverse event outcome will be classified as 1 of the following:

- 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.
  - Identify sequelae/residual effects.

- 3 = Not recovered/not resolved
  - The adverse event itself is still present and observable.
- 4 = Fatal
- 5 = Unknown

9.1.1.7. Other Action Taken for Event

Other actions taken for adverse events may include the following:

- 1 = None.
  - No treatment was required.
- 2 = Medication required.
  - Prescription and/or over-the-counter medication were required to treat the adverse event.
- 3 = Hospitalization or prolongation of hospitalization required.
  - Hospitalization was required or prolonged due to the adverse event, whether or not medication was required.
- 4 = Other.

9.2. Serious Adverse Event Reporting–Procedure For Investigators

9.2.1. Initial Reports

Within 24 hours of receiving an SAE report:

- Complete a Daiichi Sankyo Serious Adverse Event Report (SAVER) form, sign it, and fax it to Medpace PD using the designated fax transmittal form.
- Call the Medpace SAE Hotline# for any questions on SAE reporting: PPD
- Place the initial version of SAVER in the subject's file.

9.2.2. Follow-up Reports

This is NEW information received on a previously reported SAE.

Within 24 hours of the receipt of new information for a reported SAE:

- Complete a Daiichi Sankyo Serious Adverse Event Report (SAVER) form with the new information. Please complete Sections 1 through 3 even if they contain no new information. For Sections 4 through 10, provide only the new information. Sign and fax the form to Medpace PPD using the fax transmittal form.
- For fatal cases, provide autopsy reports to Medpace.

- Medpace will review and forward the follow-up SAVER form and supporting documents to Daiichi Sankyo Clinical Safety and Pharmacovigilance (CSPV-Clinical@dsi.com).
- Place the follow-up SAVER form and all supporting documentation in the subject's file.

9.2.3. Notifying Investigators or Institutional Review Board

Daiichi Sankyo and/or Medpace will inform Investigators of any serious, unexpected (not listed in the Investigator's Brochure) and related adverse events occurring in other study centers or other Daiichi Sankyo studies of the investigational product, as appropriate.

Daiichi Sankyo or Medpace will inform any central IRB, while the Investigator will inform the local IRB of serious unexpected and related adverse events reported with Daiichi Sankyo's investigational product.

9.3. Exposure In Utero During Clinical Studies

Daiichi Sankyo must be notified of any subject who becomes pregnant while receiving the study medication or within 2 weeks of discontinuing the investigational product. 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 subject using the Exposure In Utero Reporting form. Investigators, or their designees, should contact their study monitor to receive the Exposure In Utero Reporting Form upon learning of a pregnancy. The Investigator should make every effort to follow the subject until completion of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (ie, post-partum complications, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly, including that in an aborted fetus), the Investigator should follow the procedures for reporting SAEs.

9.4. Clinical Laboratory Evaluations

All standard blood and urine tests to assess safety variables will be performed as specified in Section 7 (Efficacy Assessments). Clinical safety assessments will include C-peptide at screening as well as vitamin D at screening and End of Treatment (Month 12). Subjects with a vitamin D level less than the laboratory cutoff are recommended to be supplemented with cholecalciferol.

A summary of laboratory tests by visit is presented in Figure 17.1 for reference. Normal ranges will be documented in the laboratory manual.

9.5. Vital Signs

At all visits, temperature, blood pressure, and heart rate are to be measured.

9.5.1. Seated Blood Pressure and Heart Rate Measurement

Blood pressure should be measured using the following standardized process:

- Record the arm used for the measurement. Use the same blood pressure measuring device and arm throughout the study.
- Measure and record the seated heart rate.

At the screening visit 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.

9.5.2. Height, Weight, and Body Mass Index

Measurement of height should be performed at every visit, 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 every visit with the subject dressed in indoor clothing with shoes removed. Subjects should be weighed on the same scale at all visits.

Body mass index (BMI) will be calculated at each visit as weight (kg) divided by height (m) squared. A BMI table will be provided to each site.

9.6. Electrocardiograms

Not applicable.

9.7. Physical Findings

Full physical examinations must minimally include vital signs and clinical evaluations of the head, neck, thyroid, eyes, ears, nose, throat, heart, lungs, lymph nodes, abdomen, skin, extremities, and musculoskeletal and neurological systems.

For the description of Tanner Staging, see Appendix 17.3.

9.8. Other Safety Assessments

9.8.1. Medical History and Demographics

Demographic information including month and year of birth, race, and gender 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) will be collected on all subjects. Additional information to be collected includes past surgical and medical procedures as well as medications.

9.8.2. Home Glucose Monitoring

All subjects enrolled will be provided with home glucose monitoring systems with memory to measure glucose levels throughout the study. Subjects will be instructed to obtain glucose levels every morning before having breakfast. Subjects will be instructed to call the clinic immediately if the monitoring device indicates a fasting glucose level <50 mg/dL or >240 mg/dL. Subjects will receive appropriate medical advice based on their 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. Subjects will also be instructed to monitor a random, non-fasting glucose level once a day.

10. OTHER ASSESSMENTS

Not applicable.

11. STATISTICAL METHODS

11.1. Analysis Sets

11.1.1. Randomized Population

The Randomized Population includes all subjects who give assent and obtain consent from a parent or a legal guardian, and are assigned a randomization number. Baseline and demographic characteristics will be summarized for this population.

11.1.2. Intent-to-Treat Population

The Intent-to-treat (ITT) Population includes all randomized subjects who have taken at least 1 dose of randomized study medication, have a baseline HbA1c measurement, and have at least 1 post-baseline HbA1c measurement prior to any rescue therapy. The ITT Population is the primary analysis population.

11.1.3. Per-protocol Population

The per-protocol set will be those subjects who meet the ITT definition as well as all of the following additional criteria:

- Overall study medication compliance between 80% and 120%;
- No major protocol violations; and
- Completion of first 6-month treatment without need of rescue.

All criteria for major protocol violations and subject evaluability will be established by the study team prior to unblinding of the database and will be documented in a memo by study team.

If less than 90% of the ITT set meet the per-protocol definition, a per-protocol analysis on the primary efficacy variable, change in HbA1c from baseline to Month 6, will be

performed using the same method described for the primary efficacy variable to provide supportive analysis results.

11.1.4. Safety Population

The Safety Population is defined as all randomized subjects who have taken at least one dose of randomized study medication.

11.2. General Statistical Considerations

Summary statistics will be presented by treatment group. For continuous variables, the number of available observations (n), mean, standard deviation, median, minimum, and maximum will be provided. For categorical variables, the frequency and percentage in each category will be displayed.

Safety analyses will be descriptive and will be presented in tabular format with the appropriate summary statistics.

For the primary efficacy data analysis at Month 6, the last observed post-Month 1 HbA1c value before any rescue therapy will be carried forward for imputing the missing or dropout data. Post-Month 1 value was chosen because changes in HbA1c at 1 month of therapy are expected to be negligible, and it typically takes 2 to 3 months to achieve a stable HbA1c level following any new therapy.

Those subjects randomized to the low-dose group who complete Month 6 prior to the approval of this amended protocol and its Informed Consent will complete the study on the high-dose to which they were switched at Month 6 according to the original protocol.

A detailed Statistical Analysis Plan (SAP) describing the methodology to be used in the final analysis will be prepared and finalized prior to database lock. Statistical methods described within may be changed based on advances in research. Any change will require a protocol amendment only if it changes principal features of the protocol. Any deviations from the planned statistical analyses in the protocol will be fully described in the SAP and in the clinical study report.

11.2.1 Study Medication Compliance

A calculation of study medication compliance is required to identify subjects for the per-protocol analysis set. Compliance to the study medication regimen will be evaluated by counting unused tablets and capsules:

$$\%\ \text{compliance} = \frac{(\#\ \text{of packets dispensed} - \#\ \text{of packets returned})}{(\#\ \text{days since the last visit})} \times 100$$

11.3. Study Population Data

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 screening and Day 1 values. Fasting plasma glucose and lipid measurements from a blood sample will be included in efficacy analyses only when the sample is drawn within 3 days of the last dose of study medication during the blinded treatment period and when the subject has been fasting for 8 hours or more prior to the blood draw.

Demographic and baseline characteristics will be summarized using the number of available observations (n), means, standard deviations, medians, minimum and maximum values for continuous variables, and frequencies and percentages for categorical variables.

Demographic and baseline characteristics will be displayed in both aggregate and by treatment group for the all randomized set as well as for the ITT Population.

11.4. Efficacy Analyses

11.4.1. Primary Efficacy Analysis

The primary efficacy analysis is to compare high-dose (3.75 g/day) to low-dose (0.625 g/day) colesevelam HCl oral suspension for change in HbA1c from baseline to Month 6 with LOCF using the Intent-To-Treat (ITT) population. For subjects who received rescue therapy, the last post-Month 1 HbA1c value observed prior to rescue will be carried forward. The treatment difference will be tested at a 2-sided significance level of 0.05, using an analysis of covariance (ANCOVA) model with treatment group and previous OAD treatment stratum as fixed effects and baseline HbA1c as a covariate. P-value obtained from between-treatment comparison will be presented. The LS mean, standard error, and 95% CI for each treatment as well as for the difference between high- and low-dose colesevelam HCl groups will be estimated.

The treatment-by-previous OAD stratum interaction will be evaluated for the primary efficacy variable at a significance level of 0.1. If a significant interaction is suggested by the data, further analyses will be implemented to assess the qualitative or quantitative nature of the interaction.

11.4.2. Sensitivity Analyses for Primary Efficacy Analyses

Sensitivity analyses will be performed for subjects randomized but with no Month 6 measurement by using an imputation method for the missing values of change in HbA_{1c} from baseline. This method is to impute missing change values by multiple imputation, which is implemented with two SAS procedures: PROC MI and PROC MIANALYZE. Instead of filling in a single value for each missing value, multiple imputation replaces each missing value with a set of plausible values by using PROC MI. The missing data will be filled in multiple times to generate multiple complete data sets. The MIANALYZE procedure will then be used to combine the results of analyses obtained from the multiple complete data sets and derive valid statistical inferences.

11.4.3. Secondary Efficacy Analyses

The analyses of the continuous secondary efficacy variables, including HbA1c, FPG, TC, LDL-C, HDL-C, nonHDL-C, apo A-1, and apo B, will be carried out using the same method as for the primary efficacy variable, unless otherwise stated. The between-treatment comparison for change in TG will be carried out using a non-parametric ANCOVA. . Percentages of subjects with decreases in HbA1c ≥0.7% and ≥0.5%, final HbA1c <7.0% and <6.5%, and/or a decrease in FPG ≥30 mg/dL will be summarized at

timepoints where assessed. The glycemic control rates will be compared between treatments using Fisher's exact test.

The proportion of subjects requiring rescue and the time from randomization to initiation of rescue medication will be summarized using Kaplan-Meier methods at Month 6 and Month 12.

11.5. Pharmacokinetic/Pharmacodynamic Analyses

Not applicable.

11.5.1. Pharmacokinetic Analyses

Not applicable.

11.5.2. Pharmacodynamic Analyses

Not applicable.

11.5.3. Biomarker and Exploratory Analyses

Not applicable.

11.6. Safety Analyses

Safety assessments include evaluations of adverse events, clinical laboratory measurements (hematology, blood chemistry, and urinalysis), vital signs, physical examinations, prior and concomitant medications, and vitamin D level. The Safety Population will be used for all safety analyses.

The number and percentage of subjects discontinued or requiring rescue medication as well as time to discontinuation or rescue will be tabulated.

11.6.1. Adverse Event Analyses

Adverse events, as defined in Section 9.1.1, will be grouped by system organ class and by preferred term within system organ class according to the Medical Dictionary for Regulatory Activities (MedDRA). Tables summarizing subject incidence of all adverse events, SAEs, severe adverse events, study drug-related adverse events, study drug-related SAEs, study drug-related severe adverse events, and adverse events leading to early withdrawal from study and/or death will be provided.

Only adverse events occurring on or after the first dose of randomized study medication (ie, treatment-emergent adverse events) will be included in the above summaries. Treatment-emergent adverse events are defined as adverse events that first occurred or worsened in severity after the first dose of randomized study medication. Any adverse event data collected from the single-blind lead-in will be presented separately.

11.6.2. Clinical Laboratory Evaluation Analyses

Tables summarizing baseline, post-baseline, and change from baseline for each scheduled collection time point will be provided for chemistry, hematology, and urinalysis parameters and vitamin D level.

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.

11.6.3. Vital Sign Analyses

Vital signs at each treatment visit and change from baseline at each planned post-baseline assessment will be summarized by treatment.

11.6.4. Electrocardiogram Analyses

Not applicable.

11.6.5. Physical Finding Analyses

Tables of shifts from baseline to End of Treatment may be provided for physical examination findings.

11.6.6. Other Safety Analyses

Prior and concomitant medication will be coded using the World Health Organization Drug Dictionary and will be summarized for each treatment group.

11.7. Other Analyses

Not applicable.

11.8. Interim Analyses

No interim analysis has been planned.

11.9. Data and Safety Monitoring Board

A Steering Committee will be established and will comprise 5 to 7 external experts in pediatric type 2 diabetes mellitus to provide academic leadership to the clinical study.

A Data Monitoring Committee will be established to ensure both safety of the study participants and the scientific validity of the study.

11.10. Sample Size Determination

A total of 220-230 subjects will be randomized in a 3:2 ratio to receive either high-dose or low-dose colesevelam HCl oral suspension. It is assumed that the detectable difference between high-dose and low-dose colesevelam HCl for the change from baseline in HbA1c is 0.4%, with a common standard deviation of 1.0%. Using a 2-sided significance level of 0.05, a minimum sample size of 208 evaluable subjects (125 for the high-dose group and 83 for the low-dose group) will provide 80% power to detect the difference. With an estimate of 6-10% of subjects potentially not having evaluable baseline or post-Month 1 HbA1c data, the required sample size for this study will be approximately 220-230 subjects.

12. DATA INTEGRITY AND QUALITY ASSURANCE

The Investigator/investigational site will permit study-related monitoring, audits, IRB 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 CRO 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 (eg, CRFs, source data, and other pertinent documents).

The monitor is responsible for visiting site(s) at regular intervals of 4 to 12 weeks, depending on the enrollment numbers, throughout the study to verify 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. The monitor is responsible for inspecting the eCRFs 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 eCRFs.

The monitor will communicate deviations from the protocol, SOPs, GCP, and applicable regulations to the Investigator and will ensure that appropriate action designed to correct and 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 and documented.

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from DSPD. Inspection of site facilities (eg, pharmacy, drug storage areas, laboratories, etc) 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.

12.2. Data Collection

All relevant observations and data related to the study, as per the study protocol, will be recorded on electronic CRF pages. Daiichi Sankyo Pharma Development or their designee will supply instruction books for the completion of the eCRF. Adequate and accurate case records shall be maintained, including the evaluation of inclusion and exclusion criteria, medical history, physical examination, clinical assessments, a record of clinical safety laboratory sample collection, pharmacokinetic and pharmacodynamic sample collection if available, drug administration, adverse events and final evaluation. The eCRFs must be completed for each subject who signs the informed assent or consent form and undergoes screening procedures. The eCRF data entry shall be completed on the day of clinical visit completion. 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 DSPD and stored in the archives.

12.3. Data Management

To ensure the quality of clinical data across all subjects and sites, a Clinical Data Management review will be performed on subject data according to specifications given to the CRO. Data will be vetted both electronically and manually. For electronic CRFs, 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, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. Queries from eCRFs will be raised and 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 will be coded using MedDRA.

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 case report forms 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, worksheets, and correspondence.

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 DSPD and/or applicable regulatory authorities. Essential documents include:

- Subject files containing completed case report forms, informed assents and consents, and supporting copies of source documentation (if kept).
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of relevant essential documents required prior to commencing a clinical study, and all correspondence to and from the IRB and DSPD.
- Records related to the investigational product(s) including acknowledgment of receipt at site, accountability records and final reconciliation and applicable correspondence.

In addition, all original source documents supporting entries in the electronic case report forms must be maintained and be readily available.

All essential documentation will be retained by the institution for at least 5 years after completion of the study or for a longer period, where so required by other applicable regulations or requirements.

No study document should be destroyed without prior written agreement between DSPD 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 DSPD in writing of the new responsible person and/or the new location.

12.5. Record Keeping

Records of subjects, source documents, monitoring visit logs, data correction forms, CRFs, inventory of study product, regulatory documents (eg, protocol and amendments, IRB correspondence and approvals, approved and signed informed assent and 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 site. 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 site policy. Prior to transfer or destruction of these records DSPD must be notified in writing and be given the opportunity to further store such records.

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 CRO. This agreement will include the financial information agreed upon by the parties.

13.2. Reimbursement, Indemnity, and Insurance

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

14. PUBLICATION POLICY

[redacted]

15. STUDY ADMINISTRATIVE INFORMATION

15.1. Protocol Amendments

Any amendments to the study protocol as the study progresses will be communicated to the Investigator by DSPD. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB, unless immediate implementation of the change is necessary for subject safety. In this case, the situation must be documented and reported to the IRB within 5 working days. The Sponsor will assure the timely submission of amendments to regulatory authorities.

15.2. Address List

15.2.1. Sponsor

Daiichi Sankyo Pharma Development
399 Thornall Street
Edison, NJ 08837
PPD
PPD

15.2.2. CRO

Medpace, Inc
5375 Medpace Way
Cincinnati, Ohio 45227
PPD
PPD

15.2.3. Drug Safety

15.2.3.1. Medpace

Medpace, Inc
5375 Medpace Way
Cincinnati, Ohio 45227
PPD
PPD

15.2.3.2. DSPD

Daiichi Sankyo Pharma Development
Clinical Safety and Pharmacovigilance
399 Thornall Street
Edison NJ 08837
PPD
PPD

15.2.4. Data Management

Medpace, Inc.
5375 Medpace Way
Cincinnati, Ohio 45227

15.2.5. Biological Specimens

Medpace Reference Laboratories
4620 Wesley Avenue
Cincinnati, Ohio 45212

15.2.6. Interactive Voice Response System

Medpace, Inc
5375 Medpace Way
Cincinnati, Ohio 45227

PPD

PPD

16. REFERENCES

1. Package Insert for Welchol® (colesevelam HCl), Issued: July 2011. See at http://www.welchol.com for the most current version.
2. American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care* 2010; (Diabetes Care; January 2010; 33(suppl. 1):S62-S69.

17. APPENDICES

17.1. Instructions for Specimen Collection, Storage, and Shipment

Samples will be shipped to: Medpace Reference Laboratories, 4620 Wesley Avenue Cincinnati, Ohio 45212

Specific collection, storage and shipment instructions will be incorporated into the laboratory manual for each site.

Prior-shipment notification from the central reference laboratory (CRL), acknowledgement of intact sample arrival at the CRL, and sample inventory vs. sample labeling reconciliation at the CRL should be conducted, and discrepancies should be reported and resolved promptly.

Sample Analysis

Analysis will be performed by Medpace Reference Laboratories.

Residual Samples

All residual samples will be retained by Medpace Reference Laboratories.

17.2. Listing of Laboratory Assays

Table 17.1 provides a list of laboratory assays for the study.

Table 17.1: Laboratory Assays by Visit

Blood Samples	Urine Samples
Screening (Month -1; Visit 1) NB: Fasting Required	
HbA1c Complete Serum Chemistry Hematology FPG Lipids (TC, HDL-C, LDL-C, non-HDL-C, TG, apo A-1, and apo B) Vitamin D Anti-GAD, Anti-ICA512 C-peptide β-HCG for all females	Urine dipstick pregnancy test for all females. Urinalysis
Lead-in (Visit 2)	
None	Urine dipstick pregnancy test for all females.
Baseline/Randomization (Day 1; Visit 3) NB: Fasting Required	
HbA1c Complete Serum Chemistry Hematology FPG Lipids (TC, HDL-C, LDL-C, non-HDL-C, TG, apo A-1, and apo B)	Urine dipstick pregnancy test for all females. Urinalysis
Month 1 (Visit 4)	
Complete Serum Chemistry Hematology	Urine dipstick pregnancy test for all females.
Month 3 (Visit 5)	
HbA1c Complete Serum Chemistry Hematology Lipids (TC, HDL-C, LDL-C, non-HDL-C, TG, apo A-1, and apo B)	Urine dipstick pregnancy test for all females.
Month 6 (Visit 6) NB: Fasting Required	
HbA1c Complete Serum Chemistry Hematology FPG Lipids (TC, HDL-C, LDL-C, non-HDL-C, TG, apo A-1, and apo B)	Urine dipstick pregnancy test for all females. Urinalysis
Month 9 (Visit 7)	
HbA1c Complete Serum Chemistry Hematology	Urine dipstick pregnancy test for all females.

End of Treatment Visit (Month 12, Visit 8, or Early Termination) NB: Fasting Required	
HbA1c Complete Serum Chemistry Hematology FPG Lipids (TC, HDL-C, LDL-C, non-HDL-C, TG, apo A-1, and apo B) Vitamin D β-HCG for all females	Urine dipstick pregnancy test for all females. Urinalysis
Follow-up (Visit 9)	
None	Urine dipstick pregnancy test for all females.

Rescue Visit (NB: Fasting Required if possible)	
HbA1c Complete Serum Chemistry Hematology FPG Lipids (TC, HDL-C, LDL-C, non-HDL-C, TG, apo A-1, and apo B)	Urine dipstick pregnancy test for all females. Urinalysis

apo A-1 = apolipoprotein A-1; apo B = apolipoprotein B; β-HCG = beta-human chorionic gonadotrophin; FPG = fasting plasma glucose; HbA1c = hemoglobin A1c; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; non-HDL-C = non-high-density lipoprotein cholesterol; TC = total cholesterol; TG = triglycerides.

Figure 17.1: Analytes for Safety Evaluation

Hematology

Hemoglobin	White blood cell count with differential
Hematocrit	Basophils
Red blood cell count (with indices)	Platelets
Mean corpuscular volume	Neutrophils
Mean corpuscular hemoglobin	Bands
Mean corpuscular hemoglobin concentration	Lymphocytes
Red blood cell morphology	Monocytes
Reticulocyte count	Eosinophils

Chemistry

Total and direct bilirubin	Albumin
Alkaline phosphatase	Sodium
Alanine transaminase (SGPT)	Potassium
Aspartate aminotransferase (SGOT)	Bicarbonate
Blood urea nitrogen	Chloride
Creatinine (and calculated Cr clearance)	Calcium
Uric acid	Creatine phosphokinase
Inorganic phosphorus	Glucose
Total protein	Vitamin D

Urinalysis

Chemical and microscopic assessments

Efficacy Parameters

HbA1c, FPG, and lipids (TC, TG, LDL-C, HDL-C, non-HDL-C, apo A-1, and apoB)

Safety Parameters

See hematology and chemistry above.

17.3. Tanner Staging

Stage	Pubic Hair	Breast	Penis	Testes
I	Preadolescent	Preadolescent	Preadolescent	Preadolescent
II	Sparse, long, lightly pigmented, downy straight hair	Breast bud; breast and papilla elevated, with increased areolar diameter	Slight enlargement	Enlarged scrotum, pink, texture roughened
III	Increased pigmentation, more curly	Enlarged breast and areola with no contour separation	Increased length	Increased size
IV	Adult type, but less	Areola and papilla form secondary mound	Glans enlarged, increased breadth	Enlarged, darker in color
V	Adult distribution with spread to medial thighs	Nipple elevated, areola contour continuous with breast	Adult size	Adult size

Adapted from Tanner, JM; Growth at Adolescence, 2nd ed. Oxford, England, Blackwell Scientific Publications, 1962.

17.4. Schedule of Events

Table 17.2 provides a schedule of events for the study.

Table 17.2: Schedule of Events

Study Period	Screening	Lead-in[1]	Baseline/ Randomization	On-Treatment Visits				End of Treatment[2]	Follow-up	Rescue Visit
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	
Time (month, unless noted)	**≤ -1**	**-2 wks**	**Day 1**	**1**	**3**	**6**	**9**	**12**	**+2 wks**	
Visit Window (days)			♦[1]	±7	±7	±7	±7	±7	±7	
Fasting state required	●		●			●		●		●
Study consent and assent	X									
Inclusion/exclusion criteria	X	X	X							
Demographic information	X									
Medical/surgical history	X									
Prior and concomitant medication	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X	X		X	X	X	X		X
Tanner Stage	X					X		X		X
Vital signs, height, and weight	X	X	X	X	X	X	X	X	X	X
Efficacy parameters										
Fasting plasma glucose	X		X			X		X		X
Hemoglobin A1c	X		X		X	X	X	X		X
Lipids[3]	X		X		X	X		X		X
Clinical safety laboratory tests	X[4]		X[4]	X	X	X[4]	X	X[4]		X[4]
C-peptide	X									
Anti-GAD, Anti-ICA512	X									
Vitamin D	X							X		
Pregnancy test[5]	X	X	X	X	X	X	X	X	X	X
Adverse event reporting		X	X	X	X	X	X	X	X	X
Study drug dispensing		X	X	X	X	X	X			X
Study drug compliance			X	X	X	X	X	X		X
IVRS contact	X	X	X	X	X	X	X	X	X	X
Self-monitoring of blood glucose		X[6]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]		X[7]
Diet and exercise instruction	X	X	X	X	X	X	X			X

1. All study subjects must complete a 2 week (14 day) lead-in before randomization; up to 7 days longer will be allowed.
2. Including Early Termination Visit.
3. Lipids: Total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, triglycerides, apolipoprotein A-I, and apolipoprotein B.
4. Includes urinalysis at screening, baseline (Visit 3), Month 6 (Visit 6), and Month 12 (End of Treatment or Early Termination; Visit 8).
5. A serum pregnancy will be performed for all female subjects at screening and Month 12 (End of Treatment or Early Termination; Visit 8). A urine pregnancy test will be performed for all female subjects at all visits.
6. Instructions on glucometer.
7. Review of glucose meter results and dispensing of supplies as need