Official Protocol Title:	A Phase IV, Multicenter, Randomized, Placebo-Controlled, Parallel-Group, Double-Blind Trial and Subsequent Open-Label, Extension Trial to Assess the Safety and Efficacy of Addition of Omarigliptin in Japanese Patients with Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control on Insulin Monotherapy in Addition to Diet and Exercise Therapy
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TITLE:

A Phase IV, Multicenter, Randomized, Placebo-Controlled, Parallel-Group, Double-Blind Trial and Subsequent Open-Label, Extension Trial to Assess the Safety and Efficacy of Addition of Omarigliptin in Japanese Patients with Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control on Insulin Monotherapy in Addition to Diet and Exercise Therapy

EudraCT NUMBER: Not Applicable

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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
N/A	N/A	N/A	To correct translation errors in Exclusion Criteria #3 and #32 related to the word hypoglycemia that are present in the Japanese version of P039-00. An incorrect Japanese word that means 'symptom of hypoglycemia' was used instead of the intended word 'hypoglycemia'. These errors are not present in the English version of P039-00.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
5.5.1	Prohibited medications	(1) 'TZD' was added as Item e) and the subsequent items were modified to f) to j).	Clear obvious discrepancy
5.8	Subject Withdrawal/Discontinuation Criteria	Added 'progressive' in the last sentence of a) Hypoglycemia (1).	Typographic error
7.1.1.11	Instruction for recording of patient's log and dispensing	Deleted 'the day after' to clarify the timing from when the patient's log is recorded.	Typographic error

1.0 TRIAL SUMMARY

Abbreviated Title	Omarigliptin Phase IV Study -Omarigliptin Add-on to Insulin in Japanese T2DM
Sponsor Product Identifiers	MK-3102 Omarigliptin
Trial Phase	Phase IV
Clinical Indication	Not Applicable
Trial Type	Interventional
Type of control	Placebo
Route of administration	Oral
Trial Blinding	Double-blind
Treatment Groups	Phase A; Omarigliptin 25 mg once weekly (q.w.) or placebo Phase B; Omarigliptin 25 mg once weekly (q.w.)
Number of trial subjects	Approximately 180 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 23 months from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	Each subject will participate in the trial for up to 71 weeks from the time the subject signs the Informed Consent Form through the final contact. After a screening period of up to 2 weeks followed by a pre-treatment period of 2 or 10 weeks, each subject will be receiving assigned treatment for approximately 16 weeks (Phase A) and 36 weeks (Phase B). After the end of treatment each subject will be followed for 21 days.

Randomization Ratio	Subjects will be randomized in a 2:1 ratio to omarigliptin 25 mg once weekly (q.w.) or placebo and stratified by use of oral AHA at Visit 1/Screening

A list of abbreviations used in this document can be found in Section 12.3.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a randomized, placebo-controlled, parallel-group, multi-site, double-blind trial and subsequent open-label, extension trial of MARIZEV®/omarigliptin (MK-3102) in Japanese subjects with type 2 diabetes mellitus (T2DM) who have inadequate glycemic control on insulin monotherapy in addition to diet and exercise therapy, to be conducted in conformance with Good Clinical Practices (GCP) and Good Post-marketing Study Practice.

Note: In the pre-treatment period, 'Group A' and 'Group B' are used to distinguish two groups of subjects: Subjects on oral anti-hyperglycemic agent (AHA) at Visit 1/Screening who require wash-out of the oral AHA from Visit 2/Week-10 (Group A) and subjects that are not on oral AHA at screening and therefore do not require washout (Group B). See the text provided below and Trial Diagram in 2.2 for the detail.

This trial consists of a screening period of up to 2 weeks, a pre-treatment period of 2 weeks or 10 weeks (which includes 2-week single-blind placebo run-in period), and a treatment period of 52 weeks. Subjects on insulin in combination with an oral AHA, (referred to as Group A) will have a pre-treatment wash-out period of 10 weeks (to wash-out the oral AHA),

and subjects on insulin in monotherapy with no other AHAs (referred to as Group B) will have a pre-treatment period (single-blind placebo run-in period) of 2 weeks. The treatment period is composed of a 16-week double-blind period (Phase A) and a 36-week open-label period (Phase B). Randomization will be stratified based on their use of an oral AHA at Visit 1/Screening (insulin + oral AHA or insulin monotherapy).

After the 2-week, single-blind, placebo run-in period, subjects will be randomized in a 2:1 ratio to receive either omarigliptin 25 mg once weekly (q.w.) or placebo, and they will take one tablet of trial medication (Omarigliptin 25 mg tablet or matching placebo tablet) once weekly (q.w.) orally for 16 weeks in a double-blind manner (Phase A). Subsequently in Phase B, all subjects will take one open-label tablet of omarigliptin 25 mg once weekly (q.w.) orally for 36 weeks.

Approximately 180 subjects will be randomized. The target randomized population includes Japanese patients ≥20 years of age with T2DM who have inadequate glycemic control on insulin monotherapy in addition to diet and exercise therapy, with hemoglobin A1c (HbA1c) ≥7.5% and ≤10.0% at Visit 3/Week -2.

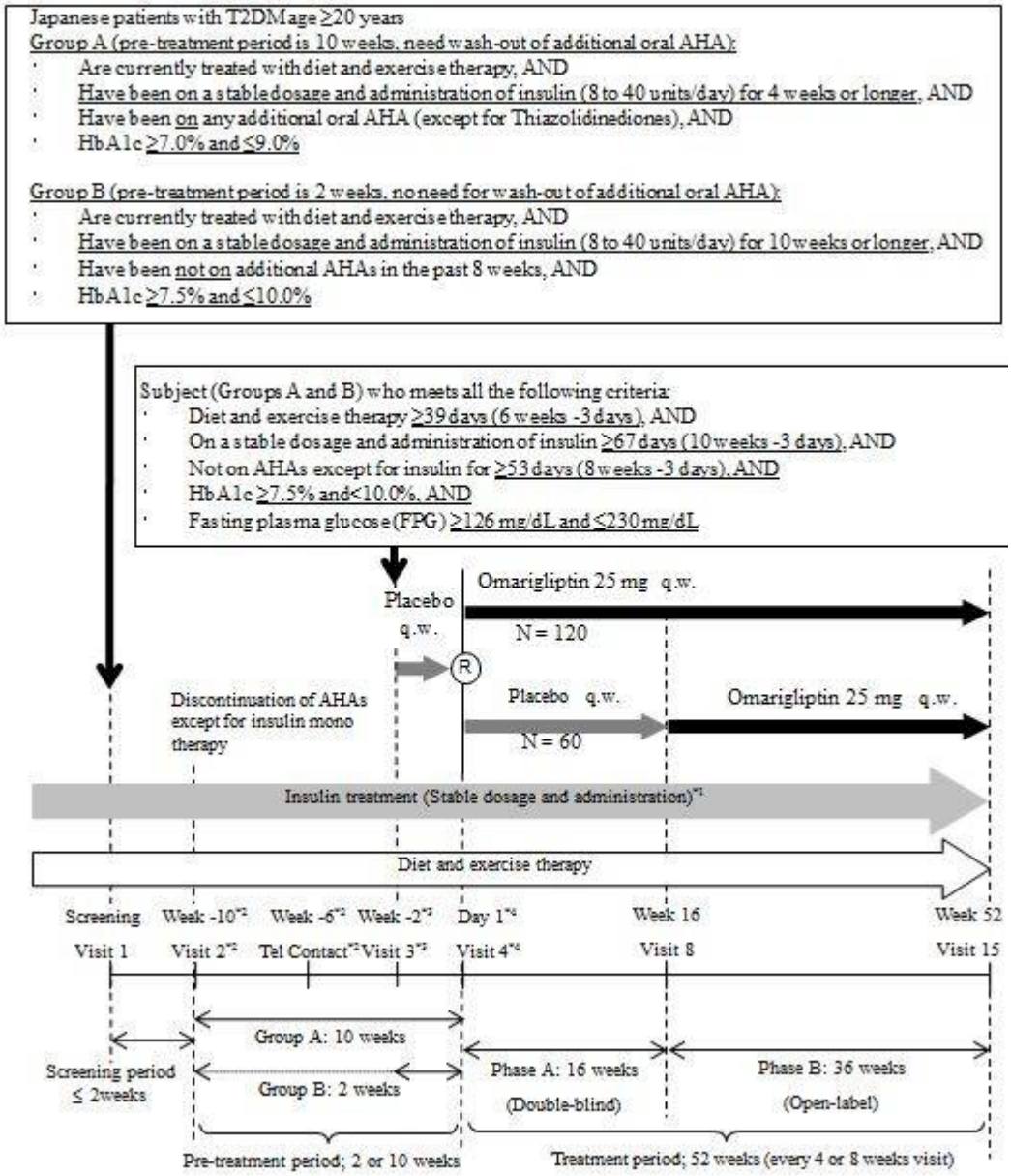
Subjects on pre-mixed/fixed ratio combination (content percentage of rapid-acting or ultra rapid-acting insulin is lower than or equal to 30%), intermediate or long-acting insulin monotherapy are eligible to participate.

Consistent dosage and administration schedule of insulin will be used during the trial. In Phase A (double-blind period), the dosage must be kept at the dosage used at Visit 1/Screening, unless the subject meets hypoglycemia criteria for down-titration, or glycemic rescue criteria for up-titration of insulin. During Phase B (open-label period), the investigator can modify dose of insulin as clinically required for appropriate glycemic control, in addition to insulin adjustment based on the protocol-specified rescue/hypoglycemia criteria.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

2.2 Trial Diagram

The trial design is depicted in Figure 1.



R = Randomization

*1 During Phase B (open-label period), dosage adjustments of insulin will be allowed as clinically appropriate to manage the subject's glycemic control.

*2 Subjects in Group B proceeds to Visit 3/Week -2 after Visit 1/Screening, skipping Visit 2/Week -10.

*3 If subjects in Group B performed the procedures of Visit 3/Week -2 within 2 weeks after Visit 1/Screening, HbA1c measurement is not needed at Visit 3/Week -2. The subjects may be deemed to meet the HbA1c criterion of Visit 3/Week -2 by HbA1c value of Visit 1/Screening.

*4 Visit 4/Day 1/Randomization is baseline.

Figure 1 Trial design

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

In Japanese patients with T2DM who have inadequate glycemic control on insulin monotherapy in addition to diet and exercise therapy:

3.1 Primary Objective(s) & Hypothesis(es)

1. **Objective:** To assess the efficacy of omarigliptin 25 mg q.w. compared to placebo based upon change from baseline in HbA1c at Week 16 [Phase A (double-blind period)].

   Hypothesis: Omarigliptin 25 mg q.w. provides greater reduction in HbA1c compared with placebo as assessed by change from baseline to Week 16 [Phase A (double-blind period)].

2. **Objective:** To assess the safety and tolerability of omarigliptin 25 mg q.w. through 16 weeks [Phase A (double-blind period)].

3. **Objective:** To assess the safety and tolerability of omarigliptin 25 mg q.w. for up to 52 weeks [Phase A (double-blind period) and Phase B (open-label period)].

3.2 Secondary Objective(s) & Hypothesis(es)

[Phase A (double-blind period)]

1. Objective: To assess the efficacy of omarigliptin 25 mg q.w. compared to placebo based upon change from baseline in fasting plasma glucose (FPG) at Week 16.

   Hypothesis: Omarigliptin 25 mg q.w. provides greater reduction in FPG compared with placebo as assessed by change from baseline to Week 16.

2. **Objective:** To assess the efficacy of omarigliptin 25 mg q.w. compared to placebo based upon proportion to goal of HbA1c <7.0% or <6.5% at Week 16.

3. **Objective:** To assess the efficacy of omarigliptin 25 mg q.w. compared to placebo based upon change from baseline in 1, 5-anhydroglucitol (1, 5-AG) at Week 16.

[Phase A (double-blind period) and Phase B (open-label period)]

4. **Objective:** To assess the efficacy of omarigliptin 25 mg q.w. for up to 52 weeks on glycemic control parameters (change from baseline in HbA1c and FPG, and proportion to goal of HbA1c <7.0% or <6.5%).

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the approved labeling for information on omarigliptin (MK-3102).

4.1.1 Pharmaceutical and Therapeutic Background

Diabetes mellitus (DM) is a metabolic disorder characterized by chronic hyperglycemia due to insufficient insulin action [1] [2]. DM is classified into two types on the basis of its etiology: Type 1 DM (due to an autoimmune mechanism, idiopathic) and Type 2 DM (T2DM) (due to insulin resistance increased and an insulin secretory defect) [1] [2]. T2DM, which accounts for more than 95% of DM [2], is associated developing with environmental factors, aging and several genetic factors [1]. Chronic hyperglycemia contributes to the development of diabetic complications such as retinopathy, nephropathy, neuropathy and atherosclerosis, and significantly poor quality of life (QOL) of patients with DM [1].

It is estimated that 415 million people worldwide (8.8% of adults) have DM in 2015, and the number of people with the disease is predicted to rise to 642 million by 2040 (Approximately 55% increase compared to 2015) [3]. The number of adult people with DM is also rising in Japan. According to the National Health and Nutrition Examination Survey by the Ministry of Health, Labor and Welfare (MHLW), the number of people ≥20 years old in Japan who are strongly suspected of DM is increasing annually, counting approximately 7.4 million in 2002, 8.9 million in 2007, and 9.5 million in 2012 [4]. Of those, approximately more than 65% of the people are expected to take some kind of AHAs [4].

In Japan, the improvement of lifestyle by diet, exercise, and patient education is the foundation of treatment for T2DM. If the target value of glycemic control is not achieved with diet and exercise for 2 or 3 months, medication treatment is initiated according to clinical condition of individual patient [1]. For the selection of medication treatment, age, degree of obesity, intensity of chronic complication, renal and hepatic function, and capacity of insulin secretion and the intensity of insulin resistance, in addition to severity of metabolic disorder, should be considered, and an oral AHA such as sulfonylureas (SU), glinides, biguanides (BGs), thiazolidinediones (TZD), α-glucosidase inhibitors (α-GI), dipeptidyl peptidase 4 (DPP-4) inhibitors, and sodium glucose cotransporter 2 (SGLT2) inhibitors or injectable AHAs, such as insulin or glucagon-like peptide 1 (GLP-1) receptor agonists can be selected [1]. When glycemic control is inadequately maintained with monotherapy and modification of lifestyle, up-titration of the oral AHA, co-administration of oral AHAs with different mechanisms of action, switching to GLP-1 receptor agonists or insulin, or co-administration of oral AHAs with a GLP-1 receptor agonist or insulin can be considered [1].

In 2013, proportion of the T2DM patients who received insulin (insulin monotherapy or co-therapy of insulin and oral AHAs) is approximately 21.6% in Japan. This percentage is the second highest following the percentage of the patients (59.4%) who were treated with any oral AHAs only, indicating that insulin treatment is commonly used in Japan [5]. When glycemic control is inadequately treatment with insulin monotherapy, up-titration of insulin or insulin intensification therapy will be administered to improve hyperglycemia after eating. However, it is considered as barrier to adequate glycemic control since it may cause risks of increasing of hypoglycemia, or it may cause increasing burden of frequently injection of insulin. On the other hand, combination with insulin and oral AHAs (SUs, BGs, TZD, α-GI, DPP-4 inhibitors) will show improving of glycemic control or decreasing insulin totally dosage [2].

DPP-4 inhibitors such as omarigliptin improve glycemic control in subjects with T2DM by increasing insulin secretion, mediated by an enhancement of the "incretin" axis. Incretins,

which are gut-derived hormones that include GLP-1 and glucose-dependent insulinotropic peptide (GIP), are endogenous insulin secretagogues that act in a glucose-dependent manner to stimulate insulin secretion [6, 7, 8 and 9]. Following a meal, incretins are released from intestinal cells into the circulation. Both GLP-1 and GIP stimulate insulin release; in addition, GLP-1 suppresses glucagon release [9].

Therapies that target the incretin axis, including DPP-4 inhibitors such as omarigliptin, have several potential advantages over conventional insulin secretagogues such as SUs. First, as noted above, incretin stimulation of insulin release is glucose-dependent. For this reason, the risk of hypoglycemia when DPP-4 inhibitors are administered as monotherapy or in combination with agents not known to cause hypoglycemia is low. Second, DPP-4 inhibitors have generally neutral effects on body weight, whereas SUs are associated with an increase in body weight [10].

Omarigliptin is unlike the presently marketed DPP-4 inhibitors that are administered once or twice daily, omarigliptin has a half-life (t1/2) that supports once-weekly dosing. The efficacy, safety, and tolerability of omarigliptin 25 mg once weekly was evaluated in two Japanese studies (in monotherapy and as add-on therapy to 5 classes of AHA) in patients with T2DM. In the double-blind period of Japan phase III placebo- and sitagliptin-controlled monotherapy study (P020) omarigliptin 25 mg once-weekly demonstrated superiority to placebo and non-inferiority to sitagliptin 50 mg once-daily in change from baseline in HbA1c at Week 24. When administered omarigliptin 25 mg once-weekly for up to 52 weeks, omarigliptin achieved a sustained effect with generally safe and well tolerated profile. In the double-blind period of Japan phase III add-on to oral AHA study (P015), omarigliptin 25 mg once weekly was added-on to other classes of oral AHA monotherapy with different mechanisms of action likely to be used clinically in Japan including SUs, glinides, BGs, TZD, or α-GI. As combination with all of the aforementioned AHA classes, the change from baseline in HbA1c at Week 24 with the addition of omarigliptin 25 mg was superior to the addition of placebo. When administered omarigliptin 25 mg once-weekly for up to 52 weeks, omarigliptin achieved a sustained effect with generally safe and well tolerated profile.

Based on above results, omarigliptin was launched in the market in Japan in November 26 2015, for the treatment of T2DM.

As indicated above, the addition of omarigliptin to the subjects with T2DM who received insulin therapy will be anticipated to show good efficacy and safety profile.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

The trial is a randomized, placebo-controlled, parallel-group, multicenter and 16 weeks of double-blinded trial, and subsequent of 36 weeks open-label extension trial of omarigliptin in Japanese subjects with T2DM who have inadequate glycemic control on insulin monotherapy in addition to diet and exercise therapy.

Recently, insulin self-injection is widely used for T2DM in addition to type 1 DM since environment of insulin therapy is dramatically improved by insulin formulation, devise was improved and/or self-monitoring blood glucose (SMBG) was familiarized. Additionally, insulin therapy is widely used combination with variant DPP-4 inhibitors [1] [2].

Omarigliptin was launched in November 2015, and it is anticipated to be used with insulin therapy similar to other marketed DPP-4 inhibitors. However, a clinical trial in which omarigliptin and insulin are used in combination to assess safety and efficacy has not yet been conducted.

Based on the above, the trial will be conducted as one of pharmacovigilance activities and investigation/study for assessment of efficacy in order to examine the safety and efficacy of omarigliptin, weekly DPP-4 inhibitor, in Japanese subjects with T2DM who have inadequate glycemic control on insulin monotherapy.

4.2.2 Rationale for Dose Selection/Regimen

Dosage and administration of omarigliptin was approved in Japan as "usually, for adults, 25 mg of omarigliptin is orally administrated once weekly". In this study, the dosage and administration is set as omarigliptin 25 mg per week according to the Japan Label.

4.2.2.1 Rationale for the Use of Placebo

4.2.2.1.1 Rationale for the use of placebo for the pre-treatment period

To exclude subjects who are unlikely to comply with the administration of study drug before entry into the treatment period, a 2-week placebo run-in period is designed into the pre-treatment period.

4.2.2.1.2 Rationale for the use of placebo for the treatment period

In addition to comparison between pre-dose and post-dose, comparison between omarigliptin 25 mg q.w. group and placebo group enables an exclusion of influences of the subject population, changes over time, and other factors, and an accurate characterization of the glycemic control potential of omarigliptin. In addition, the variability in any measurements in patients with T2DM requires a placebo group to adequately characterize any potential positive/negative effects of omarigliptin in patients with T2DM. Considering the importance of this study in adequately characterizing the efficacy and safety of omarigliptin for 16 weeks, the placebo group is designed into the treatment period.

4.2.2.2 Rationale for Duration of Treatment Period

To assess the long-term safety of omarigliptin when administered with insulin, the treatment period is defined as 52 weeks based on the "Guideline on Clinical Evaluation Methods for Oral Hypoglycemic Agents", MHLW Pharmaceutical and Food Safety Bureau (PFSB), Draft, 19th May 2014 [11](hear after "Guideline draft"). For efficacy assessment, the Guideline draft [11] recommends having 12-24 weeks double-blinded period in which dosage and administration of insulin is maintained in principle. The rationales of 16 weeks for the double-blinded placebo-controlled period for the study are followings; (1) based on the results of previous studies with omarigliptin conducted in Japan, 16 weeks will provide sufficient time to observe the maximal reduction in HbA1c with omarigliptin and (2) it minimizes the duration of the use of placebo.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

HbA1c, the primary endpoints, is recommended as a parameter during the double-blind period (during the period dosage and administration of insulin shall be stable) in long-term trial of co-administration of insulin and oral AHAs in Guideline draft [11].

The Treatment Guide for Diabetes [1] states that HbA1c is an important parameter of glycemic control in patients, and the evaluation should be complemented with FPG etc.

Based on the above, the primary efficacy endpoint is change from baseline in HbA1c, the secondary efficacy endpoint is change from baseline in FPG.

In addition, 1, 5-AG reflects postprandial hyperglycemia, therefore, change from baseline in 1, 5-AG is added as a secondary efficacy endpoint.

4.2.3.2 Safety Endpoints

The following endpoints will be collected to assess the safety of omarigliptin when co-administered with insulin.

- Adverse events (including hypoglycemia)
- Vital signs (body weight, blood pressure, and pulse rate)
- Laboratory tests
- Electrocardiogram (ECG)

4.2.3.3 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on specimens consented for future biomedical research during this clinical trial. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma) and/or the measurement of other analytes, depending on which specimens are consented for future biomedical research.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting/retaining specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that subjects receive the correct dose of the correct drug/vaccine at the correct time. The details of this Future Biomedical Research sub-trial are presented in Section 12.2 – Collection and Management of Specimens for Future Biomedical Research.

4.3 Benefit/Risk

Subjects in clinical trials generally cannot expect to receive direct benefit from treatment during participation, as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine.

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying approved labeling and Informed Consent documents.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male or female Japanese subjects with T2DM at least 20 years of age who are have inadequate glycemic control on insulin monotherapy with or without single oral AHA in addition to diet and exercise therapy will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

At Visit 1/Screening

1) Have T2DM
2) Be ≥20 years of age on the day of signing the informed consent form (ICF)
3) Meet all of following criteria for Group A or B at Visit 1/Screening:

   Group A (pre-treatment period is 10 weeks)

   (1) Are currently treated with diet and exercise therapy, AND

   (2) Have been on a stable dosage and administration of insulin (8 to 40 units/day) for 4 weeks or longer, AND

   <Note> Insulin will be administered during the trial as monotherapy of pre-mixed insulin/fixed ratio combination of insulin (content percentage of rapid-acting or ultra rapid-acting insulin is lower than or equal to 30%), intermediate or long-acting insulin. If a subject is treated with the insulin monotherapy on the consent date, but the dosage of insulin was modified within 4 weeks before on the consent date, it can be allowed to postpone Visit 1/Screening until the subject meets the requirement. In this case, the type of insulin, and the dosage and administration should not be changed/modified from those on the consent date.

   (3) Have been on a single oral AHA, AND

   <Note> Wash-out from multiple oral AHAs is not allowed in the trial.

   (4) Are not on any injectable AHA, except insulin monotherapy, AND

   (5) HbA1c ≥7.0% and ≤9.0%

   Group B (pre-treatment period is 2 weeks)

   (1) Are currently treated with diet and exercise therapy, AND

(2) Have been on a stable dosage and administration of insulin (8 to 40 units/day) for 10 weeks or longer, AND

<Note> Insulin will be administered during the trial as monotherapy of pre-mixed insulin/fixed ratio combination of insulin (content percentage of rapid-acting or ultra rapid-acting insulin is lower than or equal to 30%), intermediate or long-acting insulin. If a subject is treated with the insulin monotherapy on the consent date, but the dosage of insulin was modified within 10 weeks before on the consent date, it can be allowed to postpone Visit 1/Screening until the subject meets the requirement. In this case, the type of insulin, and the dosage and administration should not be changed/modified from those on the consent date.

(3) Have not been on any additional AHAs (except for insulin monotherapy) in the past 8 weeks, AND

(4) HbA1c ≥7.5% and ≤10.0%

4) Have a body mass index (BMI) >18 kg/m^2 and <40 kg/m^2

5) Meets one of the following criteria:

(1) Subject is a male

(2) Subject is a female not of reproductive potential defined as one who has either

a) Reached natural menopause (defined as ≥12 months of spontaneous amenorrhea in women ≥45 years of age), or

b) Had bilateral oophorectomy and/or hysterectomy, or had bilateral tubal ligation at least 8 weeks prior to Visit 1/Screening.

(3) Subject is a female of reproductive potential and:

a) Agrees to remain abstinent from heterosexual activity, or

b) Agrees to use (or have their partner use) acceptable contraception to prevent pregnancy within the projected duration of the study and for 21 days after the last dose of study medication. Acceptable methods of contraception include:

(a) Use of double-barrier methods; diaphragm with spermicide and a condom.

(b) Use of hormonal contraception (any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent [including oral, subcutaneous, intrauterine and intramuscular agents, and cutaneous patch]) with one of the following: diaphragm with spermicide; condom; vasectomy; or intrauterine device (IUD).

(c) Use of an IUD with one of the following: condom; diaphragm with spermicide; vasectomy; or hormonal contraception (see above).

(d) Vasectomy with one of the following: diaphragm with spermicide; condom; IUD; or hormonal contraception (see above).

6) Understand the study procedures, alternative treatments available, and risks involved with the study, and voluntarily agrees to participate by giving written informed consent. The subject may also provide consent for Future Biomedical Research (FBR). However, the subject may participate in the main trial without participating in FBR.

At Visit 3/Week -2

7) Be treated with diet and exercise therapy ≥39 days (6 weeks -3 days)

<Note> See Section 6.0 trial flow chart for scheduling Visit 3/Week -2. Compliance with diet and exercise therapy will be assessed comprehensively throughout the above period. In the case of exercise therapy, this condition does not necessarily need to be met if it is judged to be inappropriate for a subject because of complication[s].

8) Be on a stable dosage and administration of insulin ≥67 days (10 weeks -3 days)

9) Not be on other AHAs except for insulin monotherapy ≥53 days (8 weeks -3 days)

10) Meet all following glycemic criteria at Visit 3/Week -2

(1) HbA1c ≥7.5% and ≤10.0%

<Note> If subjects in Group B performed the procedures of Visit 3/Week -2 within 2 weeks after Visit 1/Screening, HbA1c measurement is not needed at Visit 3/Week -2. The subject may be deemed to meet the HbA1c criterion of Visit 3/Week -2 by HbA1c value of Visit 1/Screening

(2) FPG ≥126 mg/dL and ≤230 mg/dL

<Note> FPG may be re-tested once upon the investigators discretion if he/she believes that the value does not reflect the subject's recent glycemic control.

At Visit 4/Day 1/Randomization

11) Be treated with diet and exercise therapy ≥53 days (8 weeks -3 days)

<Note> See Section 6.0 trial flow chart for scheduling Visit 4/Day 1/Randomization. Compliance with diet and exercise therapy will be assessed comprehensively throughout the above period. In the case of exercise therapy, this condition does not necessarily need to be met if it is judged to be inappropriate for a subject because of complication[s].

12) Be on a stable dosage and administration of insulin ≥81 days (12 weeks -3 days)

13) Not be on AHAs except for insulin monotherapy ≥67 days (10 weeks -3 days)

14) Have 100% compliance with study medication (placebo) which is confirmed by counting remaining tablets at the trial site, and Have ≥85% compliance with insulin during the single-blind placebo run-in period (From the day at Visit 3/Week -2 to the day before Visit 4/Day 1/Randomization).

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

<Note> Subjects with laboratory screening values meeting protocol exclusion criteria may, at the discretion of the investigator, have one repeat determination performed by the central laboratory. If the repeat value does not meet the criterion, the subject may continue in the screening process. Only laboratory tests meeting exclusion criteria are to be repeated (not the entire panel). Note that repeat determination can be performed only once for each laboratory test during the Screening and Pre-treatment Period.

At Visit 1/Screening

Criteria related to Diabetes

1) Has type 1 DM or has a history of diabetic ketoacidosis.
2) Has a history of being administered any of the following AHAs including fixed dose combination (FDC) containing the following ingredients:
   (1) TZD: within 12 weeks prior to Visit 1/Screening
   (2) GLP-1 receptor agonists: within 12 weeks prior to Visit 1/Screening
   (3) Omarigliptin (including placebo for treatment period): any time

   <Note> Subjects who have previously participated in clinical studies with omarigliptin but were not enrolled into the active treatment period (i.e., only took single-blinded placebo during the observation period) may be eligible to participate in the trial.
3) Has history of severe hypoglycemia with coma or loss of consciousness, or for whom hypoglycemia was observed greater or equal to two times per week within 8 weeks prior to Visit 1/Screening.

Requiring Specific Treatments

4) Is currently participating in or has participated in another study with an investigational compound or device within the prior 12 weeks of Visit 1/Screening and does not agree to refrain from participating in any other study while participating in this study.

   <Note> A subject who has participated in a non-interventional study may be enrolled.
5) Has undergone a surgical procedure within 8 weeks prior to Visit 1/Screening or has planned major surgery during the study.

   <Note> A subject who has undergone minor surgery within the prior 8 weeks and is fully recovered or a subject who has planned minor surgery may participate. Minor surgery is defined as a surgical procedure involving local anesthesia.

6) Receives a following medication at unstable dosage and administration:
   (1) Lipid-lowering medication: within 4 weeks prior to Visit 1/Screening
   (2) Thyroid hormone replacement therapy : within 6 weeks prior to Visit 1/Screening
7) Is currently on or likely to require treatment with a prohibited medication (refer to 5.5.1), and/or subject has unstable complication such as he/she is likely to require a new treatment and/or adjustment with a limited concomitant medication.

Concomitant Disease of Organs and Systems

8) Has poorly controlled hypertension defined as systolic blood pressure of ≥160 mmHg or diastolic blood pressure of ≥90 mmHg and blood pressure is unlikely to be within these limits by Visit 3/Week -2 with an adjustment in anti-hypertensive medication (See section 5.5.2).

   <Note> Investigators are encouraged to maximize blood pressure control. Subject may have blood pressure medications adjusted and be enrolled if repeat blood pressure measurement no longer meets exclusion criterion.
9) Has a medical history of active liver disease (other than non-alcoholic hepatic steatosis), including chronic active hepatitis B or C (assessed by medical history), primary biliary cirrhosis, or symptomatic gallbladder disease.
10) Has human immunodeficiency virus (HIV) as assessed by medical history.
11) Has had new or worsening signs or symptoms of coronary heart disease or congestive heart failure within the past 3 months, or has any of the following disorders within the past 3 months:
   (1) Acute coronary syndrome (e.g., myocardial infarction or unstable angina)
   (2) Coronary artery intervention (e.g., coronary artery bypass grafting or percutaneous transluminal coronary angioplasty)
   (3) Stroke or transient ischemic neurological disorder
12) Has severe peripheral vascular disease (e.g., claudication with minimal activity, a nonhealing ischemic ulcer, or disease which is likely to require surgery or angioplasty).
13) Has a history of malignancy ≤ 5 years prior to Visit 1/Screening, except for adequately treated basal cell or squamous cell skin cancer, or in situ cervical cancer.

   <Note> The following subjects should be excluded;
   (1) A subject with a history of malignancy >5 years prior to Visit 1/Screening should have evidence of residual or recurrent disease
   (2) A subject with any history of melanoma, leukemia, lymphoma, or renal cell carcinoma.

14) Has a clinically important hematological disorder (such as aplastic anemia, myeloproliferative or myelodysplastic syndromes, thrombocytopenia).

Laboratory Abnormalities

15) Have any exclusionary laboratory values as listed in Table 1 below.

Table 1 Laboratory Exclusion Criteria (Visit 1/Screening)

Parameter	Population	Study Limit for Exclusion
Estimated glomerular filtration rate (eGFR)[1]		<35 mL/min/1.73 m^2
Alanine aminotransferase (ALT)		>two times upper limit of normal (ULN)
Aspartate aminotransferase (AST)		>two times ULN
Thyroid-stimulating hormone (TSH)		Outside central laboratory normal range
Hemoglobin	Male Female	<11 g/dL <10 g/dL
Triglyceride		>600 mg/dL
C-peptide		<0.6 ng/mL

[1] eGFR (mL/min/1.73 m^2) = 194 x serum creatinine (Cr) $^{-1.094}$ x age (years) $^{-0.287}$ (x 0.739 for female).

Insulin therapy-Specific Criterion

16) Meets any contraindication or warning listed on the package insert of each insulin products and which do not be contained in the exclusion criteria of this study protocol.

Other Criteria

17) (For women of childbearing potential) has a positive urine pregnancy test.

18) Meets any following criteria regarding pregnant, breast-feeding or donate eggs;

(1) Be pregnant or breast-feeding

(2) Is expecting to conceive during the study, including 21 days following the last dose of study medication.

(3) Subject is expecting to undergo hormonal therapy in preparation to donate eggs during the period of the trial, including 21 days following the last dose of study medication.

19) Is a user of recreational or illicit drugs or has had a recent history of drug abuse.

20) Meets any following criteria regarding alcohol consumption;

(1) Routinely consumes >14 alcoholic drinks per week

(2) Engages in binge drinking ["Binge drinking" is defined as a pattern of 5 or more alcoholic drinks (male), or 4 or more alcoholic drinks (female) in about 2 hours].

<Note> One alcoholic drink is defined as 5 oz (150 mL) of wine, or 12 oz (350 mL) of beer, or 1.5 oz (45 mL) of 80 proof liquor.

21) Meets any following criteria regarding donated blood products, phlebotomy or receive of blood products

(1) Has had phlebotomy of >300 mL or donated blood products of >300 mL within 8 weeks of Visit 1/Screening

(2) Has intends to have phlebotomy or donated blood products within the projected duration of the study

(3) Has received, or is anticipated to receive, blood products within 12 weeks of Visit 1/Screening or within the projected duration of the study.

22) Is disqualified from the study by the investigator for any reasons other than those given above.

Example: Subject has a history or current evidence of any condition, therapy, lab abnormality or other circumstance as follows,

(1) Makes participation not in the subject's best interest,

(2) Might interfere with the subject's participation for the full duration of the study,

(3) Might confound the results of the study.

23) Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this trial.

At Visit 2/Week -10 (Only for Group A)

Other Criterion

24) Is disqualified from the study by the investigator for any reasons other than those given above.

At Visit 3/Week -2

Concomitant Disease of Organs and Systems

25) Has poorly controlled hypertension defined as systolic blood pressure of ≥160 mmHg or diastolic blood pressure of ≥90 mmHg.

Laboratory Abnormalities

26) Has any exclusionary laboratory values as listed in Table 2 below.

Table 2 Laboratory Exclusion Criteria (Visit 3/Week -2)

Parameter	Population	Study Limit for Exclusion
eGFR[1]		<35 mL/min/1.73 m^2
ALT		>two times ULN
AST		>two times ULN
Triglyceride		>600 mg/dL

[1] eGFR (mL/min/1.73 m^2) = 194 x serum $Cr^{-1.094}$ x age (years) $^{-0.287}$ (x 0.739 for female).

Other Criteria

27) (For women of childbearing potential) have a positive urine pregnancy test.

28) Be disqualified from the study by the investigator for any reasons other than those given above.

At Visit 4/Day 1/Randomization

Criteria related to Diabetes

29) Is difficult to continue stable dosage and administration of insulin during Phase A (double-blind period, 16 weeks)

30) Received rapid-acting or ultra rapid-acting insulin within 10 weeks prior to Visit 4/Day 1/Randomization.

31) Received pre-mixed insulin/fixed ratio combination of insulin with a greater than 30% rapid or ultra rapid-acting insulin within 10 weeks prior to Visit 4/Day 1/Randomization.

32) Has history of severe hypoglycemia with coma or loss of consciousness, or for whom hypoglycemia was observed greater or equal to two times per week from Visit 1/Screening to Visit 4/Day 1/Randomization.

Other Criteria

33) (For women of childbearing potential) have a positive urine pregnancy test.

34) Be disqualified from the study by the investigator for any reasons other than those given above.

5.2 Trial Treatment(s)

The treatment(s) to be used in this trial are outlined below in Table 3.

Table 3 Trial Treatments

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Placebo run-in period (Single-Blind Pre-Treatment Period)					
Omarigliptin Matching Placebo	Placebo tablet	Once a week	Oral	2 weeks	Run-in medication
Phase A (Double-Blind Treatment Period)					
Omarigliptin or matching placebo	25 mg tablet or placebo tablet	Once a week	Oral	16 weeks	Experimental or experimental placebo
Phase B (Open-label Treatment Period)					
Omarigliptin	25 mg tablet	Once a week	Oral	36 weeks	Experimental

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of trial treatments in accordance with the protocol and any applicable laws and regulations.

5.2.1 Dose Selection

5.2.1.1 Dose Selection (Preparation)

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background & Rationale. There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each subject.

5.2.2 Timing of Dose Administration

5.2.2.1 Administration of study medication

Omarigliptin or omarigliptin placebo

1) Single-blind, placebo run-in period
   - At Visit 3/Week -2 (beginning of the single-blind run-in period), subjects will take one tablet of study medication (omarigliptin 25 mg matching placebo) as a witnessed dose in the trial site and take 1 subsequent dose of single-blind placebo run-in study medication at home etc. the following week on their scheduled day of dosing. Subjects will be instructed to take study medication on the same day of the week at approximately the same time of day. Study medication may be taken with or without regard to meals or time of day.
2) Phase A (Double-blind period) and Phase B (Open-label period)
   - At Visit 4/Day 1/Randomization (beginning of the double-blind period), each subject will take one tablet of study medication (omarigliptin 25 mg or matching placebo) as a witnessed dose in the clinic and take subsequent doses of double-blind study medication at home etc. the following weeks on their scheduled day of dosing. Subjects will be instructed to take study medication on the same day of the week at approximately the same time of day. Study medication may be taken with or without regard to meals or time of day.

     <Note> "The day of the week of the scheduled dosing" is the first day of the week when this study medication is administered (i.e., Visit 4/Day 1/Randomization). Since then, the subject should take study drug on every same day (i.e., Scheduled day of Dosing) throughout the trial [including Phase B (open-label period)].

The investigator will instruct the subject to contact the site if they vomit within 6 hours of taking their weekly dose of omarigliptin or matching placebo. The investigator will determine whether the subject should take another dose of study medication.

5.2.2.2 Timing of Dosing of Pre-Treatment Period, and Treatment Period Medication on Days of Study Visits

1) The first dose of each medication (Visit 3/Week -2 and Visit 4/Day 1/Randomization)

   The first dose of each medication on a day of Visit 3/Week -2 and Visit 4/Day 1/Randomization [Visit 3/Week -2: Medication for placebo run-in period (matching placebos for omarigliptin 25 mg) and Visit 4/Day 1/Randomization: Medication for Phase A (double-blind period, omarigliptin 25 mg or matching placebos)] must be taken as a witnessed dose at the trial site visit after completion of all procedures and collection of all fasting blood samples.

2) Except for the first dose of each medication (Except of Visit 3/Week -2 and Visit 4/Day 1/Randomization)

   If this is the subject's scheduled day of dosing, study medication should only be taken after completion of all study visit procedures and collection of all fasting blood samples. Otherwise, the next dose should be taken on the next scheduled day. [Same as first dose for Phase B (open-label period) at Visit 8/Week 16]

5.2.2.3 Handling of Missed Doses

Omarigliptin or omarigliptin placebo

The missed one dose of study medication should be taken as soon as the subject remembers. The missed dose can be taken at any day of the 7-day dosing period up to the day before the next scheduled dose. The day of the week of the scheduled dosing should not change as a result of the missed dose.

Example: If a subject has a scheduled day of dosing each Monday, the subject can take a missed dose up to Sunday. The next scheduled dose is still taken the following Monday, even if the missed dose was taken the day before "the day of the week of the scheduled dosing" (Sunday).

Details of each procedure are provided in Section 7 – Trial Procedures

5.2.3 Trial Blinding

A double-blinding technique with in-house blinding will be used (Phase A). Omarigliptin and placebo will be packaged identically so that blind/masking is maintained. The subject, the investigator and Sponsor personnel or delegate(s) who are involved in the treatment or clinical evaluation of the subjects are unaware of the group assignments.

See Section 7.1.4.2, Blinding/Unblinding, for a description of the method of unblinding a subject during the trial, should such action be warranted.

5.3 Randomization or Treatment Allocation

Treatment allocation/randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 2 treatment arms.

Subjects will be assigned randomly in a 2:1 ratio to omarigliptin 25 mg q.w. or placebo, respectively.

5.4 Stratification

Treatment allocation/randomization will be stratified according to the following factors:

1. Use of oral AHA at Visit 1/Screening (insulin + oral AHA or insulin monotherapy)

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the investigator, the Sponsor and the subject.

5.5.1 Prohibited medications

(1) All AHAs (Except for omarigliptin for the trial and insulin agents which will be administered during the trial)

a) Insulin agents [rapid-acting, ultra rapid-acting insulin or pre-mixed insulin/fixed ratio combination of insulin (content percentage of rapid-acting or ultra rapid-acting insulin is greater than 30%)]

b) SUs (sulfonylureas, sulfonamides)

c) Glinides (nateglinide, mitiglinide, repaglinide, etc.)

d) BGs

e) TZD

f) α-GIs

g) DPP-4 inhibitors

h) SGLT2 inhibitors

i) GLP-1 receptor agonists (Such as exenatide or liraglutide)

j) FDC products containing the above active ingredient(s) (Except for insulin agents which will be administered during the trial)

<Note> The subject in Group A can continue single oral AHA taken at Visit 1/Screening thorough to Visit 2/Week -10.

(2) Other investigational drugs

(3) Systemic corticosteroids ≥14 consecutive days or repeated courses

<Note> Inhaled, nasal, and topical corticosteroids which don't have systemic effect are permitted.

Within 10 hours before the visit

(1) Intravenous fluids (other than those having a volume <50 mL without any glucose content)

(2) Glucagon

5.5.2 Limited Concomitant Medications

Medications for complication, which are used prior to Visit 1/Screening and do not meet "Prohibited concomitant medications" in the above section, should be used throughout the study and any changes to the current regimen (e.g., the dosage or administration schedule) are prohibited throughout the study. However the regimen change of the concomitant medications is allowed, only in the case that the investigator judges that it is necessary to change the regimen considering the individual subject's condition and safety.

In addition, subjects can use lipid-lowering medication, anti-hypertension medication or thyroid hormone replacement agents during the trial period. It's preferable that those dosages of medications are stable during the trial period

<Note> Based on section 5.1.3, subjects receive unstable dosage of lipid-lowering medication within 4 weeks prior to Visit 1/Screening, or subjects receive unstable dosage of thyroid hormone replacement therapy within 6 weeks prior to Visit 1/Screening will be excluded from the trial.

5.6 Rescue Medications & Supportive Care

5.6.1 Rescue treatment (up-titration of insulin)

The subject who meets the following glycemic rescue criteria in Table 4 should initiate rescue therapy with up-titration of the insulin that they are receiving during the trial (continuing from Visit 1/Screening).

Table 4 Rescue criteria

Application Timing	Criteria	Administration Timing
After Visit 4/Day 1/Randomization to Visit 10/Week 24	FPG (as reported by the central lab) is repeatedly * confirmed >240 mg/dL two times	At the next scheduled or unscheduled Visit (= Rescue Visit)
After Visit 10/Week 24	FPG (as reported by the central lab) is repeatedly * confirmed >200 mg/dL two times	
* Repeatedly at the scheduled visit (or at unscheduled visit as needed). After initiation of rescue therapy, insulin can be adjusted by judgment of the investigator even if the FPG does not show "repeatedly" the above criteria.		

Subjects that meet rescue criteria will have their insulin dose adjusted as determined clinically appropriate by the investigator to manage glycemic control. The maximum dosage of insulin should follow the maximal approved dose based on its package insert.

During Phase A, up-titration of insulin relative to the dose at Visit 4/Day 1/Randomization may be performed only if the subject has glucose measurements meeting rescue criteria, during Phase B, up-titration will be determined by investigator's assessment of subject's need for glycemic control.

Subjects will continue on study medication after initiation of rescue therapy or down-titration of insulin until completion unless they meet discontinuation criteria (See Section 5.8).

5.6.2 Down-titration of insulin

Subjects who meet the following down-titration criteria (hypoglycemia criteria) may have their insulin down-titrated upon discretion of investigators (i.e., the insulin dose that they were receiving during the trial, which they were continuing from Visit 1/Screening, may be reduced).

1. The subject has hypoglycemic episode with hypoglycemic symptoms, and with an FPG (central lab) ≤70 mg/dL or an SMBG of ≤70 mg/dL
2. The subject has repeated (more than and equal to two times of) FPG (central lab) <80 mg/dL or an SMBG of <80 mg/dL per week, and if the subject is considered at high risk for hypoglycemia by the investigators.

Subjects that meet hypoglycemia criteria will have their insulin dose adjusted as determined clinically appropriate by the investigator to manage glycemic control. There are no restrictions on the number of units the insulin dosage may be reduced. Investigators should decide insulin dosage for each subject based on the package insert for the specific insulin being used.

Subjects will continue on study medication after initiation of rescue therapy or down-titration of insulin until completion unless they meet discontinuation criteria (See Section 5.8).

5.7 Diet/Activity/Other Considerations

5.7.1 Diet therapy

The subject will be instructed to continue the diet therapy which was undergone at Visit 1/Screening. Diet therapy is mandatory and should remain stable throughout the study.

5.7.2 Exercise therapy

The subject will be instructed to continue the exercise therapy which was undergone at Visit 1/Screening. Exercise therapy is mandatory and should remain stable throughout the study, unless it is judged by the investigator to be inappropriate for a subject to observe this rule because of concomitant diseases and adverse event (e.g., arthritis in a lower limb).

5.7.3 Insulin therapy

Insulin will be administered during the trial as monotherapy of pre-mixed insulin/fixed ratio combination of insulin (content percentage of rapid-acting or ultra rapid-acting insulin is lower than or equal to 30%), intermediate or long-acting insulin and type of insulin agents should not be changed during the trial. In addition, the dosage and administration of insulin will be required to follow each package insert.

Insulin dosage must remain unchanged from the Visit 1/Screening dose throughout Phase A (double-blind period, 16 weeks), **unless** hypoglycemia or hyperglycemia rescue criteria are met [Down-titration, see Section 5.6.2 "Down-titration of insulin" or Up-titration, see Section 5.6.1 "Rescue treatment (up-titration of insulin)"].

While during Phase B (open-label period, 36 weeks), dosage adjustments of insulin will be allowed as clinically appropriate to manage the subject's glycemic control. During Phase A (double-blind period) and also Phase B (open-label period), dosage changes are required if subject meets rescue criteria [Up-titration, see Section 5.6.1 "Rescue treatment (up-titration of insulin)"] or hypoglycemia criteria [Down-titration, see Section 5.6.2 "Down-titration of insulin"].

At morning at the each study visit, the subjects should visit the trial site before administrating insulin. The subject should administer insulin according to its package insert for each insulin agent after completion of all study visit procedures and collection of all fasting blood samples.

The missing dose should be administered in accordance with the package insert for each insulin agents.

5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal procedures; including specific details regarding withdrawal from Future Biomedical Research, are provided in Section 7.1.4 – Other Procedures.

A subject must be discontinued from the trial if:

- The subject withdraws consent.

A subject must be discontinued from treatment for any of the following reasons:

- Lack of efficacy

  The effect of the study medication is not sufficient and study continuation is judged inappropriate by the investigator. If the following case occurs, the investigator should consider the discontinuation from the trial:

  a) After Visit 4/Day 1/Randomization to Visit 10/Week 24, FPG consistently >240 mg/dL (as reported by the central lab) ≥4 weeks after maximal adjustment of insulin [Up-titration, see Section 5.6.1 "Rescue treatment (up-titration of insulin)"].

b) After Visit 10/Week 24, FPG consistently >200 mg/dL (as reported by the central lab) ≥4 weeks after maximal adjustment of insulin [Up-titration, see Section 5.6.1 "Rescue treatment (up-titration of insulin)"].

<Note> The investigator should instruct the subject to visit the trial site as soon as possible to perform the repeat test once he/she meets the threshold of FPG criteria. If result of re-test does not meet the threshold of FPG criteria, the subject can continue to attend the trial.

- Adverse event

In the case that the investigator assesses that administration of the study medication should be discontinued due to the occurrence of adverse events. When subjects meet the following criteria, they should discontinue the study, regardless of the investigator's assessment (except for hypoglycemia).

a) Hypoglycemia

Subject meets any one of the following criteria without a reasonable explanation (such as increased physical activity or skipped meal)

(1) Repeated (2 or more episodes since the prior study visit) FPG (as reported by the central lab) or finger stick glucose (FSG) <50 mg/dL with or without symptoms of hypoglycemia, which persists despite progressive down-titration of insulin agents.

(2) Repeated (2 or more episodes since the prior study visit) FPG (as reported by the central lab) or FSG ≤70 mg/dL with symptoms of hypoglycemia, which persists despite progressive down-titration of insulin agents.

<Note>The subject must be discontinued from the trial if the subject is meeting above criteria despite down-titration of insulin, or the investigator judges administrating of insulin have to be discontinued (There are no limit for down-titration of insulin. The investigator will decide dose of insulin when insulin is down-titrated, based on each package insert of insulin agents.).

b) Increased ALT or AST

(1) Elevation in ALT and/or AST ≥three times the ULN as specified in Appendix 12.5,OR

(2) Elevations in ALT and/or AST ≥ three times the ULN with concurrent total bilirubin ≥two times the ULN and alkaline phosphatase (ALP) <two times the ULN (See "Event of Clinical Interest (ECI) Guidance for Potential Drug-Induced Liver Injury (DILI) in Clinical Trials guidance document").

c) Reduction in eGFR

If the repeat measurement performed as early as possible meets the criteria in Table 5, the subject must be discontinued from the trial.

Table 5 Discontinuation criterion of eGFR

Parameter	Study Limit for Discontinuation
eGFR [1]	<30 mL/min/1.73 m^2
[1] eGFR (mL/min/1.73 m^2) = 194 x serum Cr $^{-1.094}$ x age (years) $^{-0.287}$ (x 0.739 for female).	

d) Pancreatitis

If a subject is suspected of having pancreatitis, study medication should be interrupted and if pancreatitis is confirmed, study medication should be discontinued.

- Protocol Violation

  It becomes inappropriate to continue study treatment as a result of a significant protocol deviation.

- Lost to follow-up

  When a subject stops visiting a site after initiating study drug, he or she will be contacted via letter or telephone call to confirm the reason for missed visits, dosing of study drug, and the subsequent course as much as possible.

- Subject moved

  When the subject has either moved or relocated and is no longer able to participate in the study.

- Pregnancy

  <Note> A positive urine pregnancy test requires immediate interruption of study medication until serumβ-human chorionic gonadotropin (β-hCG) can be performed and found to be negative. Subject must be permanently discontinued and followed per Section 7.2.2 if pregnancy is confirmed by a positive serum pregnancy test.

- In addition, investigator's decision that subject should discontinue for any other reason.

  Example: Requirement for one of the excluded medications listed in Section 5.5.

  If a subject discontinues study medication, he/she should complete all Discontinuation Visit procedures as listed in the Trial Flow Chart (see Section 6.0). All subjects will be followed until resolution (i.e., return to baseline values, diagnosis determined or new stable state established, based upon investigator and the Sponsor) for any adverse events or any laboratory safety test abnormality resulting in discontinuation from study medication.

Discontinuation from treatment is “permanent.” Once a subject is discontinued, he/she shall not be allowed to restart treatment.

5.9 Subject Replacement Strategy

A subject who discontinues from the trial will not be replaced.

5.10 Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent form. The overall trial ends when the last subject completes the last study-related phone-call or visit, discontinues from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator).

5.11 Clinical Criteria for Early Trial Termination

The clinical trial may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the trial population as a whole is unacceptable. In addition, further recruitment in the trial or at (a) particular trial site(s) may be stopped due to insufficient compliance with the protocol, GCP and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

6.0 TRIAL FLOW CHART

		Screening period (≤ 2 weeks)	Pre-treatment period (2 weeks or 10 weeks)[2]			Treatment period (52 weeks)											Rescue visit[4]	Discontinuation visit	Telephone contact
			(8 weeks)		Placebo run-in (2 weeks)	Phase A (Double-blinded period, 16 weeks)				Phase B (Open-label period, 36 weeks)									
		Screening	Wk-10[3]	Wk-6[3]	Wk-2	Day1	Wk4	Wk8	Wk12	Wk16	Wk20	Wk24	Wk28	Wk32	Wk36	Wk44	Wk52			
		Visit 1	Visit 2[3]	Tele-phone contact[3]	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15			
Allowed range of visit[1]	Screening period	0	≤ 2 wks(A)		≤ 2 wks(B)															
	Wash-out period (Group A)		0	±7 days	±3 days															
	Placebo run-in period				0	+3 days														
	Treatment period					0	±7 days	±7 days	±7 days	-6 days	±7 days	±7days	±7 days	±7 days	±7 days	±7 days	±3 days			
General Study Procedure																				
Informed Consent[5]		X[13]																		
Informed Consent for FBR		X																		
Providing Subject Identification Card		X																		
Inclusion/Exclusion Criteria evaluation		X	A		X	X														
Medical History evaluation		X																		
Prior/Concomitant Medication Review		X	A		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Instruction to discontinue oral AHA (except for insulin agents)			A																	
Diet/exercise therapy counseling		X	A		X	X	X	X	X	X	X	X	X	X	X	X		X		
Instruction for recording of patient's log and dispensing		X	A		X	X	X	X	X	X	X	X	X	X	X	X				
Collection and Review of Patient's Log			A		X	X	X	X	X	X	X	X	X	X	X	X	X	X[14]	X	
Providing SMBG devise and instruction			A		B															
Instructions on hypoglycemic symptoms, management, and recording of hypoglycemic assessment log (HAL)			A		B															
Dispensing HAL			A		X	X	X	X	X	X	X	X	X	X	X	X				
Patient Registration		X	A		X	X	X	X	X	X									X[15]	
Assignment of Treatment/Randomization Number						X														
Clinical Procedures/Assessments																				
Confirmation of Diet and exercise therapy		X	A		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Sign (body weight, blood pressure, and pulse rate)		X	A		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Sign (height)		X																		
SMBG at each visits			A		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Review of HAL and assessment of hypoglycemia					A	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse event monitoring			A	A	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

		Screening period (≤ 2 weeks)	Pre-treatment period (2 weeks or 10 weeks)[2]			Treatment period (52 weeks)												Rescue visit[4]	Discontinuation visit	Telephone contact
			(8 weeks)		Placebo run-in (2 weeks)	Phase A (Double-blinded period, 16 weeks)				Phase B (Open-label period, 36 weeks)										
		Screening	Wk-10[3]	Wk-6[3]	Wk-2	Day1	Wk4	Wk8	Wk12	Wk16	Wk20	Wk24	Wk28	Wk32	Wk36	Wk44	Wk52			
		Visit 1	Visit 2[3]	Tele-phone contact[3]	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15			
Allowed range of visit[1]	Screening period	0	≤ 2 wks(A)		≤ 2 wks(B)															
	Wash-out period (Group A)		0	±7 days	±3 days															
	Placebo run-in period				0	+3 days														
	Treatment period					0	±7 days	±7 days	±7 days	-6 days	±7 days	±7days	±7 days	±7 days	±7 days	±7 days	±3 days			
12-lead ECG Locally						X				X							X		X	
Assessment for necessity of rescue treatment (up-titration of insulin agents)[4]							X	X	X	X	X	X	X	X	X	X				
Laboratory Procedures/Assessments																				
HbA1c		X			X[6]	X	X	X	X	X		X		X		X	X	X[7]	X[7]	
Glucose		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
1,5-AG[8]						X				X								X[8]	X[8]	
Hematology		X				X		X		X		X			X		X		X	
Blood chemistry		X			X	X		X		X		X			X		X		X	
Endocrinological[9]		X																		
Urinalysis		X				X				X					X		X		X	
Urine Pregnancy Test[10]		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood (deoxyribonucleic acid, DNA) for FBR[11]						X														
Plasma and serum sample for FBR[11]						X				X							X	X	X[11]	
Study Medication																				
Witness Dose[12]					X	X														
Single-blinded study medication dispensing					X															
Phase A (Double-blinded) study medication dispensing						X	X	X	X											
Phase B (Open-label) study medication dispensing										X	X	X	X	X	X	X				
Medication compliance monitoring (Study medication and insulin)		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

X: Essential items, A: Only Group A, B: Only Group B

1. Origination of Visit 2/Week -10 allowance is based on Visit 1/Screening, origination of Visit 3/Week -2 allowance is based on Visit 2/Week -10, origination of Visit 4/Day 1/Randomization allowance is based on Visit 3/Week -2 and origination after Visit 4/Day 1/Randomization allowance is based on Visit 4/Day 1/Randomization, respectively.
2. For a subject who <u>needs</u> wash-out of oral AHA, the duration of the pre-treatment period is 10 weeks (Group A). For a subject who does <u>not need</u> wash-out of oral AHA, the duration of the pre-treatment period is 2 weeks (Group B).
3. For subjects in Group A. A subject in Group B proceeds to Visit 3/Week -2 after Visit 1/Screening, skipping Visit 2/Week -10.
4. See Section 7.1.5.3 for procedures to be performed at Rescue Visit.
5. Informed consent must be obtained before any study procedures of Visit 1/Screening.
6. If a subject in Group B performed the procedures of Visit 1/Screening within 2 weeks before Visit 3/Week -2, HbA1c measurement is not needed at Visit 3/Week -2. The subject may be deemed

		Screening period (≤ 2 weeks)	Pre-treatment period (2 weeks or 10 weeks)[2]			Treatment period (52 weeks)											Rescue visit[4]	Discontinuation visit	Telephone contact
			(8 weeks)		Placebo run-in (2 weeks)	Phase A (Double-blinded period, 16 weeks)				Phase B (Open-label period, 36 weeks)									
		Screening	Wk-10[3]	Wk-6[3]	Wk-2	Day1	Wk4	Wk8	Wk12	Wk16	Wk20	Wk24	Wk28	Wk32	Wk36	Wk44	Wk52			
		Visit 1	Visit 2[3]	Tele-phone contact[3]	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15			
Allowed range of visit[1]	Screening period	0	≤ 2 wks(A)		≤ 2 wks(B)															
	Wash-out period (Group A)		0	±7 days	±3 days															
	Placebo run-in period				0	+3 days														
	Treatment period					0	±7 days	±7 days	±7 days	-6 days	±7 days	±7days	±7 days	±7 days	±7 days	±7 days	±3 days			

to meet the HbA1c criterion of Visit 3/Week -2 by HbA1c value of Visit 1/Screening.

7. HbA1c should not be drawn if Discontinuation Visit or the Rescue Visit occurs within 4 weeks after Visit 4/Day 1/Randomization
8. 1,5-AG will be only collected at Phase A (double-blinded period).
9. Endocrinological: C-peptide and TSH
10. Pregnancy test: Urinary hCG. Pregnancy test will be performed at the site only for females of childbearing potential. Subjects with a positive urine pregnancy test from taking study medication for the treatment period will have a confirmatory serum β-hCG test performed in the central laboratory as a pregnancy test
11. Informed consent for FBR samples must be obtained to collect the DNA, plasma, and serum samples. The FBR sample for DNA analysis should be obtained pre-dose, at Visit 4/Day 1/Randomization, as the last sample drawn, and on subjects who qualify for randomization. The sample may be obtained at a later date during the study after the FBR informed consent is obtained. The plasma and serum samples for FBR should be collected at Visit 4/Day 1/Randomization [pre-dose of study medication for Phase A (double-blind period)], Visit 8/Week 16 [pre-dose of study medication for Phase B (open-label period)], Visit 15/Week 52 or Discontinuation Visit, and the visit when the rescue therapy is initiated (pre-dose of up-titrated insulin) (if applicable). For the FBR serum and plasma, samples should be collected at all-time points, even if the pre-dose or other time point was not collected.
12. The witnessed dose will be taken after completion of all procedures for the study visit (See Section 5.2.2.2 for details)
13. Visit 1/Screening can be conducted separately from the consent date.
14. Patient's Log will be confirmed, but it will not be collected at rescue visit.
15. Patient registration at discontinuation will be conducted during only Phase A (double-blind period)

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential subject prior to participating in a clinical trial or Future Biomedical Research. If there are changes to the subject's status during the trial (e.g., health or age of majority requirements), the investigator or qualified designee must ensure the appropriate consent is in place.

7.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent to the subject, answer all of his/her questions, and obtain written informed consent before

performing any procedure related to the Future Biomedical Research sub-trial. A copy of the informed consent will be given to the subject.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.1.2.1 Contraception

Non-pregnant, non-breast-feeding women may be enrolled if they are considered highly unlikely to conceive. Highly unlikely to conceive is defined as the relevant part of Section 5.1.2 –Subject Inclusion Criteria.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement (See Section 5.1.2) for the duration of the study and for 21 days after the last dose of study medication. If there is any question that a subject will not reliably comply with the requirements for contraception, she should not be entered into the study.

7.1.1.3 Subject Identification Card

All subjects will be given a Subject Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with a Subject Identification Card immediately after the subject provides written informed consent. At the time of treatment allocation/randomization, site personnel will add the treatment/randomization number to the Subject Identification Card.

The subject identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about trial medication/vaccination in emergency situations where the investigator is not available.

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee.

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified wash-out requirement, and record any prior medication taken by the subject below;

1. Omarigliptin (including placebo for treatment period): any time
2. AHAs other than omarigliptin: within 12 weeks prior to Visit 1/Screening.
3. Prior medications other than AHAs: within 6 weeks prior to Visit 1/Screening.

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial.

7.1.1.6 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to randomization or treatment allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

7.1.1.7 Assignment of Treatment/Randomization Number

All eligible subjects will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the subject for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization number is assigned to a subject, it can never be re-assigned to another subject.

A single subject cannot be assigned more than 1 treatment/randomization number.

7.1.1.8 Trial Compliance (Medication/Diet/Activity/Other)

Interruptions from the protocol specified treatment plan of the study medication for compliance (treatment period) <75% require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

Administration of trial medication at Visit 3/Week -2 and Visit 4/Day 1/Randomization will be witnessed by the investigator and/or trial staff.

7.1.1.9 Diet and exercise therapy counseling

From Visit 1/Screening, the subject will be instructed to continue the diet and exercise therapy which was undergone at Visit 1/Screening with reference to "Treatment Guidance for Diabetes" [1]. Diet and exercise therapy is mandatory and should remain stable throughout the study. In the case of exercise therapy, this condition does not necessarily need to be met if it is judged to be inappropriate for a subject because of complication[s] and adverse event[s] (e.g., joint disease in a lower limb).

The concrete instruction may be changed as long as it can be thought that the change does not have impact on glycemic control based on the intake/consume calories instructed at Visit 1/Screening, if the subject's physical activity changed or he/she became unable to adhere to the exercise therapy instructed at Visit 1/Screening due to an adverse event and so on.

Example:

1) *The daily intake calorie was reduced since the subject's physical activity was changed from heavy manual work to desk work due to job switch.*
2) *The instruction was changed to the exercise of the upper body which consumes similar daily calorie to walking since a walking is difficult for the subject due to ankle sprain.*

7.1.1.10 Patient Registration

The investigator or trial staff will register the subjects via the system of the patient registration center at each scheduled visit. Patient registration will be done during Phase A (double-blind period).

7.1.1.11 Instruction for recording of patient's log and dispensing

The subject will be instructed to record diet and exercise therapy compliance and insulin compliance in the patient's log from Visit 1/Screening. From Visit 2/Week -10 (Group A) or from Visit 3/Week -2 (Group B), the subject will be instructed to record SMBG data in the patient's log in addition to diet and exercise therapy compliance and insulin compliance. In addition, the subject will be instructed to record study medication compliance in the patient's log from Visit 3/Week -2.

The patient's log will be dispensed at Visit 1/Screening. The subject will be instructed to bring the subject-completed patient's log to the trial site at each visit.

7.1.1.12 Collection and review of patient's log

The patient's log dispensed at the previous visit will be collected, and the investigator should check the diet and exercise therapy compliance, insulin compliance, study medication compliance, and SMBG value. The investigator should make effort to prevent the reoccurrence of non-compliance by an instruction to the subject, if the non-compliance with diet and exercise therapy, taking insulin therapy and/or taking study medication were found. If SMBG value ≤70 mg/dL is in patient's log, the investigator should check that its information is also in the HAL.

7.1.1.13 Providing SMBG devise and instruction

Glucose meters will be supplied to all subjects at Visit 2/Week -10 (Group A) or Visit 3/Week -2 (Group B) in order to perform SMBG. The subjects will be instructed on the procedure to perform FSG measurements. The subjects will monitor their FSG concentrations with a frequency determined appropriate by the investigator with a minimum of 2 fasting (without taking insulin and study medication) determinations per week (2 or more frequency may be set based upon his/her assessment of the subject's risk of increasing glucose concentrations). The subject will also be instructed to perform SMBG without fail if any hypoglycemic symptom[s] occurs.

The subjects should be counseled to contact the trial site since it is necessary that the investigator assesses an adverse event and a need for rescue therapy and judges the continuation of the study for the subjects.

1) FSG ≤70 mg/dL throughout the duration of the entire study
2) Fasting FSG >230 mg/dL before Visit 4/Day 1/Randomization
3) Fasting FSG >240 mg/dL after Visit 4/Day 1/Randomization through Visit 10/Week 24
4) Fasting FSG >200 mg/dL after Visit 10/Week 24

7.1.1.14 Instructions on hypoglycemic symptoms, management, and recording of HAL

The subject will be informed that there is a possibility of developing hypoglycemic symptoms (e.g., weakness, dizziness, shakiness, increased sweating, palpitations, or confusion) after administration of the study medications. The subject will be instructed to complete the HAL for any symptomatic episodes he or she believes may represent hypoglycemia. If a symptom that may be considered hypoglycemia occurs, hypoglycemia for which assistance was required (i.e., severe hypoglycemia) occurs and/or FSG ≤70 mg/dL with or without symptoms, the subject will be instructed to;

1. Promptly take countermeasures, such as the ingestion of glucose (5 - 10 g) or glucose supplement
2. If a symptom that may be considered hypoglycemia occurs: Immediately (before taking glucose or within 2-3 minutes after taking glucose) perform a FSG measurement
3. Complete all symptoms which occurred in HAL
4. Contact the investigational site and report (the subject's condition and/or symptom at occurrence, with/without SMBG measurement and SMBG value, with/without taking glucose, a need for assistance, entry of HAL, etc.)
5. Bring HAL completed by the subjects at the next visit.

7.1.1.15 Dispensing HAL

The patient's log will be dispensed from Visit 2/Week -10 (Group A) or from Visit 3/Week -2 (Group B). The subject will be instructed to bring the HAL to the trial site at each visit.

7.1.1.16 Instruction to discontinue oral AHA (except for insulin agents)

Subject of Group A will be instructed to discontinue oral AHA (except for insulin agents) after Visit 2/Week -10.

7.1.2 Clinical Procedures/Assessments

In order to minimize variability, it is preferred that the same individual(s) perform the same procedure(s)/evaluation(s) for all subjects at each trial site.

7.1.2.1 Confirmation of Diet and exercise therapy

From Visit 1/Screening, subject will be confirmed to continue the diet and exercise therapy which was undergone at Visit 1/Screening with reference to "Treatment Guidance for Diabetes" [1]. Diet and exercise therapy is mandatory and should remain stable throughout the study. In the case of exercise therapy, this condition does not necessarily need to be met if it is judged to be inappropriate for a subject because of complication[s] and adverse event[s] (e.g., joint disease in a lower limb).

7.1.2.2 Measuring of Vital signs

Blood pressure, weight and height will be measured according to the procedures in Section 12.4.

7.1.2.3 SMBG at each visits

Subjects will be instructed to measure SMBG by FSG at each scheduled visit from Visit 2/Week -10 (Group A) or Visit 3/Week -2 (Group B).

7.1.2.4 Review of HAL and assessment of hypoglycemia

HAL will be reviewed to record symptoms that subjects believe are related to hypoglycemia and/or FSG measurements on the HAL. Each episode should be evaluated by the investigator and recorded on the Hypoglycemia Assessment (HA) electronic case report form (eCRF). If the event is considered by the Investigator to be an adverse event of hypoglycemia or asymptomatic hypoglycemia, the event should also be reported on the adverse event eCRF as an adverse event of hypoglycemia or asymptomatic hypoglycemia, respectively (see Section 7.2.4).

7.1.2.5 12 lead ECG

12-lead ECG will be measured in each site and the investigator will read it.

7.1.2.6 Assessment for necessity of rescue treatment (up-titration of insulin agents)

FPG (as reported by the central lab) will be assessed whether it meet rescue criteria which is shown in Table 4 after Visit 4/Day 1/Randomization. If the FPG meets rescue criteria, rescue therapy will be started to up-titrate of insulin agents that is administered from Visit 1/Screening. Details are described at Section 5.6.1.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below.

7.1.3.1 Laboratory efficacy Evaluations (Hematology and blood chemistry)

Laboratory efficacy tests are specified in Table 6.

Table 6 Laboratory Efficacy Tests (Hematology, Blood chemistry)

Hematology	Blood chemistry
HbA1c	1, 5-AG
	Glucose

Laboratory fating tests other than HbA1c will be performed after at least a 10-hour fast.

7.1.3.2 Laboratory safety tests (Hematology, blood chemistry, urinalysis and other)

Laboratory safety tests are specified in Table 7.

Table 7 Laboratory Safety Tests (Hematology, Blood Chemistry, Urinalysis and Other)

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-hCG, (if urine pregnancy test is positive)
Hemoglobin	Alkaline phosphatase	Ketones	TSH
Platelet count	ALT	pH	C-Peptide
Erythrocytes	AST	Protein	
White blood cell (WBC , total)	Blood Urea Nitrogen	Urobilinogen	
WBC (differential)	Calcium		
	Chloride		
	Creatinine/Glomerular Filtration Rate Estimation		
	Creatine Kinase		
	Direct bilirubin (if total bilirubin is over upper limit normal)		
	Gamma Glutamyl Transferase		
	High-density lipoprotein cholesterol		
	Lactate Dehydrogenase		
	Low-density lipoprotein cholesterol		
	Magnesium		
	Phosphorus		
	Potassium		
	Sodium		
	Total Bilirubin		
	Total Cholesterol		
	Total protein		
	Triglycerides		
	Uric acid		

Laboratory safety tests other than hematology tests and serum β-hCG will be performed after at least a 10-hour fast.

Pregnancy test

All pre-menopausal women who are not surgically sterilized participating in the study will have a urine pregnancy test at each study visit indicated on the Study Flow Chart. Urine pregnancy test will be performed at each trial site. Subjects with a positive urine pregnancy test after taking study medications for the treatment period will have a confirmatory serum β-hCG test at central laboratory as a pregnancy test.

A positive urine pregnancy test requires immediate interruption of study medication until serum β-hCG is performed and found to be negative. A subject must be permanently

discontinued and followed (see Section 5.8) if pregnancy is confirmed by a positive serum pregnancy test.

7.1.3.3 Future Biomedical Research Samples

The following specimens are to be obtained as part of Future Biomedical Research:

1) DNA for future research
2) Plasma for future research
3) Serum for future research

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the Visit 15/Week 52 should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events.

7.1.4.1.1 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the subject's consent for Future Biomedical Research will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the subject of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

7.1.4.2 Subject Blinding/Unblinding

When the investigator or delegate needs to identify the drug used by a subject and the dosage administered in case of emergency e.g., the occurrence of serious adverse experiences, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or delegate the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the sponsor. Prior to contacting the emergency unblinding call center to request unblinding of a subject's treatment assignment, the investigator or delegate must enter the

intensity of the adverse experiences observed, the relation to study drug, the reason thereof, etc., in the medical chart etc. Subjects whose treatment assignment has been unblinded by the investigator/delegate and/or non-study treating physician must be discontinued from study drug.

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date, reason and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Only the principal investigator or delegate and the respective subject's code should be unblinded. Other trial site personnel and Sponsor personnel directly associated with the conduct of the trial should not be unblinded. Subjects whose treatment assignment has been unblinded by the investigator/delegate and/or non-study treating physician must be discontinued from study drug.

At the end of the trial, random code/disclosure envelopes or lists and unblinding logs are to be returned to the Sponsor or designee.

7.1.4.3 Calibration of Critical Equipment

The investigator or qualified designee has the responsibility to ensure that any critical device or instrument used for a clinical evaluation/test during a clinical trial that provides important information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the trial site.

Critical Equipment for this trial includes:

Not applicable in this study.

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

1 Scheduling Visit and Study Duration

At the end of each study visit, the next study visit should be scheduled. Every effort should be made to adhere to the visit schedule (refer to Study Flow Chart – Section 6.0).

Prior to each visit, subjects should be contacted and reminded of:

1) The date and time of appointment.

   Note: Subject should visit the trial site in the morning.

2) The requirement to fast for at least 10 hours prior to the trial site visit (no food or drink except for water).

3) The requirement not to take intravenous fluids (other than those having a volume <50 mL without any sugar content) and/or glucagon within 10 hours of the visit to the trial site.

4) The requirement not to take study medication and insulin agents at home the morning of the visit. Subject should bring any unused study drugs prescribed, without disposal and intake.

   Note: Non-study medications that are not AHA medications should be taken as directed by the prescribing physician.

5) The requirement to bring study medication (including containers), blood glucose meter, HAL and Patient's Log to the study visit.

7.1.5.1 Screening

Up to 12 weeks prior to randomization, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. The subject will be identified as Group A (pre-treatment period is 10 weeks) or Group B (pre-treatment period is 2 weeks) based on their pre-treatments for T2DM (use of oral AHA) at Visit 1/Screening (See Figure 2).

For the subject who meets all the eligibility criteria of Visit 1/Screening, patient's log will be dispensed and they will be instructed for recording of patient's log. The subject will be instructed to bring the subject-completed patient's log to the trial site at each visit. In addition, the subject will be instructed to continue the diet and exercise therapy which was undergone at Visit 1/Screening.

For subject in Group A, Visit 2/Week -10 is scheduled within 2 weeks after Visit 1/Screening. For subject in Group B, Visit 3/Week -2 is scheduled within 2 weeks after Visit 1/Screening (Visit 2/Week -10 will be skipped). The subject who meets laboratory criteria of Visit 1/Screening can proceed to the next visit.

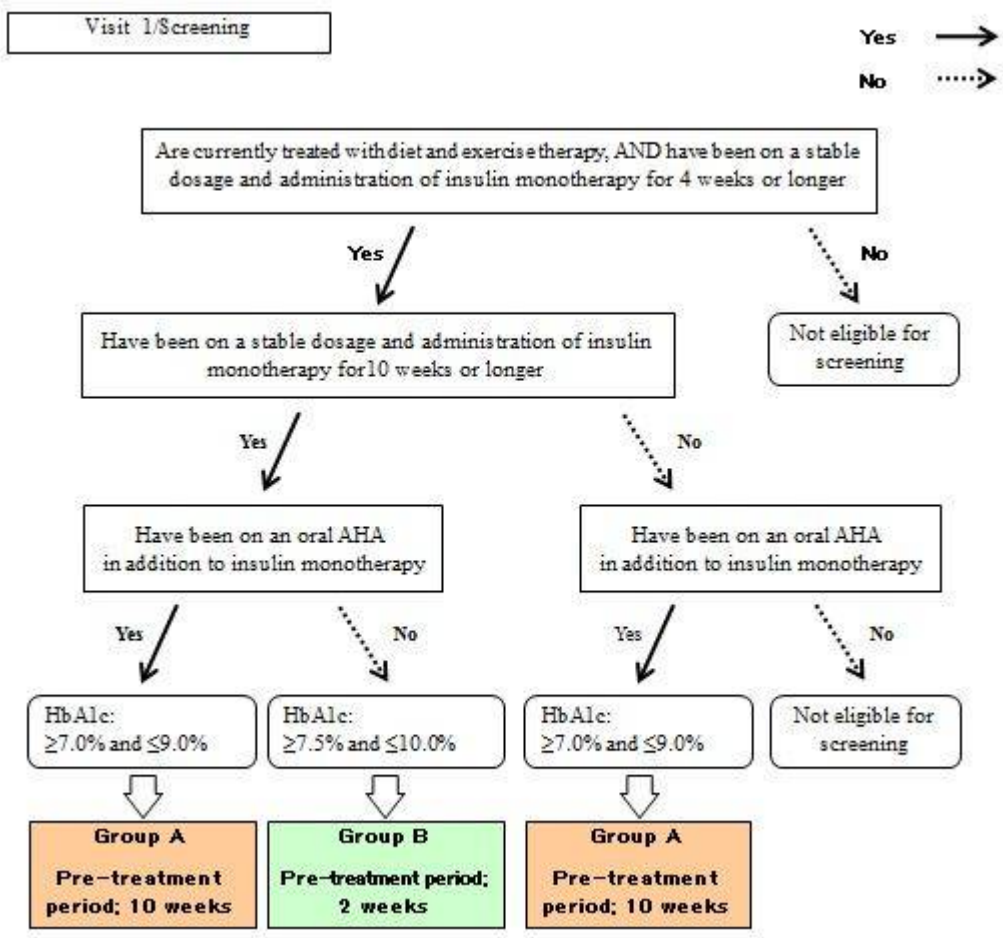


Figure 2 Selection of subject group (Visit 1/Screening)

7.1.5.2 Pre-Treatment Period

1) Visit 2/Week -10 (only for subject in Group A)

   The subject, who meets the enrollment criteria of Visit 2/Week -10 and can continue the study based on the review of concomitant medications and the monitoring of adverse events and implementation status of diet/exercise therapy, will undergo all study procedures of Visit 2/Week -10 including the following instructions:

   (1) SMBG instruction

   (2) Instructions on hypoglycemic symptoms, management of hypoglycemic symptoms and recording of HAL and subject's log

   (3) Instructions on discontinuation of an oral AHA other than insulin

After the above procedures have been completed, a SMBG meter will be dispensed. Next visit (Visit 3/Week -2) is arranged 8 weeks (± 3 days) after Visit 2/Week -10.

2) Telephone Contact/Week -6 (only for subject in Group A)

Investigators or trial staff contacts the subjects by phone at Week -6 (between Visit 2/Week -10 and Visit 3/Week -2) to confirm developments of any adverse events. If adverse events are confirmed, investigator will make a decision for continuing the subject on trial.

3) At Visit 3/Week -2

(1) For the subject in Group A: The subject, who meets the enrollment criteria of Visit 3/Week -2 and can continue the study based on the review of concomitant medications and the monitoring of adverse events and implementation status of diet/exercise therapy, will undergo all study procedures of Visit 3/Week -2.

(2) For the subject in Group B: The subject, who meets the enrollment criteria of Visit 3/Week -2 and can continue the study based on the review of concomitant medications and the monitoring of adverse events and implementation status of diet/exercise therapy, will undergo all study procedures of Visit 3/Week -2 including the following instructions:

a) SMBG instruction

b) Instructions on hypoglycemic symptoms, management of hypoglycemic symptoms and recording of HAL and subject's log

After the above procedures have been completed, a SMBG meter will be dispensed.

(3) For all subjects: After the above procedures have been completed, the study drugs will be dispensed in single-blinded manner to the subject and his/her will take them as a witnessed dose in the trial site. Next visit (Visit 4/Day 1/Randomization) is arranged 2 weeks (+ 3 days) after Visit 3/Week -2. The subject who meets laboratory criteria of Visit 3/Week -2 can proceed to Visit 4/Day 1/Randomization.

7.1.5.3 Treatment Period

1) At Visit 4/Day 1/Randomization

The subject, who meets the enrollment criteria of Visit 4/Day1/Randomization and can continue the study based on the review of concomitant medications, the monitoring of adverse events, implementation status of diet/exercise therapy, compliance of insulin and compliance of study medications, will undergo all study procedures of Visit 4/Day 1/Randomization (except for taking study medication, patient registration and dispensing of study medication). For subjects who meet the enrollment criteria of Visit 4/Day 1/Randomization and are judged as eligibility, subjects are registered via the subject registration center to be assigned the randomization number. The subjects will be randomized in a 2:1 ratio to receive either omarigliptin 25 mg q.w. or placebo, and stratified by use of oral AHA. After patient registration of Visit 4/Day 1/Randomization is completed, the study drugs will be dispensed in double-blinded manner to the subject and his/her will take them as a witnessed dose in the trial site.

2) From Visit 5/Week 4 to Visit 14/Week 44

The subject, who can continue the study based on the review of concomitant medications and the monitoring of adverse events, will undergo all study procedures of each visit (except for patient registration and dispensing of study medication).

After the above procedures have been completed, the study drugs will be dispensed to the subject in double-blinded manner from Visit 5/Week 4 to Visit 7/Week 12 and in open manner from Visit 8/Week 16, and his/her will take them if the visit is subject's scheduled day of dosing. After registration [subject registration will be done during Phase A (double-blind period)], study medication will be dispensed.

3) At Visit 15/Week 52 or Discontinuation Visit

The subject will conduct all study procedure of Visit 15 (± 3 days of scheduled visit) or the discontinuation visit.

4) At Rescue Visit

Subjects meeting rescue criteria (See Section 5.6.1 Table 4) will continue in the study until completion unless they meet discontinuation criteria (See Section 5.8). Rescue therapy must be initiated at either a scheduled or unscheduled visit at the investigational site, and not by a telephone visit. Immediately prior to initiation of rescue therapy, subjects meeting rescue criteria must undergo the Rescue Visit procedures as referenced in section 6.0.

Note: FBR (plasma and serum) samples should be collected at the Visit before initiating rescue therapy (administration of up-titrated insulin agents) before administration of insulin agents as possible.

7.1.5.4 Post trial

Twenty one days after the last dose of study drug for the treatment period or later, a follow up contact will be conducted by having subject visit or contacting the subject via telephone to collect any serious adverse events and any events of clinical interest (ECI) information that might have occurred within the 21 days.

Note: In the event any serious drug-related adverse events occurred later than 21 days after the last dose of study drug, it will be subjected to the follow-up evaluation.

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient 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 unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

Adverse events may occur during clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

All adverse events that occur after the consent form is signed but before taking study medication (including study medication for placebo run-in period) must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of taking study medication (including study medication for placebo run-in period) through 21 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Electronic reporting procedures can be found in the Electronic Data Capture (EDC) data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

In this trial, an overdose is any dose higher than defined below.

1) Dosing with higher than a total of 25 mg of omarigliptin or matching placebo at once.

2) Dosing with higher than a total of 50 mg omarigliptin or matching placebo within 8 days.

If an adverse event(s) is associated with ("results from") the overdose of Sponsor's product or vaccine, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Sponsor's product or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before taking study medication (including study medication for placebo run-in period) must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations that occur from the time of taking study medication (including study medication for placebo run-in period) through 21 days following cessation of Sponsor's product must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event.

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

- Is a cancer;
- Is associated with an overdose.

Refer to Table 8 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until taking study medication (including study medication for placebo run-in period), any serious adverse event, or follow up to a serious adverse event, including death due to any cause, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from

the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at taking study medication (including study medication for placebo run-in period) through 21 days following cessation of treatment, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

All subjects with serious adverse events must be followed up for outcome.

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

For the time period beginning when the consent form is signed until taking study medication (including study medication for placebo run-in period), any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at taking study medication (including study medication for placebo run-in period) through 21 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the Sponsor’s product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

7.2.4 Guidance on Adverse Events Related to Glycemia

7.2.4.1 Hyperglycemia

An adverse event of hyperglycemia requires that a subject have one or more symptoms (e.g., increased thirst, polyuria) typically associated with an increased glucose level. At the discretion of the investigator, this may be captured as an adverse event of "hyperglycemia." This diagnosis may be supported by, but does not require, results from a glucose meter or the trial central laboratory. Further, at the discretion of the investigator, an elevated blood glucose value without associated symptoms that is considered to be an adverse event may be reported as an adverse event of "increased blood glucose. "General guidance regarding the determination as to whether an event is considered to be an adverse event should be followed (see Section 7.2.5).

7.2.4.2 Hypoglycemia

1) Documentation

   Regardless of whether an episode is considered an adverse event, the HA eCRF must be completed for the following:

   (1) all episodes determined by the investigator to be hypoglycemia (symptomatic or asymptomatic)

   (2) all glucose values ≤70 mg/dL

2) Guidance

   All episodes considered as likely to represent symptomatic hypoglycemia by the investigator should be captured as an adverse event of "symptomatic hypoglycemia." This diagnosis may be supported by, but does not require, confirmatory blood glucose results (such as those measured using a finger stick or from a clinical laboratory sample). Further, at the discretion of the investigator, an asymptomatic blood glucose value ≤70 mg/dL may be reported as an adverse event of "asymptomatic hypoglycemia." General guidance regarding the determination as to whether an event is considered to be an adverse event should be followed (see Section 7.2.5).

7.2.5 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in Table 8. The investigator's assessment of causality is required for each adverse event. Refer to Table 8 for instructions in evaluating adverse events.

Table 8 Evaluating Adverse Events

Maximum Intensity	**Mild**	awareness of sign or symptom, but easily tolerated (for pediatric trials, awareness of symptom, but easily tolerated)
	Moderate	discomfort enough to cause interference with usual activity (for pediatric trials, definitely acting like something is wrong)
	Severe	incapacitating with inability to work or do usual activity (for pediatric trials, extremely distressed or unable to do usual activities)
Seriousness	A serious adverse event (AE) is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred [Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.]; or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect (**in offspring of subject taking the product regardless of time to diagnosis); or	
	Is a cancer (although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); **or**	
	Is associated with an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Sponsor's product to be discontinued?	
Relationship to Sponsor's Product	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event:	
	Exposure	Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Sponsor's Product (continued)	**The following components are to be used to assess the relationship between the Sponsor's product and the AE: (continued)**	
	Dechallenge	Was the Sponsor's product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Sponsor's product in this trial? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time.) NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following:	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).**	
Yes, there is a reasonable possibility of Sponsor's product relationship.	There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.	
No, there is not a reasonable possibility of Sponsor's product relationship	Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a subject with overdose without an associated AE.)	

7.2.6 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

7.3 TRIAL GOVERNANCE AND OVERSIGHT

7.3.1 Clinical Adjudication Committee

A Clinical Adjudication Committee (CAC) will evaluate the following events for the purposes of confirming them according to the criteria in Section 8.0 – Statistical Analysis Plan, as well as evaluating the presence of confounding factors.

1) Pancreatitis - There have been post-marketing reports of acute pancreatitis, including non-fatal and fatal hemorrhagic or necrotizing pancreatitis, in subjects with T2DM treated with incretin based therapies (DPP-4 inhibitors and GLP-1 receptor agonists).

When an eligible event is identified, the SPONSOR or its delegate will request copies of additional source documentation related to the event (e.g., hospital records, death certificates, etc.) from the investigator.

In some cases, it may be necessary for the investigator to request permission from the subject or his/her legally acceptable representative to obtain these documents. The investigator agrees to make every effort to obtain the necessary documentation. If any key source documents are not available, the investigator will be expected to document his/her attempts to obtain this information and to provide a narrative summarizing what is known regarding the event.

Details regarding procedures for the collection and submission of additional documentation for eligible cases can be found in separate instruction documents provided to the investigator.

All personnel involved in the adjudication process will remain blinded to treatment allocation throughout the trial. Specific details regarding endpoint definitions can be found in the Adjudication Charter.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to unblinding, changes are made to the primary and/or key secondary hypothesis, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to unblinding, will be documented in a supplemental Statistical Analysis Plan (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 8.2 to 8.12.

Study Design Overview	Omarigliptin Phase IV Study -Omarigliptin Add-on to Insulin in Japanese T2DM
Treatment Assignment	Subjects will be randomized to omarigliptin and placebo in a 2:1 ratio. The study will be conducted as a double-blind study up to Week 16 and following extension part up to Week 52 will be conducted as an open-label study.
Analysis Populations	Efficacy Full Analysis Set (FAS) population, defined as all randomized subjects who: • received at least one dose of treatment period study medication • have at least one measurement of the outcome variable (baseline or post-randomization) Safety All Subject as Treated (ASaT) population, defined as all randomized subjects who received at least one dose of treatment period study medication.
Primary Endpoint	Change from baseline in HbA1c at Week 16
Secondary Endpoint	Change from baseline in FPG at Week 16
Statistical Methods for Key Efficacy Analyses	Change from baseline in HbA1c at Week 16 will be analyzed using a constrained longitudinal data analysis (cLDA) model proposed by Liang and Zeger [12]. The model will include terms for treatment, prior AHA therapy status (yes/no), time and the interaction of time by treatment, time by prior AHA therapy status and time by treatment by prior AHA status. The primary hypothesis which is the superiority of omarigliptin to placebo, will be evaluated by using the cLDA model.
Statistical Methods for Key Safety Analyses	Safety will be assessed following a tiered-approach by clinical review of all relevant parameters including AEs, PDLCs, laboratory tests, vital signs, body weight and ECG. AEs of symptomatic hypoglycemia will be pre-specified as Tier 1 events. The percentage of subjects experiencing Tier 1 events will be analyzed using the Miettinen and Nurminen method [13]. P-Values for treatment comparisons and 95% confidence intervals (CIs) for treatment differences will be provided.
Interim Analyses	No interim analysis is planned.
Multiplicity	Given a single primary hypothesis, no multiplicity adjustment is required.
Sample Size and Power	A sample size of 180 subjects in a 2:1 ratio (i.e., 120 and 60 subjects for omarigliptin and placebo, respectively) will provide 97% power to detect a treatment difference of 0.50% in HbA1c reduction from baseline at Week 16 (α=0.05, two-sided test) based on the conditional standard deviation of 0.82% and the correlation matrix and subject attrition assumptions specified in Section 8.9. The half-width of the 95% CI is expected to be 0.26%. In addition, the sample size is expected to provide 100 or more subjects exposed for one year (omarigliptin group only), assuming 15% discontinuation rate for 52 weeks.

8.2 Responsibility for Analyses/In-House Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the SPONSOR.

This study will be conducted as a double-blind study for first 16-weeks [Phase A (double-blind period)] under in-house blinding procedures with following 36-weeks extension part [Phase B (Open-label period)], i.e. total of 52-weeks study. With regard to Week 16, the official, final database for Week 16 will not be unblinded until medical/scientific review has been performed, protocol violators have been identified, and data have been declared final and complete. With regard to Week 52, the official, final database will not be frozen until medical/scientific review has been performed and data have been declared final and complete. The Clinical Biostatistics department in Merck will generate the randomized allocation schedule for study treatment assignment.

8.3 Hypotheses/ Estimation

Objectives and hypotheses of the study are stated in Section 3.0.

8.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for within- and/or between-treatment differences are listed below.

The baseline value will be defined as the Visit 4/Day 1/Randomization measurement. If this measurement is not available, the Visit 3/Week -2 measurement will be used as the baseline value. If neither measurement is available, the baseline value will be treated as missing. The primary time point is Week 16.

8.4.1 Efficacy Endpoints

The efficacy measurements and time points at which they are measured are provided in Section 6.0 (the Trial Flow Chart).

The primary efficacy endpoint in the study is the change from baseline in HbA1c at Week 16.

The secondary efficacy endpoints in the study are the change from baseline in Fasting Plasma Glucose (FPG) and 1,5-anhydroglucitol (1,5-AG) at Week 16, and the percentages of subjects at HbA1c goals (<7.0% and <6.5%) at Week 16.

The other secondary efficacy endpoints in the study are the change from baseline in HbA1c and FPG at Week 52 and the percentages of subjects at HbA1c goals (<7.0% and <6.5%) at Week 52.

The insulin dose and percentages of subjects with up-titration and down-titration of insulin dose at Week 16 and Week 52 are other efficacy endpoints.

In describing the efficacy variables of interest below, the description is restricted to the primary time point of interest (Week 16). However, many variables are measured at additional time points, as indicated in the Trial Flow Chart (Section 6.0), and will be summarized at other time points.

Table 9 Efficacy Endpoints

Primary Endpoint
Change from baseline in HbA1c at Week 16
Secondary Endpoint
Change from baseline in FPG at Week 16
Percentages of subjects at HbA1c goals (<7.0% and <6.5%) at Week 16
Change from baseline in 1,5-AG at Week 16
Change from baseline in HbA1c at Week 52
Change from baseline in FPG at Week 52
Percentages of subjects at HbA1c goals (<7.0% and <6.5%) at Week 52

8.4.2 Safety Endpoints

The primary safety endpoint (i.e. Tier 1 safety endpoint) is the percentage of subjects experiencing one or more adverse events of symptomatic hypoglycemia, regardless of glucose value.

Other safety endpoints include adverse events, percentages of subjects meeting predefined limits of change in laboratory parameters (including blood chemistry and hematology), change (or percent change) from baseline at Week 16 and Week 52 in laboratory parameters, ECG, vital signs and body weight, and the numbers and percentages of subjects experiencing one or more of each the following:

- Adverse events of hypoglycemia (symptomatic or asymptomatic)
- Documented symptomatic hypoglycemia: An episode with clinical symptoms attributed to hypoglycemia with a documented glucose level of ≤70 mg/dL.
- Severe hypoglycemia, defined as adverse events of symptomatic hypoglycemia that required assistance, either medical or non-medical, regardless of whether such assistance was obtained. These events will be further sub-classified as:
  - Those that required medical assistance. Adverse events of symptomatic hypoglycemia that included a markedly depressed level of consciousness, loss of consciousness, or seizure will be classified as having required medical assistance, whether or not medical assistance was obtained.
  - Those that did not require medical assistance. (i.e., those episodes that required non-medical assistance to treat).
- Asymptomatic hypoglycemia: An episode with a documented glucose level of ≤70 mg/dL but without clinical symptoms attributed to hypoglycemia.

8.5 Analysis Populations

8.5.1 Efficacy Analysis Populations

The Full Analysis Set (FAS) population will serve as the primary population for the analysis of efficacy endpoints in this study. The FAS population consists of all randomized subjects who:

- receive at least one dose of study treatment.
- have at least one measurement (baseline or post-randomization).

A secondary population for analyzing efficacy endpoints will be the Per-Protocol (PP) population. The PP population consists of all randomized subjects who have a baseline (Visit 4/Day 1/Randomization) measurement and a measurement at Week 16, without the following protocol violations.

Protocol violations are not just a repetition of the exclusion and inclusion criteria in the protocol, but a clinical assessment of deviations from the protocol-specified criteria that will either affect or confound the measures of efficacy. Subjects meeting any of the following criteria will be excluded from the per-protocol population (at all time points).

- Study drug compliance <75%, with compliance based on prime therapy records using the formula provided in Section 8.11.
- Use of prohibited medications, based on the list of prohibited medications in Section 5.5, as follows:
  - Prohibited anti-hyperglycemic medications after randomization (Visit 4/Day 1/Randomization) for a total of ≥14 days or ≥7 consecutive days.
  - Pharmacologic doses of corticosteroid use ≥2 consecutive weeks during the study period of interest.
- Incorrect double-blind study medication for a total of ≥14 days (two times) during the study period of interest.

The final determination on protocol violations, and thereby the composition of the PP population, will be made prior to unblinding of the database for week 16 and will be documented in a separate memo.

Any substantial differences between conclusions based on the FAS population and the PP population will be investigated. The number of subjects included in the FAS and PP populations may vary across endpoints due to the degree of missing data for each endpoint.

Subjects will be included in the treatment group to which they are randomized for all analyses of efficacy data.

To avoid the confounding influence of rescue therapy on efficacy comparisons at Week 16, efficacy analyses in the FAS and PP populations will treat data as missing after the initiation of rescue therapy. Outlines on the approach to handling missing data are provided in Section 8.6, Statistical Methods. Sensitivity analysis to assess the impact of missing data will be described in sSAP.

8.5.2 Safety Analysis Populations

The All-Subjects-as-Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all randomized subjects who received at least one dose of study treatment. Subjects will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the ASaT population. This will be the treatment group to which they are randomized for all subjects except for those who take incorrect study treatment for the entire treatment period. Such subjects will be included in the treatment group corresponding to the study treatment actually received.

At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change (or percent change) from baseline, a baseline measurement is also required.

All safety endpoints analyses will be based on the observed data (i.e., with no imputation of missing data).

8.6 Statistical Methods

Statistical testing and inference for efficacy and safety analyses are described in 8.6.1 and 8.6.2, respectively. Nominal p-values may be computed for other efficacy analyses as a measure of strength of association between the endpoint and the treatment effect rather than formal tests of hypotheses. All statistical tests will be conducted at α=0.05, two-sided.

8.6.1 Efficacy Analysis

This section describes the statistical methods that address the primary and secondary objectives.

The estimand for the primary analysis approach for HbA1c and FPG consists of the following elements:

- Target population: Japanese patients with T2DM who have inadequate glycemic control on insulin monotherapy.
- Endpoints: mean change from baseline at Week 16 in HbA1c and in FPG.
- Measure of intervention effect: Difference in means in the effect of randomized treatments if all subjects followed the randomized treatment (without the addition of any other AHAs) through Week 16.

For the analysis of the primary endpoint (i.e., change from baseline in HbA1c at Week 16) in the FAS population, a constrained longitudinal data analysis (cLDA) method proposed by Liang and Zeger [12] will be used. This model assumes a common mean across treatment groups at baseline and a different mean for each treatment at each of the post-baseline time points. In this model, the response vector consists of baseline values and the values observed at each post-baseline time point. Time is treated as a categorical variable so that no restriction is imposed on the trajectory of the means over time. The analysis model will adjust for treatment, prior AHA therapy status (yes/no), time and the interaction of time by treatment, time by prior AHA therapy status and time by treatment by prior AHA status. The primary hypothesis which is the superiority of omarigliptin to placebo on mean HbA1c change from

baseline at Week 16 will be demonstrated using above cLDA model. The Kenward-Roger adjustment will be used with restricted (or residual) maximum likelihood (REML) to make proper statistical inference. An unstructured covariance matrix will be used to model the correlation among repeated measurements and hence avoids the potential bias that could result from the use of specific structured covariance models. If the unstructured covariance model fails to converge with the default Newton-Raphson algorithm, the Fisher scoring algorithm or other appropriate methods can be used to provide initial values of the covariance parameters. In the rare event that none of the above methods yield convergence, a structured covariance such as Toeplitz can be used to model the correlation among repeated measurements. In this case, the empirical option will be used because the sandwich variance estimator is asymptotically unbiased while the model-based variance estimator can grossly overestimate or underestimate the true variance. The cLDA model uses the maximum likelihood principle to estimate the parameters and account for missing data in an implicit fashion.

To avoid the confounding influence of rescue therapy on efficacy comparisons at Week 16, efficacy analyses in the FAS and PP populations will treat data as missing after the initiation of rescue therapy. Sensitivity analyses will be performed to assess the robustness of the results to the assumptions about missing data. The details will be described in sSAP.

Secondary efficacy endpoint of FPG at Week 16 will be analyzed using the above cLDA method described for HbA1c in the same fashion.

Analyses in the PP population for the primary and secondary efficacy endpoints at Week 16 will be performed using a repeated measures analysis of covariance (RM ANCOVA), in which the response vector consists of change from baseline at each of the post-baseline time points. The model will include the same terms for the cLDA model above, and baseline value as a covariate.

For the analysis of percentages of individuals at the HbA1c goals of <7.0% and <6.5% at Week 16, the constrained longitudinal data analysis (cLDA) model that is used for the analysis of HbA1c will also be used to impute Week 16 missing data on HbA1c. Imputations of the missing data will be based on the marginal univariate normal distributions with means equal to the predicted values and variances equal to the squared standard errors for the predicted values from the cLDA model. Ten sets of imputations of each missing value will be constructed from the cLDA model. The seed for the random number generator will be 3102039. Observed data will not be imputed. Subjects will be categorized as a responder (satisfying the HbA1c specific goal of <7.0% or <6.5%) or non-responder at Week 16 after imputations.

To estimate the within-group response rates and between-group rate difference, each of the 10 imputed data sets will be summarized to obtain the proportion of responders within each group. The estimated proportions of responders from the 10 imputed data sets will be combined using the standard multiple imputation (MI) techniques [14] to yield an overall estimate of response rate and associated variance for each group. The estimated response rates and effective sample sizes [15] will then be used to obtain the confidence intervals for within-group response rates via the Wilson score method [16], and the confidence interval and p-value for between-group rate difference via Miettinen & Nurminen (M&N) method [13].

Other efficacy secondary endpoint of change from baseline in 1,5-anhydroglucitol at Week 16 will be analyzed using the above cLDA method described for HbA1c in the same fashion.

Table 10 summarizes the key efficacy analyses. The strategy to address multiplicity issues with regard to multiple endpoints is described in Section 8.8, Multiplicity.

Table 10 Analysis Strategy for Key Efficacy Variables

Endpoint	Approach	Statistical Method	Analysis Population	Missing Data Approach
Primary				
Change from baseline in HbA1c at Week 16	P S S	cLDA RM ANCOVA Missing Data Methods[§]	FAS PP [§]	Model-based N/A [§]
Secondary				
Change from baseline in FPG at Week 16	P S	cLDA RM ANCOVA	FAS PP	Model-based N/A
Percentages of subjects at HbA1c goals (<7.0% and <6.5%) at Week 16	P	M&N	FAS	MI
Change from baseline in 1,5-AG at Week 16	P	cLDA	FAS	Model-based
Change from baseline in HbA1c at Week 52	P	Summary Statistics	FAS	N/A
Change from baseline in FPG at Week 52	P	Summary Statistics	FAS	N/A
Percentages of subjects at HbA1c goals (<7.0% and <6.5%) at Week 52	P	Summary Statistics	FAS	N/A

P=Primary; S=Secondary.
[§] Sensitivity analyses will be performed to assess the impact of missing data. Details will be provided in the sSAP.

For long-term efficacy data up to Week 52, the mean change and the 95% confidence intervals will be calculated by treatment groups of double-blind period to assess the long-term efficacy of omarigliptin. The mean change will be computed relative to baseline (Visit 4/Day 1/Randomization). Between-groups comparisons and/or estimation of between-group difference will not be performed.

For the HbA1c goals of <7.0% and <6.5% at Week 52, the percentage of individuals and the 95% confidence intervals will be calculated using Wilson score method [16] by treatment groups of double-blind period.

For long-term efficacy analyses, all data will be included in the analysis regardless of initiating the rescue therapy since insulin dose during extension period are allowed to down or up –titrate if clinically required.

The summary statistics for the insulin dose, percentages of subjects with up-titration and down-titration of insulin dose will be generated by treatment group of double-blind period at Week 16 and Week 52.

8.6.2 Safety Analysis

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse events (AEs), laboratory tests, ECG, vital signs and body weight.

The ASaT population will be employed for safety analyses. Data after the initiation of rescue therapy will be excluded from the safety analyses for primary safety approach for double-blind period but those data will be included for the secondary safety approach for double-blind period. For long-term safety analyses, all data will be included in the analysis regardless of initiating the rescue therapy, since insulin dose during Phase B (open-label period) are allowed to down or up –titrate if clinically required .

Double-Blind Safety Assessment

The analysis of safety results in the double-blind period will follow a tiered approach (Table 11). The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse events of special interest that are identified a priori constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance with p values and 95% CIs provided for between-group comparisons. Between-group comparisons will be made between active treatment groups versus placebo. Other safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% CIs provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters.

Adverse events (overall summary, specific terms, system organ class terms, confirmed adjudicated pancreatitis) and predefined limits of change (PDLC) in laboratory parameters that are not pre-specified as endpoints of special interest will be classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed. Membership in Tier 2 requires that at least 4 subjects in any treatment group exhibit the event or meet the PDLC criterion. All other adverse events and PDLCs will belong to Tier 3.

Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in review, and not as a formal method for assessing the statistical significance of the between-group differences in adverse events and PDLC.

Change from baseline in body weight at Week 16 will belong to Tier 2 and will be analyzed using a cLDA method described for HbA1c where imputation of missing data is model-based (i.e., accounting for missing data in an implicit fashion).

Continuous measures such as changes (or percent change) from baseline in laboratory, ECG, vital signs and body weight parameters that are not pre-specified as Tier-1 endpoints will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change (or percent change) from baseline values will be provided by treatment group in table format. Mean change (or Mean percent change) from baseline over time will be plotted. For safety endpoints except for body weight, all analyses will be based on the observed data (i.e., with no imputation of missing data).

Table 11 summarizes the analysis strategy for safety endpoints. P-Values and 95% CIs for between-treatment differences (vs placebo) in the percentage of subjects with AEs of symptomatic hypoglycemia identified by the investigator (Tier 1), will be calculated using

M&N method [13]. For Tier 2 endpoints, 95% CIs for between-treatment differences will be provided using the M&N method.

Table 11 Analysis Strategy for Safety Parameters

Tier	Safety Endpoint	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 1	Any AE of symptomatic hypoglycemia	X	X	X
Tier 2[1]	AE overall summary		X	X
	Specific AEs[2], SOCs, confirmed pancreatitis and PDLCs		X	X
	Any AE of hypoglycemia		X	X
	Documented symptomatic		X	X
	Severe hypoglycemia		X	X
	Requiring medical assistance		X	X
	Not requiring medical assistance		X	X
	Asymptomatic hypoglycemia		X	X
	Change from baseline in body weight at Week 16		X	X
Tier 3	All endpoints listed under Tier 2 (above) that have incidence <4 subjects in all treatment groups			X
	Additional hypoglycemia adverse event endpoints			X
	Change and percent change from baseline results (laboratory measurements, ECG and vital signs)			X

[1] Endpoints listed here will qualify for Tier 2 only if the incidence is ≥4 subjects in at least one of the treatment groups.
[2] Among those endpoints not prespecified as Tier 1 endpoints.
SOC=System Organ Class; PDLC=Pre-Defined Limit of Change; X = results will be provided.

Hypoglycemia

The Tier 1 and Tier 2 hypoglycemia endpoints defined in Section 8.4.2 will be analyzed in the same ways described above. The Tier 3 summary of hypoglycemia will include the following, based on episodes classified by the investigator as adverse events:

- The numbers and percentages of subjects with each of the following, overall and by lowest reported glucose category (<50 mg/dL, ≤70 mg/dL, >70 mg/dL, or unknown). A subject's lowest glucose category will be classified as unknown only if no glucose measurements are available for that subject.
    1. any episodes (symptomatic or asymptomatic)
    2. symptomatic episodes
    3. asymptomatic episodes
- The numbers and percentages of subjects with episodes having precipitating factors, overall and separately by factor.
- The number of episodes per subject.

- The number of each of the following (summed across all subjects). The overall summary will include an indication of whether precipitating factors were present.
  1. all episodes (symptomatic or asymptomatic)
  2. symptomatic episodes
  3. asymptomatic episodes

A summary of subjects with episodes that were reported on the hypoglycemia assessment eCRF but were not classified by the investigator as adverse events, will also be provided. If a substantial number of subjects had episodes that were not classified as adverse events, then additional summaries may be provided for the Tier 3 analyses above, including all episodes reported on the hypoglycemia assessment eCRF (i.e., not restricted to adverse events). It is expected that all symptomatic hypoglycemia episodes will be classified by the investigator as adverse events and, thus, that any episodes that are not classified as adverse events will be asymptomatic episodes.

Long-Term Safety Assessment

For safety parameters at Week 52, the incidence rates of adverse or PDLC events and/or summary statistics on the continuous safety parameters will be calculated separately based on treatment received in the double-blind period. However, the safety results will only include the period that subjects are treated with omarigliptin. For subjects who were randomized to omarigliptin in the double-blind period, who continued to be administered omarigliptin in the open-label period (referred to as the omarigliptin/omarigliptin group), the results will be reported for whole duration of the study, Phase A and Phase B (i.e., 52-weeks). For subjects who were randomized to placebo in the double-blind period, who were switched to omarigliptin in the open-label period (referred to as the placebo/omarigliptin group), the results will be reported for the duration of omarigliptin administration in Phase B (i.e., 36-weeks). The between-groups comparisons and/or estimation of between-group difference will not be performed. Mean change from baseline in body weight up to Week 52 will be calculated by treatment group of double-blind period. The mean change will be computed relative to baseline (Visit 4/Day 1/Randomization).

8.7 Interim Analyses

No interim analyses is planned for the study.

The statistical analysis for double-blind data will be performed at Week 16 and then the final analysis for long-term data will be performed at Week 52.

8.8 Multiplicity

The primary evaluation of the glycemic efficacy in this study will be based on testing the primary hypotheses for HbA1c at Week 16. Since there is only one primary hypothesis, no multiplicity adjustment will be needed.

Comparisons involving other efficacy endpoints are considered supportive or exploratory and will be made at α=0.05 nominal level (two-sided) and 95% CIs will be provided. No multiplicity adjustment will be performed for these other comparisons.

8.9 Sample Size and Power Calculations

Efficacy analyses

A sample size of 180 subjects in a 2:1 ratio (i.e., 120 and 60 subjects for omarigliptin and placebo, respectively) will be equivalent to an effective sample size of 176 at Week 16 in the power calculation for the primary hypothesis test using the cLDA model. The effective sample size accounts for information loss due to missing data and the correlation among repeated measures, and is derived using the method proposed by Lu, et al. [17] under the assumptions of cumulative attrition rates and covariance matrix at Weeks 4, 8, 12, and 16 specified below. An effective sample size of 176 will provide 97% power to detect a treatment difference of 0.5% at Week 16 (α=0.05, two-sided test) assuming the conditional standard deviation is 0.82%. In addition, it will provide 90% (80%) power to detect a treatment difference of 0.43% (0.37%). The half-width of the 95% CI is expected to be 0.26%. These calculations were based upon the following assumptions:

- Cumulative attrition rates, which include HbA1c data considered missing after rescue, at Weeks 4, 8, 12, and 16 are 0.0125, 0.0250, 0.0375, 0.0500, respectively
- A conditional correlation matrix at Weeks 4, 8, 12, and 16 is

$$\begin{bmatrix} 1.0 & 0.91 & 0.83 & 0.77 \\ 0.91 & 1.0 & 0.93 & 0.87 \\ 0.83 & 0.93 & 1.0 & 0.94 \\ 0.77 & 0.87 & 0.94 & 1.0 \end{bmatrix}$$

The cumulative attrition rates and correlation assumptions above are based on data from MK-0431 PN106.

Given the effective sample size above, the treatment difference of 25.0 mg/dL (21.6 mg/dL) can be detected with 90% (80%) power for the secondary efficacy endpoint, change from baseline in the fasting plasma glucose (FPG) at Week 16, assuming the conditional standard deviation is 48 mg/dL.

Safety analyses

The sample size is expected to provide 100 or more subjects exposed for one year (omarigliptin group only), assuming 15% discontinuation rate for 52 weeks.

The probability of observing at least one specific adverse event in this study depends on the number of subjects and the underlying percentage of subjects with a specific adverse event in the study population. If the underlying incidence of a specific adverse event is 1%, there is a 70% and 45% chance of observing at least one specific adverse event among 120 and 60 subjects, respectively. If no adverse events are observed among the 120 and 60 subjects, this study will provide 95% confidence that the underlying percentage of subjects with an adverse event is <2.5% and <4.9%, respectively.

8.10 Subgroup Analyses and Effect of Baseline Factors

To assess whether the treatment effect at Week 16 is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) against placebo for the primary efficacy endpoint will be estimated within each category of the following classification variables. The consistency of the treatment effect will be assessed in the context of the primary efficacy analysis model (i.e. cLDA model). Formal statistical testing of these interactions will not be performed.

- Baseline HbA1c levels: by categories: <8%, ≥8%
- Age: by categories: <65 years, ≥65 years
- Gender (female, male)
- BMI: by categories: <25 kg/m^2, ≥25 kg/m^2
- Duration of diabetes (≤10 years, >10 years)
- Prior AHA status (yes, no)

Results from the subgroup analyses should be reviewed cautiously. Because sample sizes within subgroups will be smaller than the overall study sample size, estimation may not be precise and 95% CIs will usually be wide in the subgroup analyses.

To assess whether the mean HbA1c change from baseline at Week 52 is consistent across subgroups, the summary statistics will be generated by subgroup in each treatment group.

8.11 Compliance (Medication Adherence)

The computation of compliance will be based on the study medication case report form. Both the assigned treatment and any matching placebo tablets will be encompassed in the compliance calculation.

The compliance will be based on the compliance week for once-weekly omarigliptin or matching placebo. According to trial design, study medication is recommended to be taken on the scheduled day of dosing, although it is acceptable for the dose to be taken at any day of 7-day dosing period up to the day before the next scheduled dose. Therefore, the week of 7-day dosing period will be considered a compliant week provided that the subject reports taking one tablet of omarigliptin or matching placebo on any day of the week. Otherwise, the week will be non-compliant. Any day within a compliant week is a compliant day for omarigliptin or matching placebo. Any day within a non-compliant week is a non-compliant day for omarigliptin or matching placebo.

For Phase A (double-blind period), compliance will be summarized for both treatment groups in Phase A, For Phase B (open-label period), compliance will be summarized for only the placebo group of the double-blind period. For Phase A+B (whole study period), compliance will be summarized for only the omarigliptin group of the double-blind period. Compliance in Phase B alone will not be summarized for the omarigliptin group of the double-blind period, and compliance in Phase A+B will not be summarized for the placebo group of the double-blind period to be consistent with safety assessments.

Summary statistics for each relevant period will be provided on percent compliance by treatment group of double-blind period. For each subject, the percent compliance for the relevant duration will be calculated using the following formula:

$$\text{Compliance} = \frac{\text{Number of Compliant Days}}{\text{Number of Days in the Respective Study Period}} \times 100\%.$$

The "Number of Days in the Respective Study Period" is defined for each subject as the total number of days from the first day to the final day as defined in Table 12 below.

Table 12 Definitions of Study Periods

Study Period	Treatment Groups	First Day	Final Day
Phase A (double-blind period)	Omarigliptin and Placebo groups	The first dose of double-blind study medication	The last scheduled day of study medication + 6 days
Phase B (open-label period)	Placebo group of double-blind period	The first dose of omarigliptin in Phase B	The last scheduled day of omarigliptin + 6 days
Phase A+B (whole study period)	Omarigliptin group of double-blind period	The first dose of double-blind study medication	The last scheduled day of study medication + 6 days

8.12 Extent of Exposure

The extent of exposure to study treatment will be summarized by treatment group.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by the Sponsor as summarized in Table 13.

Table 13 Product Descriptions

Product Name & Potency	**Dosage Form**	**Source/Additional Information**
Omarigliptin (MK-3102) 25 mg or matching placebo	Tablet	Provided centrally by the Sponsor

All placebos were created by the Sponsor to match the active product.

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

In the placebo run-in period, subjects will receive one single-blinded bottle of Omarigliptin 25 mg matching placebo. In the Phase A (Double-blind period), subjects will receive one blinded bottle of Omarigliptin 25 mg or matching placebo every four (4) weeks. In the Phase B (Open-label period), subjects will receive sufficient supplies of open label bottle of Omarigliptin 25 mg to support a period between visits. No kitting is required.

9.3 Clinical Supplies Disclosure

The emergency unblinding call center will use the treatment allocation/randomization schedule for the trial to unblind subjects and to unmask treatment identity Phase A (Double-blind period) of this trial. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

Treatment identification information is to be unmasked ONLY if necessary for the welfare of the subject. Every effort should be made not to unblind the subject unless necessary.

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date, reason and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Only the principal investigator or delegate and the respective subject's code should be unblinded. Trial site personnel and Sponsor personnel directly associated with the conduct of the trial should not be unblinded to treatment assignment. Subjects whose treatment assignment has been unblinded (by the investigator, Merck subsidiary, or through the emergency unblinding call center) must be discontinued from study drug.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Discard/Destruction/Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

10.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

1. name, address, telephone number and e-mail address;
2. hospital or clinic address and telephone number;
3. curriculum vitae or other summary of qualifications and credentials; and
4. other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

10.1.4 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this trial. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is provided in Section 12.1 - Merck Code of Conduct for Clinical Trials.

The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the trial reimbursed to the investigator by the Sponsor.

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial [Clinical Study Report (CSR) CI]. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the Protocol/CSR CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this trial or its results to those registries.

10.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

10.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. Merck will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

For multicenter trials, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual trial site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single trial site data prior to the main paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to

the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

11.0 LIST OF REFERENCES

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12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of subject safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials which are not under the control of Merck.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine subject preferences, etc.

The design (i.e., subject population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research subjects must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

Merck selects investigative sites based on medical expertise, access to appropriate subjects, adequacy of facilities and staff, previous performance in Merck trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by Merck personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. Merck funding of a trial will be acknowledged in publications.

III. Subject Protection

A. IRB/ERC review

All clinical trials will be reviewed and approved by an independent IRB/ERC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/ERC prior to implementation, except that changes required urgently to protect subject safety and well-being may be enacted in anticipation of IRB/ERC approval. For each site, the IRB/ERC and Merck will approve the subject informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that subject welfare is of primary importance. Potential subjects will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care. Subjects are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Subjects are enrolled only after providing informed consent for participation. Subjects may withdraw from a Merck trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

Merck is committed to safeguarding subject confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research subject by name.

D. Genomic Research

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck trials. Merck does not pay incentives to enroll subjects in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

Merck does not pay for subject referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible subjects.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local IRB/ERC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck trials will indicate Merck as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

Investigators will be expected to review Merck's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens consented and/or collected in this trial as outlined in Section 7.1.3.3 – Future Biomedical Research Samples will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways drugs/vaccines may interact with
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

All subjects enrolled in the clinical trial will be considered for enrollment in the Future Biomedical Research sub-trial.

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects on the visit designated in the trial flow chart. If delayed, present consent at next possible Subject Visit. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons.

A template of each trial site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of subject consent for Future Biomedical Research will be captured in the electronic Case Report Forms (eCRFs). Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

Collection of specimens for Future Biomedical Research will be performed as outlined in the trial flow chart. In general, if additional blood specimens are being collected for Future Biomedical Research, these will usually be obtained at a time when the subject is having blood drawn for other trial purposes.

4. Confidential Subject Information for Future Biomedical Research

In order to optimize the research that can be conducted with Future Biomedical Research specimens, it is critical to link subject' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical trial data to the specimen. The clinical data allow specific analyses to be conducted. Knowing subject characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for Future Biomedical Research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical trial site, unique codes will be placed on the Future Biomedical Research specimens. This code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between subject identifiers and this unique code will be held at the trial site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses utilizing the Future Biomedical Research specimens may be performed by the Sponsor, or an additional third party (e.g., a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in this sub-trial. Future Biomedical Research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and ask that their biospecimens not be used for Future Biomedical Research. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com).

Subsequently, the subject's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for Future Biomedical Research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the subject of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens

Future Biomedical Research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the trial site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular trial, the trial site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated trial administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Subjects

No information obtained from exploratory laboratory studies will be reported to the subject, family, or physicians. Principle reasons not to inform or return results to the subject include: Lack of relevance to subject health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and subjects. Subjects will not be identified by

name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

Every effort will be made to recruit all subjects diagnosed and treated on Sponsor clinical trials for Future Biomedical Research.

11. Risks Versus Benefits of Future Biomedical Research

For FBR, risks to the subject have been minimized. Risks include those associated with venipuncture to obtain the whole blood specimen. This specimen will be obtained at the time of routine blood specimens drawn in the main trial.

The Sponsor has developed strict security, policies and procedures to address subject data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

13. References

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2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf
3. Industry Pharmacogenomics Working Group. Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/
4. Industry Pharmacogenomics Working Group. Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

12.3 List of Abbreviations

Abbreviations	Definition
1, 5-AG	1,5-anhydroglucitol
AE	adverse event
AHA	anti-hyperglycemic agent
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMA	american medical association
ASaT	all subject as treated
AST	aspartate aminotransferase
BG	biguanide
BMI	body mass index
CAC	clinical adjudication committee
CI	confidence interval
cLDA	constrained longitudinal data analysis
Cr	creatinine
CSR	clinical study report
DILI	drug-induced liver inury
DM	diabetes mellitus
DNA	deoxyribonucleic acid
DPP-4	dipeptidyl peptidase 4
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EMA	European medicines agency
ERC	ethics review committee
EU	European Union
FAS	full analysis set
FBR	future biomedical research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDC	fixed dose combination
FPG	fasting plasma glucose
FSG	finger stick glucose
GCP	Good Clinical Practice
GIP	glucose-dependent insulinotropic peptide
GLP-1	glucagon-like peptide 1
HA	hypoglycemia assessment
HAL	hypoglycemic assessment log
HbA1c	hemoglobin A1c (glycosylated hemoglobin A1c)
HIV	human immunodeficiency virus
ICF	informed consend form
ICH	international conference on harmonisation of technical requirements for registration of pharmaceuticals for human use
IEC	independent ethics committee
IgM	immunoglobulin M
IRB	institutional review board

Abbreviations	Definition
IUD	intrauterine device
IVRS	interactive voice response system
IWRS	interactive web response system
M&N	Miettinen & Nurminen
MHLW	Ministry of Health, Labor and Welfare
MI	multiple imputation
PDLC	predefined limits of change
PFSB	Pharmaceutical and Food Safety Bureau
PP	per-protocol
REML	restricted (or residual) maximum likelihood
RM ANCOVA	repeated measures analysis of covariance
RNA	ribo nucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SGLT2	sodium glucose cotransporter 2
SMBG	self-monitoring blood glucose
sSAP	supplemental statistical analysis plan
SU	sulfonylurea
T2DM	type 2 diabetes mellitus
TSH	Thyroid-stimulating hormone
TZD	thiazolidinediones
ULN	upper limit of normal
WBC	white blood cell
α-GI	α-glucosidase inhibitors
β-hCG	β-human chorionic gonadotropin

12.4 Measurement of blood pressure, body weight and height

The following items should be measured in accordance with the following procedures.

If possible, a single staff person will perform the measurements across the study for a given subject.

12.4.1 Blood Pressure

Ensure subject has not had any caffeine or tobacco within 30 minutes. Patients should be fasted (no food or drink except water) for at least 10 hours prior to blood pressure measurements. Blood pressure should be measured in the sitting position. The subject will remain in the sitting position for at least 5 minutes before any blood pressure readings are recorded. The same arm, preferably the non-dominant arm, should be used for all blood pressure determinations at each visit. Systolic and diastolic blood pressure will be determined by obtaining two measurements, 1 to 2 minutes apart. The consecutive systolic or diastolic blood pressure readings should be within 5 mmHg of each other. The final blood pressure measurement must be recorded.

12.4.2 Body Weight

Weight will be measured using a standardized scale throughout the study.

Subjects should be instructed to fast for at least 10 hours prior to the measurement of body weight. Weight will be taken on a digital scale throughout the study, after voiding and while wearing only a gown and underwear (no street clothes, no shoes or socks). Subjects should step gently onto the scale, place both feet together in the center of the scale and stand straight with eyes directed ahead. Subjects should be instructed to stand still and not sway. Measurement will be recorded after the weight has stabilized.

Weight will be measured to the nearest 0.1 kg. Measurements will be collected until 2 consecutive measurements do not differ by more than 0.2 kg from each other. The final weight measurement must be recorded. The same digital scale must be used throughout the study.

12.4.3 Height

Height will be measured without shoes, using a stadiometer.

Standing height will be assessed through maximum vertical stature for persons who can stand unassisted. Hair ornaments, barrettes, braids, jewelry, or cornrows should be moved or removed from the top of the head before the measurement is taken.

A fixed stadiometer with vertical backboard, fixed floorboard and movable headboard should be used. Subjects should stand with the heels of their feet against the vertical backboard with feet pointing outward at approximately a 60-degree angle. Body weight should be distributed evenly with both feet flat on the floor. The examiner should check several contact points with the vertical backboard, including heels, buttocks, shoulder blades, and the back of the head. This may be difficult for subjects with certain body shapes. However, the head should be in the Frankfort plane (an imaginary line from the ear canal to just below the lower orbit of the eye should be parallel to the floor). Subject should be looking straight ahead, and be asked to take a deep breath and stand tall. Once the subject is positioned, the headboard or a flat ruler will be placed on top of the head, with sufficient pressure to compress the hair. The measurement is recorded in cm, to the nearest mm. Measurements will be collected until 2 consecutive measurements do not differ by more than 2.5 cm from each other. The final height measurement must be recorded. Some people may have physical conditions that may limit the ability to measure height accurately (e.g., kyphosis). In such cases, height should be measured to the best of the examiner's ability, and a note should be made of the condition.

12.5 Standard Operating Procedures for Liver Enzyme Elevations

Every increase in ALT, and/or AST, above the limits described in the protocol is defined as clinically significant (i.e., ALT or AST ≥three times the ULN). In addition, when ALT and/or AST levels are elevated beyond the clinical significant margin above, the investigators/trial staffs must recall the subject, attempt to identify the cause of the elevation, and repeat the blood test(s). Detailed instructions are provided below.

Note: For subjects who have ALT or AST increases (either ALT or AST ≥three times the ULN) with a total bilirubin lab value ≥two times ULN and, at the same time, the ALP lab value is <two times ULN, please follow the guidance document entitled " ECI Guidance for Potential DILI in Clinical Trials" located in the Investigator Trial File Binder and refer to the ECI guidance in the protocol (Section 7.2.3.2).

For subjects with ALT or AST increases (either ALT or AST ≥three times the ULN) but who do not also meet the above criteria for both total bilirubin and ALP, the process below should be followed. These events do not qualify as ECIs per protocol (see Section 7.2.3.2).

1) Subjects should return to the center within 3 days for the following: (history can be obtained over the phone in the interim)
   (1) Obtain further information.
   (2) Careful questioning of recent alcohol consumption, including a recent change in pattern of alcohol use.
   (3) Search for drug-related causes of hepatitis and liver injuries (acetaminophen; amiodarone; aspirin; chlorpromazine; dantrolene; erythromycin; halothane; isoniazid; methyldopa; phenytoin; propylthiouracil; rifampin; sulfonamides; tetracyclines) or other new medications.
   (4) Search for alternative medical causes such as cholelithiasis, recent alcohol consumption, history of intercurrent illness (e.g., viral syndrome), hepatitis, or potential exposure to viral hepatitis (transfusion).
   (5) Repeat determination of ALT, AST, total bilirubin, and ALP.
   (6) Perform serologic tests including: (a) Hepatitis A (immunoglobulin M, IgM); (b) Hepatitis B (surface antigen and core IgM); (c) Hepatitis C (antibody).
   (7) Based upon initial abnormal ALT/AST level:
      a) If ALT or AST levels are ≥three times ULN, but ≤five times ULN, consideration can be given to keeping subject on study medication until repeat determination.
      b) If ALT or AST levels are >five times ULN, subjects should have their study medication interrupted immediately.

   Note: Once interrupted, reinstatement of therapy must occur only after consultation with a Clinical Monitor (SPONSOR or its delegate).

2). Based upon repeat determination (performed within 3 days of initially reported abnormal ALT or AST level):

(1) If ALT and/or AST levels are <three times ULN, consultation with a Clinical Monitor (SPONSOR or its delegate) is required prior to continuing the subject in the trial.

(2) If ALT and/or AST levels are ≥three times ULN, subjects will be discontinued from study medication.

Note: If the repeat determination is still ≥three times elevated, but has substantially decreased (>30% decline) from the initial abnormal value, a second repeat should be performed within 3 days of the initial repeat. If ALT and/or AST levels return below the three times margin consideration can be given to continue the subject in the trial after a discussion with, and approval by, the Clinical Monitor (SPONSOR or its delegate).

All persistent elevations in ALT or AST ≥three times ULN at the completion/discontinuation of study medication will warrant follow-up including a repeat blood test within 1 week and until complete resolution of the abnormality.

12.6 Entry of Hypoglycemic Episode into eCRF

Report from Subject		Investigator's Judgment		Enter into eCRF		
Subjective symptom	SMBG	Hypoglycemic episode	Adverse event	HA eCRF	FSG eCRF	Adverse event eCRF
With (e.g., headache, feeling hungry)	>70 mg/dL or No data	Yes	Yes	X	X [1]	"hypoglycemia"
		No	Yes			Relevant adverse event term (e.g., "headache")
			No			
	≤70 mg/dL	-	Yes	X	X	"hypoglycemia"
			No	X	X	
Without	≤70 mg/dL	-	Yes	X	X	"asymptomatic hypoglycemia"
			No	X	X	

- : Investigator's judgment is not needed (SMBG ≤70 mg/dL must be handled as a hypoglycemic episode)

[1] SMBG value should be entered into FSG form if SMBG value is available.

12.7 Clinical Study Conduct System

For clinical study conduct system, refer to protocol of Japanese version.

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in Section 7.0 – TRIAL PROCEDURES (Assessing and Recording Adverse Events). I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	